

**The Challenges in Regulating  
Traditional Plant Medicines in the Era of  
Contemporary Evidence-Based Health Policy**

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## DEDICATION

This thesis is dedicated to the late  
**Sister Pauline Felder**  
traditional Swiss herbal expert, midwife, and nun  
for opening my window into a  
timeless medical world



## ABSTRACT

Traditional plant medicines are plant-derived therapeutic products prepared and applied according to long-standing medical customs. Around the world they are widely used in primary and preventative healthcare and readily available over the counter. Currently their position in New Zealand's regulatory system of healthcare is not adequately addressed. This health policy possibly impacts access, user-information, and fails to safeguard public health. In its *Traditional Medicine Strategy 2014-2023*, the World Health Organization (WHO) calls on Member States to provide a regulatory framework so that the formal and safe contribution of traditional therapeutics in national systems of healthcare can be advanced.

The health policy question arising from this is how traditional plant medicines could be incorporated into a contemporary regulatory framework which is both evidence-based *and* appropriate for these long-standing therapeutic products. Evidence of effectiveness and safety of health interventions is paramount for regulatory integration of traditional plant medicines. Presumed lack of such evidence is one reason why New Zealand and other countries are yet to make progress in regulating these remedies.

The objective of this thesis is twofold. First, it is to establish whether systematic collation of long-standing empirical evidence from the clinical knowledge base on medicinal plants can provide reliable and verifiable pharmacological data. Can it be used to substantiate traditional health claims and therefore contribute to a framework for evidence-based health policies? This empirical evidence is informed by observations in patient care, evaluated and transmitted inter-generationally by clinical experts. In written medical traditions, therapeutic uses of medicinal plants are historically recorded in medical and more recently in specialised phytotherapeutic textbooks. Second, it is to determine if the way the EU dealt with evidence and safety requirements could help shape New Zealand's policy on traditional plant medicines.

The research design of this interdisciplinary thesis spans across medical history, phytotherapy and health science. It employs a longitudinal, comparative textual analysis of European clinical textbooks from the early modern period onwards. It starts with the influential medical textbook *New vollkommen Kräuter-Buch* by the German physician, apothecary and botanist Tabernaemontanus (1522-1590) and concludes with present day teaching textbooks on phytotherapy. By way of exemplars it examines consistency and

divergence of pharmacological data recorded on two medicinal plants, Arnica (*Arnica montana*) and St. John's Wort (*Hypericum perforatum*) over 400 years. As a research instrument and to organise a large amount of historical and contemporary pharmacological records, the Historical Assessment Tool was developed and tested as a systematic and reproducible method. Traditional clinical knowledge is triangulated with information on the exemplars listed in the official Prussian and German pharmacopoeias and their commentaries, as well as with several modern regulatory and authoritative herbal monographs (i.e. by Commission E, EMA, WHO, ESCOP, and HagerROM). This bibliographic evidence is further compared with evidence of efficacy for indications as investigated with randomised-controlled trials (RCTs), and scientific evidence from experimental laboratory research.

Parallel findings of therapeutic indications on Arnica and St. John's Wort across all qualitative and quantitative sources and time periods led to concluding that long-standing traditional clinical knowledge relating to the examined medicinal plants is a reliable and verifiable source of evidence. Evaluation of Arnica demonstrated an uninterrupted medical transmission of two clusters of indications over 400 years, relating to the treatment of consequences of injuries and accidents, and for pain related to the musculo-skeletal system and nerves. Analysis of data on St. John's Wort showed congruency of medical transmission between three clusters of complaints relating, in modern terminology, to inflammation and catarrh of the gastro-intestinal system (gastro-enteritis, dyspeptic disorders), to burns and wounds, and to psychovegetative disorders (depressive moods, anxiety, nervous unrest, and hormonally driven dysphoria in relation to the female menstrual cycle). The validity of historical traditional indications was further supported when cross-checked with outcomes from clinical trials where undertaken. Data from experimental research provided insights into active constituents and possible mechanisms related to the empirically observed effects. The intergenerational professional literature on the *materia medica* represents the most comprehensive evidence source on the clinical scope of the medicinal plants investigated.

Notwithstanding the small number of exemplars analysed, clinically orientated historical and contemporary authoritative textbooks within the European *materia medica* are recommended as a comprehensive and reliable source of empirical evidence for substantiating traditional plant indications and clinically observed safety aspects. Empirical

evidence is particularly important where modern scientific evidence is wanting or absent. The Historical Assessment Tool is proposed as a feasible method for the systematic collation and evaluation of bibliographic data for traditional health claims. This would be an additional pathway to make such data operational in an evidence-based policy framework. The complexity of regulating traditional plant medicines is further illustrated by an inquiry into the European Union's approach to dealing with evidence and safety requirements for such therapeutics. This thesis concludes with health policy recommendations arising from these analyses. These relate to the regulation of traditional plant medicines as a distinct therapeutic product category:

- to advance regulation on traditional plant medicine in New Zealand
- to implement a systematic framework for the collation and evaluation of bibliographic empirical evidence
- to develop a system for safety assessments that incorporates both historical safety observations and modern pharmacovigilance
- to create a practitioner-only sub-category alongside OTC remedies.

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## ABBREVIATIONS

ADR	Adverse Drug Reaction
CAM	Complementary and Alternative Medicine
CER	Comparative Effectiveness Research
DAB	Deutsches Arzneibuch
EB	Ergänzungsbuch
EBM	Evidence-based Medicine
EMA	European Medicines Agency
ESCOF	European Scientific Cooperative on Phytotherapy
EU	European Union
HAB	Homöopathisches Arzneibuch
HMPC	Committee on Herbal Medicinal Products
IDC	International Disease Classification
MA	Marketing Authorisation
NHPs	Natural Health Products
OTC	Over-the-counter
RCT	Randomised Controlled Trial
TCM	Traditional Chinese Medicine
TEM	Traditional European Medicine
THMPD	Traditional Herbal Medicine Products Directive
THMPs	Traditional Herbal Medicinal Products
THR	Traditional Herbal Registration
TK	Traditional Knowledge
TOU	Tradition-of-use
TPM	Traditional Persian Medicine
WHO	World Health Organization
WW1	World War 1
WW2	World War 2
QALY	Quality-Adjusted Life Year

In this thesis plants and foods used as medicines are spelled in upper case.

# 1 INTRODUCTION

## 1.1 Traditional plant medicine and its regulatory position in Western systems of healthcare

Regulation is a prominent feature of Western healthcare systems. Its purpose is to safeguard public health by ensuring that therapeutic interventions are of high quality, safe, and effective (Kelber et al., 2014, p. 448). There are three key areas of regulation in healthcare: of professions, of products, and of procedures (Burton, Smith, & Falkenberg, 2015; World Health Organization, 2013, p. 13). This thesis addresses the regulation of products sold over the counter (OTCs), specifically traditional medicines prepared from medicinal plants which consumers use for self-care. Such products contain plant materials as active ingredients, being herbs, seeds, berries, roots, leaves, bark, flowers, algae, lichens, certain exudates, and macroscopic fungi. Typical traditional preparations are teas, tinctures, extracts, essential oils, expressed juices, and processed exudates (Knöss, 2018, p. 368). These preparations are variously termed plant medicines, herbal medicines, herbal remedies, herbal drugs, herbal drug preparations, botanical medicines, phytomedicines, phytotherapies, or traditional medicines (Iannitti, Morales-Medina, Bellavite, Rottigni, & Palmieri, 2016, p. 1; World Health Organization, 1999). In New Zealand, traditional plant medicines are categorised under Natural Health Products (NHPs) and are a widely used form of natural healthcare (Barnes, McLachlan, Sherwin, & Enioutina, 2016). Despite their prevalence and increasing popularity, current regulations for plant medicines neither adequately address their place in New Zealand's healthcare system nor protect public health.

Although the therapeutic effects of medicinal plants are well known in clinical practice, relatively few have been fully investigated with the modern scientific methodologies that form the basis of decisions in current health regulation. In contemporary clinical practice, plant-based medicines are predominantly prescribed according to empirical traditional knowledge which is concerned primarily with the observed effects on health (Evans, 2009; Wiese, 2016). Could, therefore, long-standing empirical knowledge as historically documented and transmitted in the clinical literature on plant medicines contribute to the validation of traditional remedies? In particular, could such bibliographic evidence of consistent medical use provide a valid evidence base for their effectiveness and safety, and

therefore a pathway for the registration of traditional medicines? If so, could such therapeutic products take their place in a contemporary regulatory framework that is informed by evidence-based policy?

The long history of cross-cultural use of plant medicines demonstrates their ongoing importance and value to communities. The practice of using plants as medicines is universal and as old as human life itself. Plant medicines have been used for millennia with known therapeutic effects. While contemporary Western medicine predominantly makes use of chemically manufactured drugs, it is historically rooted in plant medicine. Many original synthetic drugs are derivatives from medicinal plants native or naturalised in Europe, such as morphine and codeine from *Papaver somniferum*, digoxin from *Digitalis lanata* or aspirin from *Philipendula ulmaria*. Medicinal plants have been empirically proven to regulate biological processes. The mechanisms that drive their wide-ranging effects across the human genome are increasingly explained via contemporary scientific methodologies (Sen & Samanta, 2015). Systems biology and network pharmacology offer novel explanations of their high safety, effectiveness and pleiotropic effects by examining the influence of traditional plant medicines on higher human regulatory and over-arching processes (Rezadoost, Karimi, & Jafari, 2016; Schwabel, Vennos, & Saller, 2014; van der Greef et al., 2010). The long-term use of judiciously selected plants by humans as a source of nutrition and medicine has confirmed that their bioactive compounds exert low toxicity for humans, maybe due to plants' and humans' millennia of co-evolution leading to morphogenetic and phylogenetic closeness (Douros et al., 2016; Lasek & de Smet, 1999; Loew, 2005, p. 123; Yarnell & Abascal, 2014).BJM

The World Health Organization (WHO) states that traditional therapeutics that have been administered over a long period of time usually result in medicines where the dosage and formulation have empirically evolved to maximise their therapeutic effectiveness and minimise risk (World Health Organization, 2012, p. 17). Thus, their toxicity, formulation and dosage are seen to be established. In contrast to traditional plant medicines, synthetic substances are a relatively recent form of therapy, becoming increasingly prevalent from the end of the 19<sup>th</sup> century and then widespread in the 20<sup>th</sup> century. Due to their novelty, they required stringent investigation to assess their safety and efficacy in relation to human physiology. Throughout the 20<sup>th</sup> century, regulations have been introduced, primarily to deal with synthetically-derived chemical entities. In New Zealand, pharmaceutical drugs are

regulated under the Medicines Act 1981 but plant-based medicines are regulated separately from pharmaceutical drugs via the Dietary Supplements Regulations 1985. New Zealand regulations are different from international regulations in currently prohibiting statements about the therapeutic purposes of traditional remedies. This prohibition applies even when scientific research has determined a traditional product to be effective.

The Dietary Supplement Regulations 1985 further complicate the matter by placing traditional plant medicines in the same category as modern and often synthetically derived nutritional supplements that were developed in the 20<sup>th</sup> century to address nutritional deficiencies. These contain vitamins, amino acids, antioxidants like  $\beta$ -carotene, taurine and lycopene, minerals, trace elements, and lipids. Traditional plant medicines are, however, distinct from nutrients in foods and dietary supplements, and from pharmaceutical drugs. It has thus been suggested that their different characteristics and purpose necessitate a separate regulatory framework that adequately reflects their natural, non-synthetic composition and their place in long-standing traditional systems of medicine (Abdel-Tawab, 2018, pp. 387-388). Traditional medicines transcend nutritional purpose: they have pharmacological effects that are used to prevent and treat illnesses. While health claims are not permitted under the current New Zealand regulations, health claims are inferred by consumers who seek these medicines out for their attributed benefits.

A WHO global survey has confirmed that many governments of its Member States, including New Zealand, do not recognise traditional medicine and their therapeutics as an integral part of their healthcare system and do not provide regulations, funding or access to them (Cordell, 2014, xxix). Through socio-economic and political-legal factors that shaped healthcare systems in Western and westernised countries since the 20<sup>th</sup> century, non-biomedical treatment options are now commonly not taught in medical schools or universities lacking such schools, have only minimal access to research funding, laboratories, or general medical infrastructure, and are not provided in hospitals or covered by government health insurance systems (Willis & Coulter, 2007, p. 218). Moreover, the professions using traditional therapeutics do not obtain registration in many Western countries, and private educational institutions teaching traditional strategies for health usually do not receive educational funding, impeding their appearance of legitimacy. As Eskinazi (1998, p. 1622) explains in his policy perspective, Western academics who have tried to conduct scientific research into non-biomedicine fields have struggled with threats,

discrimination, and career impediments. This indicates that non-scientific factors are shaping the current privileging of Western biomedicine. Such hegemony disallows multiple epistemologies and pluralism in medicine, marginalising many forms of discovery and knowledge (Holmes, Murray, Perron, & Rail, 2006, p. 181; Jagtenberg et al., 2006). Some researchers argue that science does not occur in a vacuum but is a social phenomenon, a practice that is embedded in wider cultural values and power relationships in society (Myers, Xue, Cohen, Phelps, & Lewith, 2012, p. 70). Anti-trust laws in the USA now make such economic and professional dominance and restrictions on competition illegal, even for medicine (Wardwell, 1994). If biomedicine, only a portion of the medical field, controls or limits access to non-biomedical services and non-pharmaceutical therapeutics, it results in a monopoly. This is not seen to be in the public interest (Bodeker, 2000, p. 5; Ho, 2013; Willis & Coulter, 2007, pp. 218-219).

## **1.2 Challenges for integration**

The pertinent policy question therefore is how can traditional plant medicine be incorporated into a contemporary regulatory framework that is both evidence-based *and* appropriate for traditional therapies? Evidence-based policy subscribes to the notion that only those healthcare options which are based on scientific information about what works should be sanctioned (Rycroft-Malone et al., 2004, p. 81). The evidence-based medicine (EBM) movement claims that such evidence should be drawn from clinical trials set up for the proof of efficacy, and that evidence requirements should be the same for all therapeutic interventions regardless of whether they are long-standing or novel (Angell & Kassirer, 1998; Parker, 2007). Archie Cochrane, the forerunner of the EBM movement, strongly argued for the privileged use of randomised-controlled trials (RCTs) for determining the use of finite health resources (O'Donnell, Atkinson, Freebairn, & Rychetnik, 2017, p. 163). Consequently, EBM proceeded to hierarchically privilege RCTs above all other forms of knowledge generation (Daly et al., 2007; Howick, 2011; O'Donnell et al., 2017).

Notably, there are numerous similar 'hierarchies of evidence' but there are marked inconsistencies and disparities between them. Such difference is one of the reasons why some policy advisors see evidence hierarchies as unsuitable replacements for more case-specific judgements in public healthcare based on broader considerations (Rawlins, 2008, pp. 33-34; Sanderson, 2003). There is no finite answer to the question of which evidence framework is most appropriate for patient-centred healthcare (McCarthy & Rose, 2010;

Sanderson, 2003). Although EBM focuses on RCTs and systematic reviews—forcing health professions to notice the totality of published literature and to stop the perpetuation of ineffective or outdated practices (Epstein, 2017) —it is an insufficient method for establishing which evidence facilitates appropriate decision making in clinical practice (Rawlins, 2008). While biomedicine is based on a medical paradigm that is informed by natural science, the core of its evidence base persists in empirical form. Technology assessment reports and disease intervention analyses estimate that up to 80% of treatments in conventional Western biomedicine have not been subjected to EBM criteria (Imrie & Ramey, 2000; Smith, 1991; US Congress Office of Technology Assessment, 1978, 1983). Acquired skills and expertise passed on in the medical curriculum, in clinical practice, and in peer-reviewed professional education underpin this empirical body of medical knowledge. In this, the challenges of producing EBM evidence on efficacy through clinical trials are no different from the challenges faced in traditional plant medicine.

Healthcare interventions in real life patients are inherently complex. No medical system could function in a clinically sound way if the currently acclaimed gold standard of medicine, RCTs, were the only means to validate interventions and achieve regulatory approvals. This is because RCTs establish internal validity of efficacy of interventions within a highly-selected, homogenous population under ideal conditions (Feinstein & Horwitz, 1997; Jackson & Waters, 2004; Rychetnik, Frommer, Hawe, & Shiell, 2002; Sanderson, 2003). Moreover, the assessment of efficacy in a clinical trial is not designed to inform the real-life effectiveness of an intervention, but rather to clear regulatory hurdles for product registration (Khan, Mar, & Brown, 2018, p. 247). These interventions may not show external validity when applied to a heterogeneous population of patients. Real life patients may suffer from co-morbidities or have individual variations that were not present in patients selected for the RCT. There is also a gap between the approach of evidence-based medicine and the principle of patient-centred medicine (Bensing, 2000). The significance of this potential variability is illustrated in a regional review of family-practice patient records in Canada that confirmed multi-morbidity as the rule rather than the exception (Fortin, Bravo, Hudon, Vanasse, & Lapointe, 2005). It is therefore impossible to know if a therapy approved on EBM criteria is appropriate or effective for sub-populations that were not included in a trial (Coulter, 2012).

The EBM pathway to evidence-based therapeutics also ignores the fact that disease has

genetic, individual, social, cultural, economic, and environmental factors that are not easily discernible from RCTs (O'Donnell et al., 2017, p. 205). Moreover, clinical efficacy is only one aspect of healthcare delivery. The preferences, concerns, and expectations that patients bring to clinical encounters need to be integrated in patient-centred and values-based healthcare systems where the therapeutic context and therapeutic relationship between patients and care providers make significant contributions to health outcomes (McCarthy & Rose, 2010; Saller, 2006b). In contrast, EBM approaches to healthcare by design cannot respond to individual patients' health goals as they treat patients as impersonal subjects (Greenhalgh, Snow, Ryan, Rees, & Salisbury, 2015; Reuben & Tinetti, 2012). Although RCTs are convenient and have become synonymous with the scientific method, they are—when taken as stand-alone evidence—limited in their knowledge base (Madjar & Walton, 2001). This disconnect between research and real-life practice limits the usefulness of RCTs, not only for clinicians, but also for regulators. The substantial costs of RCTs in money, time, and energy, are further issues that hamper their practicality (Rawlins, 2008, pp. 18-19). In addition, in 2008 the revised Declaration of Helsinki elevated ethical considerations for research on humans. It restricted placebo-controlled trials to areas of research where no other effective treatment exists (World Medical Association, 2008). Even though these restrictions were revised in 2013, placebo-controlled studies continue to cause ethical issues by potentially violating the principle of beneficence (Batra & Howick, 2017).

The regulatory systems in many Western countries that were established for the regulation of newly developed pharmaceutical drugs create legal and commercial disadvantages for traditional plant medicines, thus impeding patient access to them. The issues with scientific evidence that have been raised give currency to the proposition that RCTs should not be a prerequisite for the registration of established therapies. Such an exclusive pathway to their legitimacy would ignore the empirical evidence base of long-standing medicines (Clark-Grill, 2007; Evans, 2009; Flatt, 2012, 2013; Holmes et al., 2006, p. 184; Jagtenberg et al., 2006; K.A. Jobst, 1998; Schwager, 2012; Walach, 2009). Where data on effectiveness and innocuousness already exist, the compulsory establishment of these parameters via the pharmaceutical research model is not compelling. Moreover, such a regulatory prerequisite would financially prevent the reintegration of traditional plant medicines into a contemporary healthcare system: the Western healthcare model does not usually fund traditional plant medicines and data generation of scientific evidence on non-patentable natural therapeutics is cost prohibitive without the public funding granted to biomedicine

(Eskinazi, 1998, p. 1622).

The evidence base for traditional medicines is currently compromised by the persistent resistance of governmental and private research funding agencies to support the development of a comprehensive, modern evidence base for traditional plant medicines. Clearly, the call for evidence is not matched by resources to gather it (Coulter, 2004, p. 109; Lewith, Jonas, & Walach; Saller, 2006a, p. 113; Spencer & Jacobs, 2003). This underfunding of research contributes to a perpetual marginalisation of traditional plant medicines. At the same time the pharmaceutical-based healthcare model becomes more normative as governments use tax payer funds for biomedical schools, public hospitals, diagnostic testing and synthetic drugs, but not for traditional therapeutics. This is often justified on the grounds that there is a lack of modern scientific evidence for many such medicines. Yet an elevation of traditional empirical knowledge is in line with the WHO strategy on traditional medicines (World Health Organization, 2012). In this approach, RCTs become part of the mix of evidence but not as the gold standard for clinical practice, research, and policy (Jagtenberg et al., 2006, p. 323). Various researchers have proposed different models to replace EBM evidence-based pyramids, such as an evidence house (Jonas, 2005), a circular model of evidence (Walach, Falkenberg, Fønnebø, Lewith, & Jonas, 2006), or a matrix based approach, which emphasises the need to match research questions to specific types of research (Petticrew & Roberts, 2003). Given the long-established practice of using plants as medicines and the sheer volume of such therapeutics in traditional medical systems worldwide, it is urgent to investigate ways to substantiate their effectiveness. Such exploration is the topic of this thesis.

### **1.3 Seeking regulatory solutions for traditional medicines**

Given this context and the current dominant position that international regulators afford EBM, the New Zealand Government faces a difficult question: how can it best develop appropriate evidence-based policies for traditional plant medicines and its empirical knowledge base? As New Zealand has not yet implemented its own regulatory framework for traditional medicines, this study first seeks to understand the regulatory solutions that other governments have implemented, and to see whether such information could help shape New Zealand's policy.

New Zealand is not the first country to face this regulatory challenge for traditional

medicines. Such regulations have been implemented in other countries such as Australia, Canada, Switzerland, and the USA. However, the greatest effort in the West to harmonise policies around this issue and the most complex attempt involving multi-cultural societies have occurred in Europe as part of the integrative process of the European Union (EU). The main regulatory body for medicines in this economic and political union is the European Medicines Agency (EMA), but each of the 28 Member States also has their own separate regulatory agency. The Economic and Social Committee of the European parliament mandated that the EU Member States harmonise their guidelines on registration of traditional medicines (Europäisches Parlament, 2004). This mandate resulted in the European Union Directive 2001/83/EC, later updated to 2004/24/EC. After an initial transition period it took full effect in 2014. Its purpose is to have established quality criteria, to protect the consumer, and to facilitate free movement of herbal products within Europe (Kroes, 2014; Sammons et al., 2016). Traditional medicines must now be licenced for sale, which can be achieved via a Marketing Authorisation (MA) or a Traditional Herbal Registration (THR). As each of the 28 Member States of Europe has a different approach to the regulation and integration of traditional medicines into their domestic healthcare systems, harmonising policy across the EU has presented multiple challenges. As a multi-cultural society, New Zealand may therefore benefit from examining how the EU has dealt with the dilemma of integrating traditional medicines into a contemporary health system while subscribing to the principles of evidence-based health policy.

#### **1.4 Sources of evidence**

A key feature of this thesis will be the identification of sources of evidence that can substantiate the therapeutic use of traditional plant medicines. In traditional systems, knowledge is typically conveyed in two main ways: through oral and written transmission. This research will deal with written evidence only, as an investigation of evidence from oral transmission requires methodologies beyond the scope of this study. Traditional Māori healing, Rongoā Māori, is not suitable for an exploration of written documentary evidence about traditional medicines because its medical knowledge was and is transmitted orally (Boulton, Hudson, Ahuriri-Driscoll, & Stewart, 2014; Mark, 2012; Mark & Lyons, 2010). Consequently, this study turns to documentary evidence of another prevalent medical tradition practised in New Zealand, that of Traditional European Medicine (TEM). Pākehā New Zealanders, those of European descent, represent the ethnic majority in contemporary

New Zealand as per the 2013 Census. European plant medicines are commonly available over-the-counter in New Zealand pharmacies, health stores, supermarkets, and online. They are also key therapeutics prescribed by registered Medical Herbalists and Naturopaths (Leach, 2013). This tradition carries sufficient importance that there are NZQA approved colleges that teach traditional European plant medicine. Thus, documentary evidence on European plant medicines provides a suitable exemplar for this thesis.

Rycroft-Malone (2004, p. 298) proposes that evidence in evidence-based practice should be considered to be “knowledge derived from a variety of sources that has been subjected to testing and has found to be credible”. Systematic historical research could play a part in establishing and validating data on the effectiveness and safety of medicinal plants thus informing regulations (Helmstädter & Staiger, 2014). There are various historical sources that help to establish whether long-standing traditional medical knowledge has been consistently and accurately transmitted textually. If so, these texts can now be used to support the evidence base of traditional plant medicines.

## **1.5 Objective of the research**

The objective of this thesis is to establish whether judiciously selected historical and contemporary clinical sources on the European *materia medica* could provide a pathway to substantiate therapeutic claims for traditional plant indications and therefore contribute to a framework for New Zealand’s evidence-based policies on NHPs. Is this professionally documented medical knowledge about the effectiveness and safety of traditional European plant medicines a reliable and verifiable source of evidence that can be incorporated into a regulatory framework? Do such historical documentary sources adequately and accurately describe medicinal plants, their uses, therapeutic effects, and safety to support the regulatory acceptance of traditional medicines?

To examine conformities and differences in the use of traditional plant medicine in the context of formal European healthcare delivery and regulation, this research takes an interdisciplinary approach across medical history, phytotherapy and health science. The research design employs a longitudinal, comparative textual analysis from the early modern period onwards to the present day, using two medicinal plants as exemplars, *Arnica montana* (Arnica) and *Hypericum perforatum* (St. John’s Wort). The results of this bibliographic analysis are further cross-validated with evidence of efficacy for specific

indications derived from RCTs, and results from experimental laboratory research. Such triangulation of data derived from both qualitative and quantitative methods aims to strengthen conclusions drawn from the research.

This thesis will further examine how the EU dealt with evidence and safety requirements to substantiate traditional indications (Cranz, 2010; Gallagher, 2013; Peschel, 2014; Quintus & Schweim, 2012; Sammons et al., 2016). The aim is to determine whether such information could help shape New Zealand's policy on traditional plant medicines.

## 2 BACKGROUND

### 2.1 Historical and contemporary context of traditional plant medicine

The first tangible evidence of humans using plants as medicines is in fossil discoveries dating back to the Middle Palaeolithic age some 60,000 years ago. An analysis of the soil around a discovered burial site revealed extraordinary quantities of plant pollen of eight species, seven of which were medicinal plants still used in traditional medicine today (Solecki, 1975). In Europe, the earliest evidence of prehistoric peoples' use of plants as medicine stems back to a mummified body of a man who lived 5,300 years ago. 'Oetzi', the ice-age man, was discovered in a retreating alpine glacier in Tyrol at the Austrian-Italian border in 1991. He carried with him fine slices of *Fungus chirugorum* threaded on a leather band, presumably to treat abdominal problems caused by the infestation of whipworm (*Trichuris trichiura*) that was found in him (Heinrich, Barnes, Prieto-Garcia, Gibbons, & Williamson, 2017). This remedial fungal species was officially listed until the 6<sup>th</sup> edition of the German pharmacopeia (*DAB EB6* 1968) (Schneider, 2001, p. 242). Such ongoing use of plant medicines for communities around the world has been described by medical historian Crellin (2001) as "social validation". The unabated popularity of plant medicines points both to their usefulness and their effectiveness. It is unlikely that their application would have persisted if no relief had been gained (Schneider, 2001).

The consistently observed health effects of plant medicines were transmitted orally from generation to generation. In many literate societies, including those in Europe, Egypt, India, Tibet, and China, this medical knowledge was also codified in specialised written texts reflecting the authoritative scientific knowledge of a given time (Balick, 1994; Cox, 1994; Farnsworth, 1990, 1994; Müller-Jahncke & Friedrich, 1996; Touwaide, 1998, 2005; Tschirch, 1910, pp. 787-844). The European medical tradition provides a rich textual record of clinical applications of medicinal plants spanning more than two millennia (De Vos, 2010; Toby, Denham, & Whitelegg, 2011). Over this period, plant-based therapeutics dominated European healthcare delivery, with remedies derived from animals and minerals playing only a minor role. The therapeutic effects of herbal drugs in patient care were extensively recorded in medical textbooks, formularies, antidotaries, dispensatories, herbals, monographs, and official pharmacopoeias and their compendia. It was only in the 20<sup>th</sup> century with the increased dominance of synthetic drugs that plant-based medicines

were relegated in Western healthcare systems (Schmitz, 1998, pp. 405-406).

The large body of information that underpins traditional medicine is referenced as traditional knowledge (TK). The International Council for Science defines TK as “a cumulative body of knowledge, know-how, practices and representations maintained and developed by peoples with extended histories of interaction with the natural environment” (International Council for Science, 2002, p. 2). This knowledge provided the historical foundation for all pharmacological medicines. There is now a schism between traditional medicine which is based on TK, and biomedicine which is based on more recent natural science methodologies, mainly chemistry, biology, and physics. Yet this distinction is a relatively new phenomenon driven by paradigmatic changes in Western medicine since the 19<sup>th</sup> century. Today, there is a move to canvass TK once more for the development of contemporary medicines, including pharmaceutical drugs (Cordell, 2000; Cragg, Newman, & Snader, 1997; Farnsworth, 1994; Gurib-Fakim, 2006; Khazir, Mir, Pilcher, & Riley, 2014; Lahlou, 2013; Mulzer & Bohlmann, 2013; Oubre, Carlson, King, & Reaven, 1997; Phillipson, 2007). This is because traditional medical knowledge has frequently uncovered verifiable botanical drugs (Atanasov et al., 2015; Bladt & Wagner, 2007; Buss & Butler, 2010; Butler, 2004; Cox, 1994; Cragg et al., 1997; Duke, n.d.; Fabricant & Farnsworth, 2001; Mustafa et al., 2015; Oubre et al., 1997; Patwardhan, 2005). Seventy-five percent of 119 widely used modern drugs are either compounded from medicinal plants or synthesised based on plant structures and they have the same or similar use as in traditional medicine (Farnsworth, 1994, p. 43). Of 1355 small-molecule new chemical entities that were used as a source for disease treatment from 1981-2010, more than 71% were natural or ‘inspired’ by natural substances (Buss & Butler, 2010; Newman & Cragg, 2012). Of the anti-tumour drugs, almost half were based on natural substances. Overall, about 40% of all contemporary medicines are either natural products or their semi-synthetic derivatives (John, 2009). The 2015 award of the Nobel Prize in medicine to Tu Youyou for her research on *Artemisia annua* is a strong signal that plant medicine has once again become pertinent to the scientific community (Efferth et al., 2015).

Plants continue to provide the largest and most economical collection of therapeutically active compounds. Over 35,000 species worldwide are used for the manufacture of plant medicines (Saller, Melzer, & Rostock, 2011, p. 204). They belong predominantly to 67 drug-producing botanical families (Zhu et al., 2011). Research trends indicate that they will

be amongst the most important sources of new drugs in the future (Atanasov et al., 2015, p. 1606; Fabricant & Farnsworth, 2001; Gilani & Rahman, 2005; Katiyar, Gupta, Kanjilal, & Katiyar, 2012; Mulzer & Bohlmann, 2013; Phillipson, 2001, 2003; Pieters & Vlietinck, 2005). With global issues such as rapidly increasing antibiotic resistance to several common and serious bacterial infections now confirmed in over 500,000 patients (World Health Organization, 2018a), research teams increasingly look to nature for new leads. Apart from their therapeutic value, plant medicines are well-regarded as a cost-effective therapy since the development of a synthetic single compound into an approved drug takes an average time of 12-13 years at a cost of up to \$800 million USD (Festel, Schicker, & Boutellier, 2010). This cost is particularly striking when compared with the increasing number of low-cost traditional plant medicines with proven equivalence to synthetic drugs, for example St. John's Wort in mild to moderate depression (Schulz, 2002).

### **2.1.1 Traditional systems of medicine as resources for solving health problems**

Access to and development of effective, safe, affordable, and acceptable medicines is an ongoing challenge for healthcare worldwide (World Health Organization, 2012). The WHO emphasizes traditional medicine systems and their therapeutics as key resources for solving the world's unabated health problems. It defines traditional medicine as "the sum total of the knowledge, skill, and practice based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness" (World Health Organization, 2013, p. 15). Systems of traditional medicine differ from more recent complementary and alternative medicine modalities through a medical paradigm with practices, strategies, and beliefs that were in existence well before the development and spread of modern scientific medicine, often for centuries if not millennia (Akerlele, 1992). They represent congruent and complete medical paradigms that continue to be practised today such as TCM (traditional Chinese medicine), Ayurveda (traditional medicine of the Indian subcontinent), Unani-Tibb (traditional medicine of Arabic countries), and Traditional European Medicine (TEM).

TEM is a relatively recent terminology (Bruchhausen & Schott, 2008, p. 18). It is applied to differentiate the principles of pre-modern European medicine from those of modern medicine in Europe. TEM refers to a treatment approach, both therapy and prevention, that evolved over 2,500 years and is based on the philosophy of classical European medicine

rooted in antique Greek medicine (Uehleke, 2007, p. 203). Aristotelian philosophy was a key influence on this medical paradigm which gave rise to humoralism, vitalism, the treatment of the individual, and a focus on healthy lifestyle management. It is distinctly separate from biomedicine, also known as modern medicine, Western medicine, mainstream medicine, allopathic medicine, conventional medicine, or orthodox medicine which developed rapidly in Europe from the 19<sup>th</sup> century onwards. The philosophy and therapeutics underpinning TEM are sometimes referred to as *classical* naturopathy (Joos, Eicher, Musselmann, & Kadmon, 2008) or as the Western herbal tradition (Evans, 2009; Toby et al., 2011; Waddell, 2016). In contrast, the term naturopathy, without the adjective *classical*, is not a synonym for TEM. Naturopathy (*Naturheilkunde*) was developed in the second half of the 19<sup>th</sup> century as a counter-movement against the scientific revolution and its new chemical and technology-based medicine (Roth, 1991). The term includes more recent natural treatment approaches from the 19<sup>th</sup> century onwards (Jütte, 1996). This health movement laid the ground for what is termed today complementary and alternative medicine (CAM) (Gaboury, April, & Verhoef, 2012; Uehleke & Saller, 2011).

It is estimated that today as much as 80% of the world's population applies traditional medicine as a primary form of healthcare, either as part of an official healthcare system or in self-care (Saad & Said, 2011, p. 47). According to data published by Euromonitor, the global expenditure on herbal products in 2010 was around US\$30 billion of an overall total of US\$176 billion global consumer healthcare expenditure (Gallagher, 2013, p. 15). The EU market for medicinal herbal products is estimated at about 6 billion Euro (Cranz & Anquez-Traxler, 2014, p. 495). Consumers worldwide are projected to spend US\$140 billion on plant-based healthcare and wellness by 2024 (Paine & Roe, 2018, p. 410). Although this projection seems high compared with the US\$30 billion global expenditure in 2010 and includes the wellness industry, it confirms an upwards trend. However, in markets such as Western Europe, where plant medicine is already well established, year-on-year growth rates are minimal (Gallagher, 2013, p. 14).

The WHO data suggests that societies around the world take a pluralistic approach to medicine which includes their traditional medicines because pharmaceutical drugs cannot address all health needs, are not easily accessible to all, are too expensive and not always appropriate (World Health Organization, 2012). Moreover, the WHO recognises that "...herbal medicines (phytomedicines) have often maintained popularity for historical and

cultural reasons” (World Health Organization, 1999, p. 1). For example, consumers of Western and Northern European countries such as France, Germany, Switzerland, Austria, UK, and Sweden use herbal medicines to complement contemporary pharmaceutical treatments. In contrast, difficult economic conditions in Eastern European countries limit access to expensive pharmaceutical medicines prompting the respective populations to seek more economically priced traditional herbal products for their primary healthcare needs (World Health Organization, 2010). This situation is also reflected in developing countries, where traditional medicines are often the only accessible form of healthcare (Cordell, 2011; International Bioethics Committee (IBC), 2013).

From a public health perspective, Western pharmaceutical biomedicine has made its biggest contributions in emergency medicine, in the treatment of acute infectious diseases, and in surgical treatments. Higher survival rates in critical health events are significant achievements. Furthermore, advanced technology allows the screening of otherwise difficult to detect disease states, enabling intervention and treatment of such diseases. Yet according to the WHO, the biomedical approach is ill prepared for the public health challenges ahead. It has been unable to increase the overall health of the world’s population or reduce health expenditure since health problems worldwide have shifted from acute illnesses to often preventable chronic disease (World Health Organization, 2005). This has been most strikingly illustrated in the USA since the Flexner report (Flexner, 1910). That report prompted a transformation of the medical curriculum to a model exclusively built on basic science and pharmaceutical drug applications, and which eliminated non-pharmaceutical methods of prevention and treatment of disease (Oubré, 1995, p. 47). Subsequently, the listings of plant drugs in the US pharmacopoeia fell from 59% in 1890, to 28% in 1940 and to less than 2% by 1990 (Hughes, 2006). During these decades advances in hygiene, social measures, and targeted biomedical care lowered mortality rates of infectious diseases (Ackerknecht, 1992), but despite massive investment in biomedical health services, including the ‘war on cancer’, there was a steady rise in chronic ill-health by the end of the 20<sup>th</sup> century. According to regional US community health statistics, Americans experienced in the 1920s an average of 0.82 episodes of disabling illness a year compared to 2.21 by the 1980s (Barsky, 1988, p. 415). There may be many contributing reasons for the overall decline of health, such as an ageing population, changes in diet, prevalence of smoking, environmental toxicity, and a decrease in manual labour and exercise, but the privileging of biomedicine as the sole funded healthcare provider neither

kept chronic illnesses from increasing nor provided preventative solutions.

Based on their persistent use by the population, some governments, for example in Switzerland, Japan and China, officially fund both traditional and modern synthetic medicines as part of their healthcare systems, but most consumers in Western countries must fund traditional plant medicines privately. This situation is an outcome of historical, political, economic, and epistemic factors that led to the privileging of biomedicine in Europe, and its dominance across the globe as a consequence of the European colonial encounter (Ijaz & Boon, 2018; Wartmann, 1993). Disparities are seen in regulations at national levels where plant medicines may be defined variously as a medicine, medical device, plant food supplement, natural health product (NHP), traditional herbal medicinal product (THMP), dietary supplement, food, or cosmetic. In some jurisdictions they are not regulated at all or even prohibited (International Bioethics Committee (IBC), 2013).

### **2.1.2 The patient's perspective**

The current public healthcare system in Western or westernised countries is problematic for two reasons. Firstly, the cost of biomedicine is prohibitive even for affluent countries and secondly it does not meet consumer expectations. The significant level of patient dissatisfaction with biomedicine first came to prominence with the Eisenberg report (1993) which sampled adults over 18-years-old from across the USA. It showed that the number of self-funded visits to practitioners of unconventional therapies that were neither taught widely in U.S. medical schools nor generally available in U.S. hospitals exceeded the number of visits to *all* U.S. conventional primary healthcare physicians. During the 1990s, expenditures for non-conventional medicine further increased. This was primarily attributed to a larger proportion of the population seeking alternative therapies, rather than to increased visits per patient (Eisenberg, Davis, Ettner, & et al., 1998). By the 1990s almost half of the public in most industrialised countries regularly used complementary forms of medicine (Astin, 1998; Eisenberg et al., 1998; Gardiner & Wornham, 2000; MacLennan, Wilson, & Taylor, 1996). Numerous surveys indicate that such high prevalence of use persists and that the use of complementary healthcare is here to stay (de Souza Silva et al., 2014; Ducrest et al., 2017; Eardley et al., 2012; Euromonitor, 2011; Fennell, Liberato, & Zsembik, 2009; Gonzalez-Stuart, 2011; Green, Santoro, Allshouse, Neal-Perry, & Derby, 2017; Hall & Jolly, 2014; Harris, Cooper, Relton, & Thomas, 2012; Hung, Kang, Bollom, Wolf, & Lembo, 2015; Institut für Demoskopie Allensbach, 2010; Paine & Roe, 2018;

Thomson, Jones, Browne, & Leslie, 2014).

Disenchantment with biomedicine is reflected in numerous surveys into patient behaviour in several Western countries. While consumer behaviour is dynamic and influenced by local conditions, there are some common trends. Since the 1990s the pressure to shift from a sick care model to a more humanised well care model has been mounting (Micozzi, 1995).

Dissatisfaction with the current Western drug model is apparent, particularly when treatments of chronic and terminal conditions are perceived inadequate, i.e. “doctor’s medicine not working” (Crellin, 2001, pp. 48-49), when pharmaceutical drugs have side effects or treatments are experienced as invasive, when doctors are insensitive to patients’ physical, emotional, and spiritual needs, when patients desire more personal control, when household health-care costs for a biomedical approach become prohibitive, when sufficient consultation time with a conventional physician is limited, or when patients prefer a more holistic health promotion (Mitchell, 2014; Thomson et al., 2014). Other surveys have identified that the rise in demand for CAM healthcare approaches, including plant medicines, is part of a wider social, mainly female-driven consumer movement that links with postmodernist values about nature, science, technology, health, authority, individual responsibility, and consumerism (Astin, 1998; Willis & Coulter, 2007, pp. 216-220). The holistic health movement from the late 1970s also resurrected many aspects of traditional medicine (Oubré, 1995, pp. 47, 51). Proponents of this movement reject the reductionist scientific view of humans and demand a shift back to Western medicine’s own tradition of personalised healthcare and Hippocratic principles such as “do no harm” (Wolpe, 1990, p. 917). Undoubtedly, the Western ecology movement (Drengson & Inoue, 1995) has also had a major influence on patient preference for natural medicines (Houghton, 1995, p. 136). Their starting point for decision-making is not Western science with its focus on clinical studies and scientific evidence on active constituents, mechanisms of action, and efficacy (Abdel-Tawab, 2018, p. 388; Bardia, Nisly, Zimmerman, Gryzlak, & Wallace, 2007). Instead, the popularity of traditional therapeutics suggests that many patients perceive value in these therapies even if they lack academic and scientific explanation (Bardia et al., 2007; Willis & Coulter, 2007). Their preferences are based on traditional healthcare that is familiar, has shown to be effective and non-harmful, and is local and affordable (Bodeker, 2000, p. 3; Little, 2009, p. 300; Welz, Emberger-Klein, & Menrad, 2018, p. 6). Representative surveys of the German population suggest that patients appreciate the effectiveness of plant medicines in resolving their health issues and their lack of side-effects

compared to conventional synthetic OTC products (Nieber, 2014, p. 207). Accordingly, many synthetic drugs are gradually becoming less attractive to consumers due to side-effects, serious adverse effects, the risk of dependency, and the widespread resistance of microorganisms to modern antibiotics (Sen & Samanta, 2015, p. 66). That said, in countries with both well-established traditions of plant medicine and ready access to Western biomedicine, consumers are generally aware of the limitations of plant medicines in contexts where pharmaceutical drugs are deemed more appropriate (Institut für Demoskopie Allensbach, 2010).

Patient attitudes are congruent with an analysis published by the British Medical Journal of evidence for 3000 medical treatments. It found that only 11% were definitively beneficial, 23% were probably beneficial, and 51% were of unknown effectiveness (BMJ, 2012). The pharmaceutical industry itself estimates that 90% of Western drugs are ineffective for about 60% of the patients using them (Petit-Zeman, 2003; "What happened to personalized medicine?," 2012). In addition, a review of the top 10 drugs in the USA further point to their limited usefulness for many patients, confirming that they work at best for one in four people and at worst for one in twenty-five—even though regulatory approvals for these drugs had been gained based on EBM evidence (RCTs) and mechanistic essays (Vergeres, 2017, p. 42). In New Zealand the preparation for a new Medicines Strategy also highlighted issues with synthetic drugs. It discovered that 50% of New Zealand patients do not take their pharmaceutical medicines or do not take them as prescribed, and 9% of patients are given the wrong medicine or the wrong dose with harmful effects (Ministry of Health, 2006). At the same time, NHPs for self-medication have steadily grown in this country over the past 20 years despite a lack of regulation (Barnes et al., 2016).

## **2.2 Situation assessment in New Zealand**

Traditional systems of medicine are used by indigenous and migrant populations in New Zealand to address their primary healthcare needs, as broadly consistent with the majority of people around the world (Barnes et al., 2016; Fabricant & Farnsworth, 2001). Nationally representative population-based data on the prevalence of use of plant medicines are not available. However, there are some localised studies that explore the prevalence of use of NHPs in specific patient populations. These studies estimate that about 50% of adults and 70% of children use therapies and preparations from sources outside conventional healthcare, with plant medicines being the most prevalent non-conventional form of self-

medication (Barnes et al., 2016, p. 909; Chrystal, Allan, Forgeson, & Isaacs, 2003; Wilson, Dowson, & Mangin, 2007). In recent decades there has been increased interest and use of NHPs in New Zealand, which is reflected in their industry value to the New Zealand economy of \$1.4 billion NZD (Barnes et al., 2016, pp. 905-909; Natural Products New Zealand, 2017). Note that this sum contains non-herbal dietary supplements as well as infrastructure value. The frequent use of parallel health paradigms by the New Zealand population has implications for health policy. Patients' choice of healthcare is protected in New Zealand under the Code of Health and Disability Services Consumers' Rights Regulations 1996, which falls under the Health and Disability Commissioner Act 1994. Similarly, in Australia, a Position Statement of the Council of Australian Therapeutic Advisory Groups (CATAG) confirmed that in most instances Australian hospitals cannot legally prevent the use of complementary medicines by their in-patients (CATAG, 2015).

### **2.2.1 WHO directives and policy support for the integration of traditional medicines into New Zealand's healthcare system**

Despite being a signatory to the WHO—an organisation which requests that governments harness the contribution of traditional medicines to healthcare by promoting, regulating, researching, and integrating them into their healthcare systems (Burton et al., 2015, p. 13)—successive New Zealand governments have not implemented key objectives of the WHO's traditional medicines strategies. Forty years ago, the *Declaration of Alma-Ata* called for the inclusion of traditional medicine into primary healthcare (Wartmann, 1993; World Health Organization, 1978). Building on subsequent strategies (World Health Organization, 2002), the current global *Traditional Medicine Strategy 2014-2023* (World Health Organization, 2013) and the corresponding *Regional Strategy for the Western Pacific (2011-2020)* emphasise people's rights to quality health services that are available, accessible, affordable, and culturally acceptable (World Health Organization, 2012, p. v). The *Beijing Declaration*, which informs the current *WHO Traditional Medicine Strategy 2014-2023*, recognises that “[g]overnments have a responsibility for the health of their people and should formulate national policies, regulations and standards, as part of comprehensive national health systems to ensure appropriate, safe and effective use of traditional medicine” (World Health Organization, 2008, p. 1). The 2018 Declaration of Astana, unanimously endorsed by all Member States, re-emphasises the critical role of primary health care around the world which is to be implemented with a wide range of healthcare services,

including traditional medicines:

We support broadening and extending access to a range of health care services through the use of high quality, safe, effective and affordable medicines, including, as appropriate, *traditional medicines*, vaccines, diagnostics and other technologies (emphasis added). (World Health Organization & United Nations Children's Fund (UNICEF), 2018, p. 9)

Traditional medicines are also considered by other international regulations. The enduring use of medicinal plants is understood as intellectual heritage within a culture, which international organisations such as World Intellectual Property Organisation (WIPO), World Trade Organisation (WTO), and United Nations Educational, Scientific and Cultural Organization (UNESCO) formally acknowledge and aim to protect (Commission on Intellectual Property Rights, 2002, p. 73; Lenzerini, 2011). The International Bioethics Committee (IBC) of UNESCO links the promotion of traditional medicine with its mandate to promote cultural diversity. Under the Universal Declaration on Bioethics and Human rights (International Bioethics Committee (IBC), 2013, pp. 1, 17) freedom of choice in medicine is seen as consistent with obligations to respect cultural diversity and pluralism (Article 12) and respect for traditional knowledge (Article 17). There are various parameters within which traditional medicine and its knowledge base are understood and encouraged to be respectfully handled: The Universal Declaration on Cultural Diversity (2001), The Convention for the Safeguarding of the Intangible Cultural Heritage (2003), the Convention on Biological Diversity (2003), and the United Nations Declaration on the Rights of Indigenous Peoples (2007) (International Bioethics Committee of UNESCO, 2012).

With its long-standing strategy for supporting systems of traditional medicine, the WHO provides practical policy support to Member States for integrating traditional medicine into their healthcare systems (World Health Organization, 2012, 2013). It also provides normative and standard-setting guidelines for the collection of medicinal plants through to their release as safe and efficacious medicines. Such guidelines relate to the assessment of herbal medicines (Akerele, 1992), to GMP quality control systems in their manufacturing (World Health Organization, 1994), to methodologies on research and evaluation of traditional medicine (World Health Organization, 2000), to good agriculture and collection practices (World Health Organization, 2003), to quality control methods for medicinal plant materials (World Health Organization, 1998), and to the conservation of medicinal plants

(World Health Organization, International Union for Conservation of Nature, & World Wildlife Fund, 1993). The need for stringent quality control methods from collection of medicinal plants to their commercial release as a therapeutic product is also understood by many regulators (Knöss, 2018). The *WHO Monographs* on selected medicinal plants (World Health Organization, 1999, 2004, 2009, 2010) summarise the scientific and traditional empirical knowledge identified at the time of their publication. Moreover, in line with its strategy to provide regulatory support for the integration of traditional medicines into contemporary healthcare, the WHO recently added a traditional medicine chapter to the International Classification of Disease (ICD) system *ICD-11 for Mortality and Morbidity Statistics (2018)* for non-biomedical, traditional disease classifications (chapter 26) (World Health Organization). This addition is an important recognition of traditional systems of medicine (Morris, Gomes, & Allen, 2012). In a first step, *ICD-11* accommodates TCM classification of disease; sub-chapters to accommodate disease classifications from other medical traditions are pending. The WHO further offers a global platform for communications amongst regulatory agencies via the International Regulatory Conference on Herbals (IRCH).

In addition to being a member of the WHO, New Zealand is also a member of the Commonwealth, which established in 1998 a Working Group on Traditional and Complementary Health Systems to address policy issues to reflect public healthcare demands and patterns of use (Commonwealth Secretariat, 2001, p. 472). The management of the integration of traditional and conventional medicine is named as a key point of the action plan (Bodeker, 2000, p. 3).

### **2.2.2 Legislative and political impediments for the integration of traditional medicines**

Regardless of extensive policy resources provided by the WHO, New Zealand trails other signatories in introducing legislation on traditional medicines for several reasons. For the past 100 years, New Zealand's regulatory system has been set up to regulate synthetically-derived Western medicines. The colonisation of New Zealand had a significant impact on the pre-European traditional medical system with legislative consequences (Berghan et al., 2017). The Tohunga Suppression Act 1907 was initially aimed at the elimination of improperly trained tohunga, Māori healers, but mainly drove all tohunga and their traditional therapeutics underground as the Act did not distinguish between traditional

practice and deliberate deception (Te Ara. The encyclopedia of New Zealand, 2018). This Act in effect breached the second article of the Treaty of Waitangi 1840, the fundamental legal document that addresses for New Zealand the relationship between the Crown and the indigenous Māori population. The Tohunga Suppression Act 1907 was eventually repealed in 1962 (Te Ara. The encyclopedia of New Zealand, 2018). However, there was another Act that further impeded the use of traditional medicines. A year after the Tohunga Suppression Act 1907 was passed, the Quackery Prevention Act 1908 was passed to stop the sale of sham medicines (Duke, 2005, p. 11). It became a means to provide state sponsored legitimacy of Western biomedicines while marginalising those without ‘scientific proof’ to the medical fringe.

With these two Acts, traditional medicines—whether the healing practises of Rongoā Māori or those of immigrant populations—were marginalised or outlawed. These actions resulted in significant loss of traditional medical knowledge in New Zealand during the 20<sup>th</sup> century. Despite these impediments for the public and for non-physician practitioners, specific plant-based drugs were used in regular medicine at least until WW2 when sulphonamides and penicillin became prevalent (personal communication Dr. Marian Stewart (1909-2003), Graduate of Medical School, Otago University, February 24, 2000). This continuation explains why the First Schedule to the Medicines Regulations 1984, based on the Medicines Act 1981, contains several plant drugs that are listed as prescription medicines, restricted pharmacist-only medicines, or pharmacy-only medicines, as well as their synthetic analogues. Unlike in the UK, access to those medicinal plants is illegal in New Zealand for those who have not graduated as physicians or pharmacists even though New Zealand physicians and pharmacists are usually not trained in the appropriate clinical use of these medicines in patient care.

The outlawing of traditional remedies during the 20<sup>th</sup> century as *therapeutic substances* in the context of traditional systems of medicine created obstacles for the co-existence of systems of traditional medicine alongside Western biomedical practices. In 2001, a Ministerial Advisory Committee on Complementary and Alternative Health was established under section 11 of the New Zealand Public Health and Disability Act 2000 to advise the Minister for Health on how to integrate traditional medicine and CAM into mainstream healthcare practice (Ministerial Advisory Committee on Complementary and Alternative Health, 2004). This mandate led to the formulation of the Māori Health Action Plan in 2002, to guidelines and cultural health requirements for tackling persistent concerns over

Māori health statistics and inequalities (Fraser & Tilyard, May 2008; Mark, 2012), to the passing of the Health Practitioners Competence Assurance Act 2003 for enabling the legitimisation of CAM practices by statute (Duke, 2005, pp. 12-13), and to various attempts at regulating NHPs. However, there is still no tangible progress on these interrelated issues. There are at least three key reasons for this problem: the lack of political urgency in progressing a regulatory framework for NHPs and professions using them; the failed pursuit of a joint regulatory authority for medicines and other therapeutic products with Australia under the joint Australia New Zealand Therapeutic Products Act (Medsafe, 2012), and the withdrawal by the incoming Labour-led Government in October 2017 of the subsequently developed domestic Natural Health and Supplementary Products Bill. The proposed trans-Tasman regulatory system met strong concerns from consumers and politicians for being overly restrictive and harmful to New Zealand consumers and the NHPs industry (Ellena, 2005, p. 106). The much lighter and more appropriate New Zealand-only regime which reflected the low risks of NHPs enjoyed political cross-party and industry support with minor but vocal opposition (Natural Products New Zealand, 2017). The domestic bill was intended to protect consumer choice and to provide a low-cost access to NHPs that are safe, effective, and suitable for use in self-treatment (Ministry of Health, 2017). At the time of writing, the Health Minister is yet to announce how the Government will proceed with regulation of NHPs.

This unresolved situation is particularly severe for the traditional healing system of New Zealand. The Waitangi Tribunal report on the Wai 262 claim notes that a lack of urgency of the Crown to redress the current lack of support and funding for Rongoā Māori in general and rākau rongoā (plant medicines) specifically may be driven by several reasons: political sensitivities towards claims raised in Parliament of a perceived lack of evidence of efficacy for such traditional therapeutics, continued lack of belief in the efficacy of Rongoā Māori by the Crown itself, and the lingering scepticism sown by the Tohunga Suppression Act 1907 (Legislation Direct, 2011, p. 225-226). A recent report released by the Health Quality & Safety Commission has identified continued institutional racism against Māori, medical advice regularly being delivered in a culturally insensitive way, and a health system that delivers significant health inequity ("Racism in health 'killing and harming Maori'," 2019, July 29). This provides currency to the argument that regulations supportive of traditional healing practices are urgent not least because they are well positioned to address gaps of care.

From an international perspective, the current New Zealand legislative framework is out of step with the international regulatory landscape and does not align with WHO directives to integrate traditional and complementary medicine as a vital part of state-funded healthcare. From a domestic perspective, current regulations do not adequately support consumer choice. According to Peter Davis (1992, p. 15), emeritus professor in Population Health and Social Science at the University of Auckland, the current situation represents a problematic institutional and regulatory framework that supports corporate pharmaceutical power, raising basic policy issues of control and regulation. Under this framework, the scope of traditional, non-pharmaceutical medicines cannot be accurately stated under the Medicines Act 1981. Although the Dietary Supplement Regulations 1985 and the Food Act 1981 provide some framework for quality requirements, they too disallow therapeutic claims on NHPs, even when a long-standing empirical knowledge base or scientific evidence is available. Such restrictions promote either underutilisation of these low or non-toxic health products or the inappropriate use of them due to a lack of valid consumer information. As NHPs are widely used in the community, recent initiatives to enhance their integration and quality such as the formerly proposed domestic Natural Health and Supplementary Products Bill are key for the future of New Zealand healthcare needs; they were created to help New Zealand achieve consistency in the principles of best practice regulation.

Once introduced, new regulations for over-the-counter NHPs would be part of the overall regulatory framework of the New Zealand healthcare system. They should enable informed choice by consumers, meet standards for quality, provide evidence to support health claims, and address the legal requirements for therapeutic preparations that are safe, effective, and true to label. The introduction of such regulations should support the integration of traditional medicines into a more sustainable healthcare model and help align New Zealand with the policy goals of the WHO's *Traditional Medicine Strategy 2014-2023*. They should also provide a regulatory framework that enables their inclusion in healthcare funding.

NHPs are ideally placed to help prevent and treat chronic illnesses. New Zealand, like other countries around the world, grapples with complex public health problems associated with an ageing population and an exponential increase of degenerative diseases such as obesity, diabetes, and cancer. Chronic disease is increasing in Western countries not only because of an ageing population. Apart from genetic and individual risk factors, lifestyle choices and

social, economic, and environmental factors also contribute to this upsurge in chronic disease (O'Donnell et al., 2017). The associated pharmaceutical drug costs and medical interventions are spiralling. They account for a large portion of a nation's health budget, hampering the ability to provide adequate healthcare across the entire population (Keene et al., 2016). Although biomedicine has alleviated suffering of millions of people, a Western healthcare system that uses high technology medicine with drugs and surgery as the first line of defence is not financially sustainable and can have long-term negative health consequences due to focusing on symptom management rather than healing. This approach is also out of step with patient preferences for pluralistic medicine. New Zealand's need to focus on regulatory support of NHPs is urgent, given the strain on the public healthcare system and the WHO position on the prevention of illness, the promotion of self-care, and healthy lifestyle coaching as ways to combat the global epidemic of non-communicable chronic diseases.

### **2.2.3 The urgent need to progress regulations on traditional plant medicines**

Despite the obvious gaps in New Zealand regulation to support the co-existence and integration of NHPs, there are bigger hidden pitfalls to avoid. Milio (1987, p. 264) reasoned that for health policies to fulfil their potential of promoting good health in communities, it is necessary to have high-level political leaders who understand that human health is in an ecological relationship with our natural and human-made habitats. In such an ecological perspective, people's health cannot be simply approached by a disease model that tidily segments health needs into medical diagnosis, symptoms, and risk factors to be targeted and eliminated. Instead, Milio (1986) argues, health policies should set a framework within which individuals and communities are enabled to take control of their own health and wellbeing. Thus, health policies should take the interests of the public into account, recognising that they may be different from the interests of the mainstream medical sector or paradigmatic stances of policy makers (Milio, 1987, p. 264). Consequently, a government has a broad responsibility to provide a policy framework that not only targets the treatment of diseases, but also enables their prevention. Successfully applied, this strategy would translate into healthier childhoods, a more vigorous life in the middle decades, and a less debilitating old age, all of which have personal and economic value (Milio, 1986, pp. 217-218). This policy framework is also an attractive proposition from a health economics viewpoint. Preventative and patient empowering approaches to healthcare

enable patients to be proactive about staying healthy—whereas reactive approaches focus on remedial care of manifested diseases which may require expensive drugs and hospital stays once patients are already ill. Milio’s reasoning is in line with the WHO statement which argues that well-applied policies targeted at the prevention and control of chronic diseases are urgent (World Health Organization, 2005). The trend in chronic, debilitating, and mostly preventable diseases is reflected in global figures which reveal that chronic diseases represent double the number of deaths from all infectious diseases including: HIV/AIDS, tuberculosis, and malaria; maternal and perinatal conditions; and nutritional deficiencies combined (World Health Organization, 2005, p. 2). While the most recent New Zealand data for chronic diseases are not currently available, a recent Australian study reflects the global data, concluding that chronic diseases are amongst the most common, costly, and preventable of all health problems (O'Donnell et al., 2017, p. 205).

Milio (1987, p. 266) also maintains that health policies sit in the cultural context of broadly shared and implicit expectations as derived from historical, socio-political, and organisational experience. Consequently, health policies must take into account the values and cultural framework within communities (Barnes et al., 2016, p. 906). This conclusion is particularly relevant for the drafting of a regulatory framework that is set up to support the use of traditional medicine. Health policies should make it easy for people to choose NHPs if they desire to do so. This is pressing given the high prevalence of their use in New Zealand to prevent chronic disease and the need to treat health complaints before they become more imperilling. Such policy support would support citizens to take greater care for their own health, promoting the concept of self-care.

If a political decision is made in New Zealand to emphasise a preventative healthcare approach and provide a supportive framework for access to lower-cost and safer interventions, then traditional and complementary medicine can provide an important contribution to the current health crisis. Such medicines are shown to lead to positive healthcare cost savings and productivity gains. For example, an Australian study calculated productivity gains of ASD \$7.38 per \$1 spent on a treatment regime with St. John’s Wort for depression (Shanahan & de Lorimier, 2014, p. 78). Moreover, two economic evaluations comparing St. John’s Wort preparations with generic antidepressants for the treatment of mild to moderate depression confirmed the plant-based treatment to be more cost-effective, with reduced incidences of adverse effects and increased compliance and positive outcomes (Schulz, 2002; Solomon, Adams, & Graves, 2013). The higher QALY score (Quality-

Adjusted Life Year) compared with synthetic antidepressants is particularly important from a patient perspective (Jeanning & Meier, 2014a, p. 191). A German study comparing a Passionflower preparation with benzodiazepine medication showed a reduction of health insurance costs of several millions of Euro per year, alongside an increase of quality of life for patients using the herbal drug (Michels, Gibbert, Kreimendahl, & Trompetter, 2016). Such trends are also observed in a dataset from a Dutch health insurer that points to lower costs from fewer hospital stays, fewer prescription drugs, and higher life expectancy in patients whose GP engage with non-biomedical treatment modalities (Kooreman & Baars, 2012). A Swiss Health Technology Assessment report evaluating the suitability of phytotherapy for general health insurance funding concluded that the existing data indicate positive cost-effectiveness for individual plant medicines (Wolf, Maxion-Bergemann, Bornhöft, & Matthiessen, 2005). Publicly subsidised patient access to phytotherapy is now permanently guaranteed by the Swiss constitution (Eidgenössisches Departement des Innern 2005; Jeanning & Meier, 2014b; Saller, 2009, p. 268; Schweizerischer Bundesrat, 2017). These results align with other cost-benefit analysis research on natural medicine interventions (Tais & Oberg, 2013). Accordingly, when Germany reduced the Social Health Insurance funding for herbal medicinal products, it did not reduce its overall drug expenditure, but increased it more sharply than ever before (Schulz, 2002, p. 193).

In the face of unsustainable growth in medical spending, important objectives for health policy makers should be primary prevention that directly decreases the risk of initially developing a disease, and secondary prevention that helps to reduce the severity of a disease (Woolf, 2009; Woolf et al., 2009). Apart from increasing the quality of life for a population, targeted strategies in public health lead to positive healthcare cost savings and productivity gains (Shanahan & de Lorimier, 2014). The mainstream health system and the public would therefore benefit if policy-makers explored health strategies that promote good health, prevent and treat disease, and ease discomfort by integrating traditional medicines into official healthcare. Modern pharmaceutical medicine and traditional plant medicine each have their strengths, uniquely contributing to healthcare. It is well recognised that physical and mental illness are driven by multiple factors; it would be impossible for any one modality to deal with every single aspect of disease phenomenon (Lyng, 1990, p. 82). At present, the New Zealand healthcare system divides the two types of medical practices into traditional versus pharmaceutical for patients, perhaps raising its own expenses, but certainly preventing patients from choosing between two equitably-presented options.

Given that such economic and individual benefits have been documented, the New Zealand government and its citizens would have an interest in progressing regulations on traditional medicine and integrating traditional medicine into the healthcare system. Policy-making activities are sensitive to the times, timing, and timeliness (Honari & Boleyn, 1999). Milio (1985, pp. 273-274) emphasises that timeliness is a key principle for policy success because improvements in health through primary healthcare interventions take time to become apparent. These principles have not been observed in New Zealand: regulations for NHPs remain unresolved for several decades. There are no data available that quantify the loss of quality of life or life expectancy when New Zealanders are prevented from fully practising their traditional medical customs, a gap of knowledge that also exists elsewhere (Helmstädter & Staiger, 2012, p. 96). The lack of progress on regulations for NHPs is compounded by the fact that in countries where regulations on NHPs and natural healthcare practitioners are lacking, physicians have been seen to be hesitant to recommend NHPs or to refer to natural health specialist highlighting the urgency for such regulations (Botting & Cook, 2000).

#### **2.2.4 Threshold of proof of scientific type efficacy as impediment for integration**

Why is the regulation of NHPs not gaining faster traction in New Zealand despite strong patient preference, potential therapeutic and economic benefits, and policy support from the WHO for the integration of traditional medicine into mainstream healthcare? A letter from the Minister of Health (6<sup>th</sup> of October 2014) may provide some insights into how the New Zealand government intended to implement the WHO *Traditional Medicine Strategy 2014-2023*: “The Government supports people having choice about their personal health care, including choosing traditional and complementary therapies when these are safe. However, such therapies can only be considered for public funding *when there is sufficient evidence of efficacy*” (letter reference 14001516; emphasis added). According to this statement, New Zealand’s healthcare system embraces an evidence-based approach to its healthcare policies by requesting efficacy proof (RCTs) even for well-established therapies such as traditional plant medicines. While evidence-based policies aim to improve the efficiency and beneficial outcomes of healthcare (O'Donnell et al., 2017, p. 204), McQueen (2002, p. 83) argues that accurately defining “evidence-based” is difficult given the broad range of public health actions and the social and cultural contexts in which health interventions take place. The methodologies provided by EBM, specifically RCTs and related systematic reviews

and meta-analysis, are therefore problematic when dealing with what constitutes evidence in public health and how evidence should be evaluated given the complexities of clinical practice (Jackson & Waters, 2004; Rychetnik et al., 2002; Speller, Learmonth, & Harrison, 1997). Other authors note that evidence-based policies may be employed to justify the argument for biomedical funding criteria in Western healthcare systems at the cost of other treatment options (Learmonth & Mackie, 2000; Traynor, 2002). In this context the relationship between contemporary Western biomedicine and traditional medicine, frequently mislabelled as alternative medicine, is often expressed in terms of dichotomies such as science versus anti-science or rationality versus irrationality. In this view, EBM is promoted as objective, quantifiable and the foundation of “real” knowledge creation while traditional knowledge is judged to be anecdotal, imprecise and irrelevant.

As Cornelius Borck (2016, pp. 140-150), Director of the Institute for History of Medicine and Science at the University of Lübeck, Germany, identifies, the definition of ‘evidence’ is not value-free, being made legitimate by its cultural, socio-economical, and political context. The disciplines of social and political science, and medical anthropology provide many studies that illustrate the cultural underpinnings of medicine; as such therapeutic interventions are not neutral or devoid of moral and social colouring (Davis, 1992, p. 293; Hahn & Gaines, 2012; Whyte, van der Geest, & Hardon, 2002). Indeed, biomedicine and traditional medicine were both informed by evidence long before the arrival of EBM less than 30 years ago. It is therefore not a lack of evidence that is the topic of discussion here, but rather the privileging and legitimisation of one form of evidence over another. Disputes between medical empiricism and various scientific or paradigmatic theories are not new. As medical history from antiquity illustrates, Western medicine has embraced various different medical concepts that employ inductive or deductive approaches to the establishment of scientific knowledge (Diepgen, 1941, 1949, 1951, 1955; Rothschild, 1953, 1978; Schipperges, 1999; Schmitz, 1998; Schmitz, Friedrich, & Müller-Jahncke, 2005; Stolberg, 2011). Different explanatory models for illness are underpinned by different forms of evidence that justify the recommended treatment (Bauer, 1997; Pieringer, 2000; Wood, 2006). Such debates link to the evaluation of competing therapeutic strategies and more recently to their eligibility for funding (Borck, 2016, pp. 150-151). Various therapeutic approaches with their related forms of evidence co-exist in the pluralistic landscape of contemporary Western healthcare—even though biomedicine receives almost exclusive public funding (Clark-Grill, 2004; Schmitz, 1998; Schmitz et al., 2005).

Contemporary Western medicine is informed by three key forms of evidence (Borck, 2016, p. 142): firstly, evidence based on empiricism as a source of knowledge acquired by means of repeated and reflected empirical observation and evaluation of therapeutic use; secondly, evidence based on pathophysiological explanatory models relating to experimental science with laboratory-based evidence; and thirdly, evidence based on clinical studies such as RCTs conducted mainly under ideal conditions with selected patients. The first methodology of empiricism provides the backbone of all medical systems, including biomedicine (Sackett, 1997). It is a fundamental tool of scientific and medical research (Kosso, 1992) that provides evidence for decision making in healthcare (Fugh-Berman, 1997). The term comes from the Greek word for experience, ἐμπειρία (empeiría). It is based on reproducible, real-world practice-based evidence which goes beyond anecdotal observations (Crellin & Philpott, 1990). In this thesis, this empiricist-based evidence is termed empirical evidence. In the context of traditional medicine, this term has also been equated with traditional knowledge (Evans, 2006; World Health Organization, 2013) or traditional evidence (Ministry of Health, 2015, p. 9). Traditional evidence is based on a natural experiment where practitioners have been prescribing and patients have been using therapeutics over a long period of time. There has been some confusion in the literature where authors have conflated the term empiricism with clinical trials (i.e. RCTs) (Wood, 2006, p. 9). Yet, empiricism and experimentalism are two entirely different scientific methods that should not be conflated. Empiricism refers to observation and experience yielding open system data, whereas experimentation refers to designed experiments yielding statistically significant data within a closed system. Empirical evidence is the foundation of traditional plant knowledge, a foundation which is reflected in the German term *Erfahrungsmedizin*, *Erfahrung* being the German term for empiricism, as commonly used to describe traditional medicine.

The second methodology is grounded in natural science and inspired a new medical paradigm from the 19<sup>th</sup> century onward, leading to a pathophysiological treatment model that became preferentially state-sponsored in Western countries in the 20<sup>th</sup> century. Pathophysiology and experimental laboratory-based research continue to feature strongly in biomedicine and are also applied in the research of plant medicines. This methodology is, however, increasingly challenged by EBM. Knowing the biological basis and mechanism of action of a therapy does not necessarily help the patient or the treatment provider in determining if such therapy is appropriate in their individual situation. Moreover, *in vitro*

studies on the molecular mechanisms of action of medicinal plants may point to explanatory models but they cannot be automatically correlated to their therapeutic effects. Plant compounds may or may not be physiologically effective *in vivo* due to metabolic processes and issues with bioavailability and absorption (Gertsch, 2009, p. 181; Bast et al., 2002, p. 204).

The third methodology uses controlled clinical studies to generate evidence. RCTs were developed initially to establish evidence of efficacy and to a lesser degree safety for biomedical healthcare interventions. They are advocated by proponents of EBM as conclusive proof for inclusion or exclusion of an intervention in state-funded healthcare (Sackett, Rosenberg, Gray, Haynes, & Richardson, 1996; Sackett, Straus, Richardson, Rosenberg, & Haynes, 2000). EBM emphasises treatment outcomes and is less concerned about the underlying explanation for *why* treatments might work (Willis & Coulter, 2007, p. 217). The EBM movement hierarchically privileges RCTs above other forms of knowledge generation (Howick, 2011; O'Donnell et al., 2017). Although it is debatable if EBM constitutes a new paradigm according to Kuhn (1970), it was announced as such by its proponents (Evidence-Based Medicine Working Group, 1992, p. 2420 ). Evidence-based medicine de-emphasises intuitive, un-systematic real-life clinical experience, and pathophysiological rationale as sufficient grounds for clinical decision making. It stresses the examination of evidence from clinical research for all clinical decisions, treatment guidelines, and regulations. Although RCTs can help establish internal validity of a selected treatment group under observation, difficulties arise when an attempt is made to privilege such evidence for clinical and policy decisions. This is because patients selected for clinical trials may not wholly reflect the features of populations who will undergo the treatment in real life, thus affecting the external validity of a trial (Loke, Price, & Herxheimer, 2007). Moreover, RCTs have been shown to be an inadequate tool for measuring safety, in particular in relation to infrequent and uncommon adverse effects as they are commonly limited in study size and observational period (Chou et al., 2010, p. 503; Vandembroucke, 2004, p. 2).

These three key forms of evidence are not mutually exclusive. They drive different research questions. However, evidence-based policies in healthcare are increasingly taking the lead from the principles of EBM despite limitations in the usefulness of RCTs in real world patient care and despite calls by the founders of the EBM movement to use RCTs as *one* but

not *the* ultimate tool for establishing evidence (Sackett et al., 2000). Within a very short period, EBM has become the major political and philosophical approach in the development of clinical guidelines and in healthcare regulations (Churchill & McGuire, 1998; Holmes et al., 2006; O'Donnell et al., 2017). Although EBM privileges knowledge derived from RCTs over other forms of knowledge, it has not been shown as actually superior to other forms of knowledge generation (Borck, 2016, p. 148). It is currently unknown if this relatively new approach to healthcare has led to better health outcomes in patients. Only scarce evidence to substantiate this assumption could be found (Djulbegovic, Morris, & Lyman, 2000; Emparanza, Cabello, & Burls, 2015, p. 101; Fakhry, Trask, Waller, & Watts, 2004). There is, however, evidence that it takes a long time to adopt outcomes from clinical trials into standard care even when treatments have shown to be unnecessary, harmful, or unhelpful (Epstein, 2017).

There is a move towards Comparative Effectiveness Research (CER) and pragmatic trials to provide research outcomes that better reflect proof of effectiveness and safety under normal practice conditions (Coulter, 2011). Such research is now mandatory in some countries, for example in the USA, and it replicates more closely the type of evidence that underpins traditional medicine (Coulter & Khorsan, 2011, p. 173). Even though this is a positive move for traditional medicine systems, there are equally important and immediately available sources of evidence to support the use of traditional plant medicines. These sources of evidence will be examined in this thesis.

## 3 LITERATURE REVIEW

### 3.1 Context to the literature search

The importance of bibliographic evidence of systematically appraised pharmacological data was already highlighted almost 20 years ago (Benedum, Loew, Schilcher, Nicolai, & Steinhoff, 2000). The 2004 EU Directive that governs the registration of Traditional Herbal Medicinal Products (THMPs) recognises bibliographic proof of an ingredient's or a product's recorded traditional use as central evidence for the designated tradition use category. Directive 2004/24/EU builds on the previous pan-European guideline 65/65/EWG, article 4.8 a (ii), which provided a pathway for market approvals of known substances based on bibliographic evidence (Nicolai & Steinhoff, 2001, p. 4). However, experience with the implementation of Directive 2004/24/EU has shown that bibliographic evidence of historical indications, modes of application, efficacy, product safety and innocuousness has not been comprehensively considered for traditional uses (Jütte et al., 2017).

Bibliographic evidence on traditional plant medicines has been found in the literature of three key disciplines, namely medicine, pharmacy, and botany. Until the end of the 19<sup>th</sup> century, botany and pharmaceutical compounding were integral sciences for the professional development of physicians (Freyer, 1995). A database search strategy was constructed to find relevant papers on the therapeutic uses of traditional plant medicines from these disciplines (see Appendix 1). It returned 2,026 articles of which 1991 were unique hits. The electronic database search was further complemented by a physical literature search undertaken at libraries and archives in Germany and Switzerland. Appendix 2 provides the preliminary list of historical and contemporary medical textbooks and pharmacopoeias selected in this manual search. Those texts were vetted as potential bibliographic evidence sources for regulatory purposes. The selection criteria that were developed as part of the research method and the final selection of medical texts evaluated for this research project will be discussed in the Materials and Methods chapter (Chapter 4.4.2).

The following literature review is not exhaustive; rather it highlights areas of existing

research into the traditional *materia medica*<sup>1</sup> of continental Europe. In line with the focus of this thesis, the review will examine research into the German language medical literature only. It will not examine research on linguistics, literary structure, or artistic aspects of illustrations printed in historical medical textbooks. Moreover, the large body of experimental research into plant drugs, as discussed in specialised magazines such as *Planta Medica*, is not examined as it is not the topic of this thesis.

Despite a large body of literature on medicinal plants, as exemplified by the high hit rate of articles from the search strategy, the phytotherapeutic evaluation of historical medical data for regulatory purposes is only a recently emerging field. For this, a further manual search had to be executed. There exists, however, a good body of academic research into related domains: pre-modern medical theories, the central place of medicinal plants in the history of European medicine, and their lasting cultural significance (Baader, 1987; Baumann, 1998; Benedum et al., 2000; Bergdolt & Keil, 1980; Diepgen, 1949; Dressendörfer, 2003; Eckart, 2009; Fahrig, 1992; Feldmann, 1996; Freyer, 1996; Friedrich & Müller-Jahnke, 2005; Giesecke, 2006; Helmstädter, Hermann, & Wolf, 2001; Isphording, 2008; Keil, 1982, 1985; Keil & Dilg, 1991; Kusche, 1990; Mägdefrau, 1992; Martin, 1991; Müller-Jahnke & Friedrich, 1996; Pavord, 2005; Rohland, 1982; Rothsuh, 1978; Rösen, 1986; Schipperges, 1999; Schmid, 1939; Schmitz, 1998; Stille, 2004; Stolberg, 2011; Telle, 1982a; Tillmann, 1988; Wulle, 1999; Zander, 2000). This historical and cultural background to the European *materia medica* helps frame research on evidence of long-standing pharmacological knowledge for regulatory purposes. A further body of literature, which will be discussed in more detail in the Materials and Methods chapter, provides linguistic and conceptual translation aids for the systematic appraisal of the pharmaceutical content recorded in historical medical books.

The deficit of research into the regulatory relevance of historical medical textbooks may be because the effectiveness of traditional therapeutics has been questioned in academic circles despite their longevity (Riddle, 1985, pp. xx-xxii; Watkins, Pendry, Corcoran, & Sanchez-

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<sup>1</sup> Note: when *materia medica* is spelled in lower case, the term refers to the body of remedial substances used in the practice of medicine; when the initial letters are capitalised (either *Materia medica* or *Materia Medica*), the term refers to a book title.

Medina, 2011, p. 1070). Many historians of medicine and pharmacy did not consider indications documented in early modern European pharmacopoeias and textbooks to be clinically relevant for today's regulatory environment or medical practice (Dressendörfer, 2003). Academia frequently resists the notion that historically prescribed plant medicines are valid treatments. This is despite the fact that physicians of the early modern period listed about 80% of the European plant species positively assessed in the regulatory monographs by the German Commission E (Heide, 2001). Even in 1993, the *Deutsche Gesellschaft für Pharmakologie und Toxikologie* (German Association for Pharmacology and Toxicology) described phytotherapy as a 'scientifically retarded, historical form of pharmacology' (Benedum, 2001, p. 13). It is therefore unsurprising that a method to evaluate systematically the transmission of historically documented pharmacological knowledge for regulatory purposes has yet to be formalised. Thousands of unstudied Latin, Greek, Arabic, and early modern German herbal texts and recipe books across Europe, northern Africa, and the Middle East await such an exploration (Buenz et al., 2004, p. 495). Schanz (2009) is one of the few authors who focused his historical research on the regulatory potential of historical medical texts, thus demonstrating the relevance of such research. His investigation on clinical indications of Hawthorn (*Crataegus spp.*, Rosaceae) and Motherwort (*Leonurus cardiaca*, Labiatae) recorded over 2000 years of European medical history provides a comprehensive, detailed, and evaluated assessment of their pharmacological uses up to the present day. Remarkably, he was the first applicant to receive a registration in Germany under the 2004 EU Directive for a mono-preparation, a medicinal Hawthorn tea, by submitting his historical longitudinal comparative research (Schanz, 2009, p. 144). The investigation by Kazemekaitis (2010) into plant medicines primarily used in Lithuania, but also in Latvia, Estonia, and parts of Poland, identifies dozens of medicinal plant species that have been used in Eastern European healthcare for at least 100 years but are not currently officially recognised in the EU. The author of this study concludes that these plant species could qualify for positive traditional use monographs under Directive 2004/24/EU and could thus become available as traditional medicines for all EU Member States (Kazemekaitis, 2010, p. 5). The studies of Schanz and Kazemekaitis demonstrate how historical research can support traditional medicine in the registration of its therapeutics.

Lichtenthaeler (1987, pp. 395-398) argues that the reluctance to acknowledge historical medical knowledge stems from the subconscious metaphysical attitude that derived from the positivistic, progressive and scientific worldview prevailing immediately following the

Age of Enlightenment. Much of the 19<sup>th</sup> and 20<sup>th</sup> century literature on medical history has focused on an alleged post-Hellenistic decline of medicine following a highpoint of Western medicine as represented by illustrious Graeco-Roman physicians. This decline was said to have continued throughout the Middle Ages when political and religious developments unfavourably influenced science in general and medicine in particular. Since the Age of Enlightenment, new medical and biochemical insights are claimed to have enabled the “triumphal march” (De Vos, 2010, p. 2) of scientific Western medicine in the modern era (Diepgen, 1914, pp. 7-10; Touwaide, 2005). The notion of history as continuous progress since the Age of Enlightenment contrasts with the concept of oscillation of medical insights and practices, including radical changes in some centuries. For example, the paranoia elicited during the European witch hunts led to the discontinuation of long-established but hallucinogenic pain-relieving and anaesthetic medication from the late 16<sup>th</sup> century until the 19<sup>th</sup> when such drugs were re-introduced, albeit in a different format (Schmitz, 1998, pp. 413-414). Significant shifts in medicine were illustrated by medical historian Tsouyopoulos (2008), drawing on Michel Foucault’s (1973) notion of discontinuities in history. In contrast, the otherwise informative *Chronik der Medizin* (Chronicle of Medicine) edited by Schott (2000) illustrates inept historiography as new breakthrough discoveries being implied to have heroically superseded established therapies for the prevention, treatment, and healing of many illnesses. In this view, traditional medicines are framed at best as a source of precursors for synthesizing phytochemicals into drugs (Huwer, 2008; Müller-Jahncke & Friedrich, 1996) and at worst as a retrograde, inferior, and romantically-influenced form of knowledge compared with cutting-edge bioscientific knowledge (Tobyn et al., 2011, p. ix). The regulatory environment is not immune to such views as is evident in New Zealand legislation. The exclusion of traditional medical practices from mainstream medicine and funding was—as already mentioned—solidified by several Acts, namely the Tohunga Suppression Act 1907, the Quackery Prevention Act 1908, the Medicines Act 1981, and the Dietary Supplements Regulations 1985.

The following literature review summarises first the current state of research into pharmacological data documented in historical European medical textbooks, beginning with Tabernaemontanus’ influential work *New vollkommen Kräuter-Buch*. This medical textbook, first published in 1588, is selected as *pars pro toto* to represent the body of pharmacological knowledge of the early modern period in German speaking countries of

Europe. It incorporates local, foreign and experientially-gained knowledge covering the pharmacological effects of medicinal plants spanning back to medical schools of antique Greece, Byzantine and medieval Europe while integrating contemporaneous insights from the early modern era. The review then gives an overview of research on other historical medical texts, where methods of medical history alone or in combination with ethnopharmacology were applied to ascertain their pharmacological data. Lastly, it discusses historical research into empirical knowledge on medicinal plants used as bibliographic evidence for regulatory purposes.

### 3.2 Tabernaemontanus and the *New vollkommen Kräuter-Buch*: current state of research

In the 1980s, Tillmann observed that Tabernaemontanus and his encyclopaedic medical textbook *New vollkommen Kräuter-Buch* is an influential but insufficiently researched resource of the European botanical pharmacy (1988, p. 4). Whereas Tabernaemontanus' biography is now reasonably well understood (Bofinger, 2004; Clair, 2011), a comprehensive transcription and translation of pharmacological data from his body of work are lacking. Some plant monographs of the 1625 edition (Tabernaemontanus, 1625) have been transcribed by a lay historian, albeit without pharmacological evaluation (Neü vollkommen Kräuter-Buch, n.d.). Thus, gaps of understanding remain about Tabernaemontanus' pharmaceutical and pharmacological information (Tillmann, 1988, pp. 4,5) and about how this data could be canvassed for regulatory purposes. Consequently, the *New vollkommen Kräuter-Buch* awaits a comprehensive appraisal of its body of knowledge. Recent scientific investigations into selected indications listed in this medical textbook point to the reliability of its data (Adams, Alther, Kessler, Kluge, & Hamburger, 2011; Adams, Berset, Kessler, & Hamburger, 2009; Adams, Gmünder, & Hamburger, 2007; Adams, Gschwind, Zimmermann, Kaiser, & Hamburger, 2011; Adams, Kessler, Kluge, & Hamburger, 2010; Adams, Schneider, Kluge, Kessler, & Hamburger, 2012).



**Figure 1. Jacobus Theodorus Tabernaemontanus. Reprinted with permission of the Stadtmuseum Bad Bergzabern.**

Although scholarship has yet to evaluate systematically all therapeutic information documented in Tabernaemontanus' *New vollkommen Kräuter-Buch*, a few researchers have begun work on certain sections. The two main researchers are Baumann (1998), who investigates the therapeutic uses of medicinal plants in the Umbelliferae family recorded in the *New vollkommen Kräuter-Buch*, and Bofinger (2004), who compares clinical recommendations relating to medicinal plants of the Solanaceae and Lamiaceae family with current known active constituents and pharmacological actions. Both studies confirm the rationale behind many traditional applications. Bofinger highlights the logical structure of Tabernaemontanus' plant monographs by using the exemplar of Tormentil (*Potentilla erecta*, Rosaceae; *Potentilla tormentilla* Neck, Rosaceae), confirming that this medical textbook is an accessible and suitable source for regulatory purposes.

### **3.3 Studies relating to the therapeutic history of medicinal plants**

Some scholars apply a different research approach to Baumann and Bofinger by exploring Tabernaemontanus' clinical information and that of other medical authors longitudinally, attempting to cross-validate modern scientific research with historical indications for specific plants as recorded across medical history. In Germany and Switzerland, many of these explorations were undertaken as doctoral dissertations in medicine, pharmacy, or natural science. The following synopsis highlights exemplars of research relating to consistently transmitted historical uses of medicinal plants compared with contemporary knowledge.

Wulle's study of the European *materia medica* recognises that over 1,000 drugs from plants (*vegetabilia*), animals (*animalia*), and minerals (*mineralia*) have been recorded since antiquity (Wulle, 1999, p. 8). He reviews the pharmacological actions of several of them, comparing the actions with contemporary use. Notably, based on their empirical observations, historical authors discuss both the therapeutic benefits and the safety concerns of quick-acting and potent drugs such as *Papaver somniferum*, *Hyoscyamus niger*, *Atropa belladonna* and *Mandragora officinarum*. They examine how such drugs can be safely administered through correct dosage, careful preparation, and appropriate combination with moderating plants (Wulle, 1999, pp. 34-44).

Putscher (1968) tracks the therapeutic history of one of the oldest healing plants, Licorice (*Glycyrrhiza glabra*, Fabaceae), from pre-classical antiquity to the 1960s. She demonstrates

how traditional indications have been recorded consistently, and their congruence with modern biochemical and pharmacological data. The interdisciplinary research group Fiore, Eisenhut, Ragazzi, Zanchin, and Armanini (2005) expand on these data with a study on the independent medicinal uses of Licorice in several unrelated ancient cultures. They claim that consistent indications for Licorice across different ethnic groups with different cultural backgrounds, and its universally reproducible therapeutic effects, are unequivocally beyond a placebo response. Li, Myers, Leach, Lin, and Leach (2003) have also noted such cross-validation of indications from other medicinal plants across different traditional systems of medicine (Australian aboriginal medicine and TCM).

Kreutzer (1988) longitudinally compares European pharmaceutical applications of native Orchids (*Orchis spp.*, Orchidaceae) from antiquity to the end of the 20<sup>th</sup> century, with an emphasis on 16<sup>th</sup> century herbals. In his investigation, Kreutzer identifies Tabernaemontanus' *New vollkommen Kräuter-Buch* as a precursor to contemporary official pharmacopoeias. Kreutzer confirms that the native Orchid disappeared as a botanical drug from the German Pharmacopoeia in the 1960s—even though it had been used medically for over two millennia and its therapeutic active constituents have long been validated. Freyer (1998) recognises that medicinal plants have been used since pre-historic times and that written pharmacological data have been transmitted in European medical literature for more than two millennia. He compares several plants used throughout the European medical history with contemporary knowledge on their active principles and with registered consumer products in today's European market place. He usefully catalogues historical synonyms for medicinal plants. Richter (1998), in turn, undertakes a comparative longitudinal study of the medical history of Lemon balm (*Melissa officinalis*, Labiatae). He observes that Tabernaemontanus' indications are very close to the scientific appraisals of *Melissa officinalis* recorded in today's official pharmacopoeias, recognising that Tabernaemontanus accurately described the pharmacognosy of the plant, its phytopharmacology and related pharmaceutical compounding techniques (Richter, p.234).

Other longitudinal studies briefly discuss Tabernaemontanus' work in the context of the pharmaceutical and pharmacological characteristics of medicinal plants. Tschupp (1998) provides a longitudinal medicinal plant study on St. John's Wort (*Hypericum perforatum*, Hypericaceae), focusing on the wealth of recorded historical recipes and pharmaceutical techniques. He compares the historical uses of St. John's Wort with confirmed active

constituents and pharmacokinetics and pharmacodynamics properties. Tschupp additionally appraises scientific trials and highlights validation of several traditional uses. Pollio, De Natale, Appetiti, Aliotta, and Touwaide (2008) investigate continuity and changes in the Mediterranean medical tradition by tracing the therapeutic indications of Rue (*Ruta spp.*, Rutaceae) prescribed in Hippocratic medicine, and comparing them with contemporary practices in countries along the Mediterranean Sea. Their study gives insights into the correlation of humoral and modern medical concepts. Rue was credited in humoralism as having hot and dry properties. According to the ‘principle of contraries’ (*contraria contrariis*) that aimed at restoring the right balance of all physiological components of the body, Rue was used historically to reduce any excess of fluid in the body through heat against moisture or cold and was frequently administered to cure pulmonary and ocular infections, menstrual ailments, and aches. It was also used as an antidote against poisons and various venomous bites. Notably, humoralism at times used other therapeutic strategies, such as the ‘principle of similarity’ (*similia similibus*). Thus, Rue was further recommended to treat inflammation through heat against heat, similar to today’s strategies in chronic inflammations (Pollio et al., 2008, p. 473). In contemporary Mediterranean practice, Rue continues to be prescribed to cure menstrual and digestive disorders, as an anthelmintic and vermifuge, as an anti-rheumatic, and illegally as an abortifacient—all medical issues that were historically seen to benefit from accelerated ‘flow’. Anti-inflammatory and analgesic properties are, as in antiquity, also applied, but secondarily to the previously mentioned applications (Pollio et al., 2008, p. 479). These modern applications mean that while in today’s phytotherapy practice the explanatory humoral concepts have fallen away, the key historical applications stayed on in clinical practice.

As already noted, Schanz (2009) investigates Hawthorn (*Crataegus spp.*, Rosaceae) and Motherwort (*Leonurus cardiaca*, Labiatae) in the context of over 2000 years of medical history and comprehensively assesses their pharmacological uses up to the present day. He determines that the extraction medium and dosage requirements listed in Bock’s early modern period herbal from 1577 are almost identical with today’s official guidelines for preparation and dosage as determined by the Commission E monograph on Hawthorn (Schanz, 2009, pp. 142-143). Mersi (2011) provides an overview of the medical uses of Ginger (*Zingiber officinale*, Zingiberaceae) and Lesser Galangal (*Alpinia officinarum*, Zingiberaceae) in the history of European phytotherapy. Mersi compares almost 90 historical texts with current phytotherapeutic texts, including contemporary official

monographs. Unlike other researchers, Mersi investigates not only authoritative textbooks, but also previously unknown medical, folkloristic, and popular science texts. In her appraisal of Tabernaemontanus' *New vollkommen Kräuter-Buch* she notes that this medical text provided recipes for the tropical plant Lesser Galangal but not for the equally exotic Ginger, because Tabernaemontanus preferentially recommended European medicinal plant species where an equivalent to an exotic or imported plant was available. Many of the historic indications of Lesser Galangal and Ginger have remained stable over the centuries, especially in the treatment recommendations for the gastrointestinal tract, a feature also noted with other oriental spices (Fabre, 2003). Many of Ginger's and Lesser Galangal's indications are now confirmed with modern scientific research methodologies. Mersi further explores how the humoral qualities of medicinal plants relate to disease targets. This qualitative analysis of phytotherapeutic information contained in historical medical textbooks had not been undertaken to this extent by other researchers and is therefore useful for future studies into botanical drugs and historical treatment strategies.

Zorn (2013) examines the therapeutic significance of Hyssop (*Hyssopus officinalis*, Lamiaceae) in European healthcare, investigating humoral nosology and contrasting it with scientific studies. The author focuses on clinical applications for patient care and excludes pharmacopoeias and regulatory monographs. His study demonstrates that most antique therapeutic indications remained stable over time and only a few were added, for example by Tabernaemontanus in the early modern period. Similarly, Anagnostou (2005) offers a longitudinal study on the therapeutic tradition of Passionflower in the history of medicine and pharmacy in America and Europe. While the consistency of indications across time and in separate continents suggests its therapeutic benefit, the author highlights that contemporary scientific methodology and the decoding of its active constituents now provide an additional scientific rationale to traditional uses.

Verhoeven (2012) applies both a qualitative and quantitative method to his historical research on medicinal uses of Wood Betony (*Stachys officinalis*, Lamiaceae). The author states that it was a dominant botanical drug from antiquity to the early modern period, rated by physicians for over 1800 years as an effective medicine; yet, its official importance in line with many other medicinal plants started to decrease by the early 19<sup>th</sup> century when the new natural science based medical paradigm emerged. It ultimately led Wood Betony to disappear from regular medicine by the 20<sup>th</sup> century. Today, Wood Betony is almost

exclusively used as a traditional medicine or in homeopathy. Verhoeven's study is particularly useful for regulatory purposes as it evaluates the historic indications with current pharmaceutical knowledge as recorded in *Hagers Enzyklopädie der Drogen und Arzneistoffe* (HagerROM, 2005). As a novelty in this line of research, he further incorporates into the comparison *Dr. Duke's Phytochemical and Ethnobotanical Databases* (Duke, n.d.), which list the transmission of indications documented in European healthcare after immigration of European physicians to the Americas. In the quantitative section of his study, Verhoeven statistically analyses the plausibility of the thirteen main historical pharmaceutical indications of Wood Betony as well as its use as an analgesic; all these indications can now be explained with current pharmacological knowledge (Verhoeven, 2012, pp. 184-186). The study further concluded that the 16<sup>th</sup> century medical authors Pietro Andreae Matthioli and Tabernaemontanus have high level of convergence with indications listed in *Hagers Enzyklopädie der Drogen und Arzneistoffe* and *Dr. Duke's Phytochemical and Ethnobotanical Databases* at 84% and 74% respectively (Verhoeven, 2012, pp. 187-189). Verhoeven's study illustrates that now-dismissed historical indications by regulatory monographs can be validated with the scientific methodology.

Verhoeven's results are echoed by other authors, such as Piwowarski, Granica, and Kiss (2015) whose systematic review of historical sources from antiquity to the 20<sup>th</sup> century confirm the benefits of Purple Loosestrife (*Lythrum salicaria*, Lythraceae) as an effective remedy for the treatment of gastrointestinal tract ailments and complaints of the skin and mucous membranes. Phytochemical studies confirm high levels of polyphenols and heteropolysaccharides. The whole plant extract, as well as isolated compounds, has demonstrated antidiarrheal, antimicrobial, anti-oxidant, anti-inflammatory, and anti-diabetic properties. Piwowarski et al. claim that Purple Loosestrife was unjustifiably relegated to history by the introduction of synthetic corticosteroids and sulfasalazine drugs in the 1950s. Purple Loosestrife lacks the significant adverse effects that the long-term use of synthetic anti-inflammatory drugs cause when used for treating severe gastrointestinal diseases (Piwowarski et al., 2015, p. 247). Another series of essays on the therapeutic history of medicinal plants similarly confirms that now obsolete traditional uses of medicinal plants could be reconsidered in the light of scientific insights, such as for Gentian (*Gentiana lutea*, Gentianaceae) (Seitz, Lange, & Franz, 2005), Tormentilla (*Potentilla erecta*, Rosaceae) (Latté, 2006; Tomczyk & Latté, 2009), leaves of Red Vine (*Vitis vinifera*, Vitaceae) (Schneider, 2009) and leaves of Strawberry (*Fragaria vesca*, Rosaceae) (Schiedermaier,

2007).

Although all these studies comprise a substantial body of research into traditional plant indications, these explorations would benefit from a summary of which historical indications have been consistently transmitted, which have been discontinued and why if known, and which are underpinned by scientific trials and pharmacological studies. Such a critical appraisal of documented evidence on the effectiveness and safety of medicinal plants would enhance the usefulness of historical research for a bibliographic approval process as for example required by European regulations. In conclusion, the results from the aforementioned studies support the assessment that pre-modern medicine with its millennia-old humoral paradigm provided an independent practical therapeutic framework that was coherent and logical in itself. Where traditional indications are investigated with modern scientific methodologies, they are usually validated.

### **3.4 Statistical analysis of herbals**

Quantitative methods can further help verify if historical medical books provide reliable bibliographic sources of evidence for the registration of traditional plant medicine applications. The analyses into the medical textbooks of Hieronymus Brunschwig, Hildegard von Bingen and Leonhart Fuchs are exemplars of this type of analysis.

#### **3.4.1 Hieronymus Brunschwig**

The *Liber de Arte Distillandi de Simplicibus* (Small Book of Distillation) was written by the German surgeon Hieronymus Brunschwig (circa 1450 - 1512/13) and was first published in 1500. It describes the distillation of drugs predominantly of plant origin and their therapeutic applications. It became one of the most popular medical and botanical textbooks of the 16<sup>th</sup> century and served as a technological reference encyclopaedia for professional distillers. Will's (2009) study investigates humoral indications of the historical distillates with folk medicine and current official indications listed in *Hagers Handbuch der Drogen und Arzneistoffe* (HagerROM, 2005). The statistical analysis on accordance and divergence of traditional indications with contemporary medical use confirmed a 65% average of convergence to a 100% convergence in the case of bitters (Will, 2009, p. 47). In contrast to saponins where the lowest convergence was noted, bitter substances are particularly well extracted in a distillation process.

### **3.4.2 Hildegard von Bingen and Leonhart Fuchs**

The study of Mayer-Nicolai (2009) investigates the medical textbooks of Hildegard von Bingen (1098–1179) and Leonhart Fuchs (1501–1566). Mayer-Nicolai compares the historical indications assigned to botanical drugs with their scientifically accepted contemporary use. A statistical analysis was developed to validate whether the recorded historical indications were randomly assigned or if there is an empirical basis for these indications. This study showed that both historical authors awarded indications with a higher accuracy than random distribution of indications. The statistical findings served as evidence that traditional indications were not assigned haphazardly but based on clinical knowledge. Mayer-Nicolai concluded that the probability of beneficial clinical effects of medicinal plants historically recorded in medical textbooks, but since relegated to history, is high (Mayer-Nicolai, 2009, p. 74).

Apart from the statistical analyses employed by Will and Mayer-Nicolai, there are further examples of statistical approaches for quantifying convergence of traditional and modern knowledge (Leonti, Cabras, Castellanos, & Weckerle, 2012; Leonti, Cabras, Weckerle, Solinas, & Casu, 2010; Uehleke, Hopfenmueller, Stange, & Saller, 2012). Such statistical comparisons between traditional and modern approaches to phytotherapy showed that there is a high convergence between the main traditional indications and contemporary indications of a medicinal plant. Yet a difference is that modern official monographs tend to restrict applications to one or only a few indications for each medicinal plant whereas medieval and early modern medicine reflect more comprehensively the complex nature of plants that leads to their broad clinical uses (Uehleke et al., 2012, p. 189). This may explain why modern European phytotherapy, which is influenced by the biomedical approach to the human body, is narrower in its applications than is traditional plant medicine, which was practised in the context of humoralism and its holistic, personalised healthcare approach. The differences in traditional and contemporary medical approaches should be taken into consideration in a regulatory framework that genuinely aims to support the practice of traditional plant medicine. Otherwise, many traditional indications might be excluded from regulatory approvals despite their longevity and probability of effectiveness based on empirical evidence.

### **3.5 Historical *materia medica* researched via ethnopharmacology**

In the last two decades, research into pharmacological and pharmaceutical information on

the historical European *materia medica* received a boost with the attention paid by ethnopharmacology and ethnobotany to this written source of knowledge as exemplified by numerous research projects (Adams et al., 2010; De Vos, 2010; Heinrich, Edwards, Moerman, & Leonti, 2009; Heinrich, Kufer, & Leonti, 2005; Heinrich, Kufer, Leonti, & Pardo-de-Santayana, 2006; Helmstädter, 2016; Katiyar et al., 2012; Leonti, 2011; Leonti et al., 2010; Leonti, Casu, Sanna, & Bonsignore, 2009; Leonti et al., 2017; Leonti & Verpoorte, 2017; Moore, Hamza, Berke, & Umar, 2017; Piwowarski et al., 2015; Santic, Pravdic, Bevanda, & Galic, 2017; Staub, Casu, & Leonti, 2016; Valiakos, Marselos, Sakellaridis, Constantinidis, & Skaltsa, 2015; Waldstein, 2006, 2014). Ethnopharmacology has a good track record of uncovering verifiable botanical drugs from indigenous plant knowledge for public health interventions (Etkin, 1993, 1994; Etkin & Elisabetsky, 2005). It is important to note that indigenous plant medicines are not only used for health maintenance or the treatment of self-limiting ailments, but also for serious, life-threatening events such as venomous snake bites (de Moura et al., 2018). In Western healthcare systems, the current limitations imposed on traditional plant medicines to the treatment of minor, self-limiting ailments are due to regulatory restrictions which do not take into account the original scope of historical uses and the therapeutic potential of traditional plant medicines.

There are many links amongst ethnopharmacy, ethnopharmacology, and phytotherapy, in particular the acknowledgment that empirical observations recorded in traditional systems of medicine are verifiable with contemporary scientific research (Etkin, 2001).

Ethnopharmacology has begun to focus on ‘bioprospecting’ historical herbals for three reasons: generational loss of traditional medicinal plant knowledge; intellectual property issues related to botanical drugs developed and patented with the exploitative use of indigenous knowledge; and the desire to discover new drug leads (Buenz et al., 2006; Buenz, Johnson, Beekman, Motley, & Bauer, 2005; Buenz et al., 2004). This emerging discipline has been coined by French researchers as “archeo-pharmacology” (Staub, Geck, Weckerle, Casu, & Leonti, 2015), but as this term has not been taken up by other researchers, a widely accepted term remains to be determined for this method.

The ethnopharmacological research to date confirms that medicinal information held in historical medical textbooks represents the ethnobotanical reports of that time (Touwaide, 2005). Thus, they are considered to reflect actual medical practice resulting from a

pragmatic and empirical approach to the botanical environment (Leonti et al., 2012; Leonti et al., 2010). Truly irrational uses of herbal medicines or individual opinions are filtered out in this method. To be considered, the herbal medicines need to have been well-established through generations of practice or they must have identical uses in two or more independent, geographically-separated cultures. Such recorded medicinal plant uses provide a high likelihood of universally reproducible therapeutic effects beyond placebo responses that might arise from expectations or from the therapeutic encounter itself (Fiore et al., 2005; Li et al., 2003).

The ethnopharmacological approach to historical medical texts has produced significant results. Perhaps the most reported example of successful ‘bioprospecting’ of herbals came with the award of the Nobel Prize in Physiology or Medicine in 2015 to Youyou Tu, who studied medicinal plants prescribed in TCM to treat fever and chills caused by malaria (Efferth et al., 2015). The breakthrough for the isolation of artemisinin came when the scientist followed the precise and reproducible ancient extraction technique noted in an over 1700-year-old textbook authored by the ancient Chinese physician Ge Hong. Rather than the standard hot decoction process applied for the extraction of most other medicinal plants, the ancient text prescribed a low-temperature extraction of pressed juice from the plant *Artemisia annua*. This extraction led to the most active drug against malaria, an isolated sesquiterpene lactone containing an unusual peroxide bridge (Su & Miller, 2015). Antimicrobial assays by researchers at Nottingham University on a thousand-year-old recipe found in *Bald’s Leechbook* against eye infections also headlined worldwide when they proved to be effective against antibiotic resistant Gram-positive *Staphylococcus aureus*. The topical solution prepared with two species of *Allium*, Garlic, and Onion or Leek, together with wine, and oxgall bile from a cow’s stomach was most efficacious when prepared precisely according to its historical brewing instructions (Harrison et al., 2015). The discovery was made possible with the collaboration of an Anglo-Saxon scholar and a microbiologist, highlighting the importance of interdisciplinary collaboration in this emerging field of research. Further, antimicrobial studies into medieval Anglo-Saxon and Welsh recipes for wound healing also confirmed antimicrobial activity against common wound pathogens (Wagner et al., 2017; Watkins, Pendry, Sanchez-Medina, & Corcoran, 2012). Over two decades earlier, a recipe from an 8<sup>th</sup> century monastic medical textbook (*Lorscher Arzneibuch*) was attested, at least theoretically via a simulated reproduction of the recipe, to be penicillin producing (Schneider, 2001).

An ethnopharmacological examination of a 13<sup>th</sup> century recipe book spotlights the historical pharmacological knowledge of plant synergy; for example, when Saffron and Poppy are combined, they have been scientifically proven to enhance the analgesic effects of opium alkaloids (Tamaddonfard & Hamzeh-Gooshchi, 2010; Valiakos et al., 2015). This combination is recorded in the early modern period by Tabernaemontanus in his monograph on Poppy (Tabernaemontanus, 1664, pp. 961A-965K). Furthermore, historical Greco-Roman pharmacology was well aware of the dangers of using strongly and immediately acting drugs such as *Papaver somniferum*, such as addiction and death, and the benefits in analgesic and anaesthetic effect (Scarborough, 1995; Valiakos et al., 2015, p. 80). Therapeutic effects were demonstrated by the recreation of a popular medieval opiate drug called the ‘Great Rest’, recorded in the 12<sup>th</sup> century Italian medical recipe book *Antidotarium Nicolai* that was influential well into the early modern period. An interdisciplinary research team at the University of Toronto calculated the effective (ED50), toxic (TD50), and lethal (LD50) dose rates for the ingestion of raw opium from Poppy in combination with Henbane and Mandrake. Notwithstanding some judicious assumptions in the simulation of the recipe, the researchers established that the optimum dose of the Great Rest would have proved beneficial for most patients while the lethal dose was double the efficacious dose, providing a substantial safety margin. A modern pharmacological review on the synergistic combination of morphine, hyoscyamine, and scopolamine confirmed that tropane alkaloids which are present in Henbane with morphine which is present in Poppy are beneficial in combination because they increase sedative effects, deter the user from self-administration of multiple doses in a short period of time, and diminish opiate addiction (Everett & Gabra, 2014, p. 448; Kentala, Scheinin, Kaila, Seppälä, & Kanto, 1998). Although the plausibility of effectiveness and safety of historical recipes must be vetted on a case-by-case basis, their dosage and instructions evidently demonstrate clinical judgement. Where they have been tested the results to date indicate that traditional directions for use stand up well against contemporary knowledge.

Ethnopharmacological approaches to historical herbals have also been applied to the investigation of historically prescribed medicinal plants for specific illnesses. A research team at the Institute of Pharmaceutical Biology of the University of Basel investigated five of the most important European herbals of the 16<sup>th</sup> and 17<sup>th</sup> century, including Tabernaemontanus’s *New vollkommen Kräuter-Buch*, for phytochemical activity in relation to rheumatic disorder, epilepsy, malaria, and brain disorders (Adams, Alther, et al., 2011;

Adams et al., 2009; Adams et al., 2007; Adams, Gschwind, et al., 2011; Adams et al., 2012). Their research demonstrates that Renaissance botanical medicines containing Great Water Plantain (*Alisma plantago-aquatica* L., Alismataceae) show anti-malarial activity against *Plasmodium falciparum* K1 strain with 77% growth inhibition (Adams, Gschwind, et al., 2011). Likewise, over 60% of medicinal plants traditionally recommended for the treatment of rheumatic disorders show activity in relevant assays and some are still used today for the same indications (Adams et al., 2009, p. 356). These results support the authors' assessment that Renaissance-inspired herbals from the early modern period are a promising source of medical knowledge for the rediscovery of effective plant medicines.

Similarly, Iranian researchers have been examining the main pharmaceutical manuscripts of Traditional Persian Medicine (TPM), comparing their historical medicines with evidence-based clinical aspects and phytochemistry. Because antique Greek medicine is the historical root of both Arabic and European medicine, TPM shares many common therapeutics also recorded in the traditional European medical literature. Examples of ethnopharmacological research into historical medical textbooks relate to cardio-vascular diseases (Siddiqui & Aziz, 1963; Zarshenas, Jamshidi, & Zargarani, 2016), metastatic breast cancer (Zarshenas & Mohammadi-Bardbori, 2017), abnormal uterine bleeding (Mobli et al., 2015), and plant-based diuretics (Shoja et al., 2015). Although not all medicinal plants or their indications have survived the arrival of biomedicine, none of these cross-validated studies suggest that the pharmacological treatment strategies described in the examined historical medical literature were random or irrational.

As most of the medicinal plants listed in historical medical textbooks have not yet been clinically tested against disease-relevant targets or receptors, they could provide potentially useful botanical leads for drug discovery (Adams et al., 2012, p. 11). The authors rightfully caution, however, not to restrict research into traditional plant indications to biomedical principles of known or assumed molecular pathways involved in modern aetiology, thus to avoid the 'magic bullet' approach. Instead it is the hallmark of traditional medical systems that they approach health in a holistic way and emphasise health maintenance, disease prevention, and personalised curative treatments; applications of plant remedies play an important role in all three of these healthcare areas (Adams et al., 2007, p. 378). Therefore, an ethnopharmacological approach to the investigation of historical herbals will need to be mindful of limits that a narrow biomedical research focus on new drug leads might impose

as exemplified in the research by Teiten, Gaascht, Dicato, and Diederich (2013). Conversely, when the traditional medical paradigm that generated the empirical body of knowledge in the first place is considered in the research design, the likelihood of creating a meaningful body of evidence to support traditional applications of medicinal plants is not only enhanced but also safer (Etkin, 1993). Such an approach to the historical *materia medica* might provide outcomes that integrate cultural aspects and patient preferences alongside bioscientific knowledge so that sustainable, respectful and effective primary healthcare options can be achieved (Evans, 2006; Yaniv & Bachrach, 2005, pp. 459-462). Otherwise, ‘bioprospecting’ of herbals for the sole purpose of discovering patentable single-entity drugs does not make use of the full potential of traditional medicines nor provide necessary information to advance a regulatory pathway model for them. Dal Cero (2016) demonstrates how a meaningful body of evidence can be created to support traditional applications of medicinal plants through her systematic analysis of the knowledge transmission of the Swiss medicinal flora over the last two millennia.

### **3.6 Historical *materia medica* informing modern phytotherapy**

An emerging branch of research explores clinical applications recorded in historical textbooks for clinical uses by modern phytotherapists. For example, Toby et al. (2011) elucidate the depth of pharmacological knowledge contained in medical scripts from antiquity onwards and assess it against the background of applied modern phytotherapy and scientific research. Their critical exploration of the Western herbal tradition across millennia is aimed at inspiring the current generation of herbal experts in prescribing plant-based medicines. In an earlier work on the British physician Culpepper (1616-1654), Toby (1997, 2013) explores historical concepts of humoral medical diagnosis for today’s holistic healthcare, emphasising the ongoing therapeutic relevance of such concepts. Francia and Stobart (2014) deliver a critical approach to the history of Western Herbal Medicine from classical antiquity to the early modern period. They contribute practical insights and linguistic tools to support historical research into pharmacological data contained in historical medical textbooks. Mayer, Uehleke, and Saum (2002) in turn appraise monastic and early Renaissance medicine alongside current phytotherapy and scientifically researched applications. This text is written for the lay person interested in the use of medicinal plants for self-care. Investigations into Anglo-Saxon (Thomas, 2011; Watkins et al., 2011) and Welsh (Wagner et al., 2017) historical medical texts are further examples of

historical research for contemporary phytotherapy. The historical body of non-German medical literature pertaining to Great Britain or other systems of traditional medicine is, however, not the topic of this thesis and therefore will not be explored further.

### **3.7 Research of the historical *materia medica* for regulatory purposes**

The literature reviewed above suggests that historical research into traditional plant applications can support modern scientific methodologies and inform an evidence-based approach to healthcare. The current regulatory framework in the EU permits bibliographic evidence of traditional plant applications. Such historical evidence must be prepared explicitly to fulfil regulatory criteria that govern the registration of Traditional Herbal Medicinal Products; in particular, it must document consistent transmission of medicinal plant applications. To date, systematic research of historical textbooks prepared as bibliographic evidence for regulatory purposes remains minimal, as most historical or ethnopharmacological studies have not focused on this outcome. However, a discussion has been initiated on a pathway forward that would provide such outcomes (Anton, Serafini, & Delmulle, 2012a, 2012b; Benedum et al., 2000; Helmstädter & Staiger, 2012, 2014; Kazemekaitis, 2010; Müller, 2001; Neely et al., 2011; Saad & Said, 2011; Schanz, 2009; Tims, 2016). This area of research is vital to ensure that verified traditional plant indications continue to be available under today's regulations. The next chapter describes how such traditional evidence might be generated in the era of contemporary evidence-based health policy.

## 4 MATERIALS AND METHODS

### 4.1 The research questions

Historical medical textbooks have not been methodically scrutinised and evaluated for regulatory purposes, despite their significance as medical documents of literate European societies. This chapter will outline a method for exploring the systematisation of medical knowledge on the effectiveness and safety of traditional European plant medicines, knowledge that was transmitted professionally through key historical sources. The study seeks to determine if such historical documentary evidence consistently and accurately describes medicinal plants, their uses, and their therapeutic effects such that it could be admitted to substantiate therapeutic claims. Hence the question of interest is: does systematic bibliographic evidence of traditional medical use provide a pathway for registration of traditional medicines for countries that are yet to regulate traditional plant medicines? And, if so, what method and selection criteria would need to be applied to the selection of historical and contemporary sources so as to have representative sources of evidence on traditional plant medicines and their indications of use, including health claims?

Such an analysis is pertinent. The WHO states that traditional preparations which have been clinically administered in patient care over a long period of time have empirically evolved to maximise their therapeutic effectiveness and minimise risk (World Health Organization, 2012, p. 17). By implication, their toxicity, formulation and dosage are seen to be established. The premise of this thesis is that medical information that was consistently recorded by independent official or authoritative sources and employed to guide regular medical practice and education, represents legitimate information. The European *materia medica* as recorded in medical textbooks represents the accumulated, inter-generational knowledge of benefits and risks of medicinal plants used for healing. This repository of knowledge is the basis of current phytotherapeutic teachings, clinical use in patient care, and OTC remedies. Long-standing traditional medicines have been carefully evaluated and re-evaluated by many generations of professionally trained clinicians. This thesis proceeds under the assumption that such knowledge is not the anecdotal accounts of a few practitioners but represents a cumulative body of clinical data and expert consensus sufficient to cancel out aberrations from so-called placebo effects and observer bias.

A consultation document relating to the former New Zealand Natural Health and Supplementary Products Bill suggested that health claims for natural health products (NHPs) could be made based on evidence of traditional use (Ministry of Health, 2015, p. 9). This Bill proposed to establish several sources of traditional evidence: repositories on traditional plant knowledge such as the *Encyclopaedia of New Zealand*, pharmacopoeias, monographs, treatises and other undefined medical texts. For oral traditions it was anticipated that testimony of individuals within a specific culture who have the authority to speak on such matters would be recognised (Ministry of Health, 2015, p. 10). There was a proposed list of 11 pre-approved bibliographic sources that could be used as evidence for health claims. The pre-approved list did not, however, include any textbooks on the traditional *materia medica* used in traditional systems of medicine practiced in New Zealand, yet these are the most important repository of traditional knowledge for contemporary clinical use.

Medical text sources on the traditional *materia medica* are also underrepresented as sources of bibliographic evidence in other jurisdictions. In 2004, the EU Traditional Herbal Medicine Products Directive (THMPD) recognised traditional evidence to substantiate traditional claims for the registration of traditional herbal preparations (Europäisches Parlament, 2004). To qualify for this alternative proof of effectiveness, data from credible sources had to confirm a consistent line of transmission of medical uses (Müller, 2001, p. 256). In theory a systematic evaluation of historical textbooks could therefore provide bibliographic tradition-of-use (TOU) data for regulatory purposes. Such evaluation could provide critically evaluated information on botanical species identification, therapeutically active parts, specific preparations, and therapeutic applications (Müller, 2001, p. 254). Systematic collection of empirical observations on safety from long-standing traditional use of a plant part or a plant preparation may also contribute to safety data relating to long-term use in a large population (Anton et al., 2012a). Nonetheless, such TOU data has not been systematically appraised for the establishment of the official EU monographs (Jütte et al., 2017), and possible reasons for this are investigated as part of this thesis.

## **4.2 Challenges of research into historical medical texts**

Until recently academia has given little focus to systematic appraisal of historical evidence on the effectiveness and safety of traditional plant medicines *for regulatory purposes*, as noted in the Literature Review. There are several reasons. Pre-modern historical texts

require an interdisciplinary approach because there are substantial conceptual, linguistic, and taxonomical challenges to overcome, making explorations into such sources complex. Furthermore, many of the older historical herbal textbooks are rare and hard to access, being preserved in libraries, museums, archives, and monasteries in wide-ranging locations, often with limited or no public access. There are now efforts in place to digitise such texts, as with the digitisation of the pharmaceutical-historical library of Dr. Vester at the *Universitäts- und Landesbibliothek Düsseldorf*, Germany, but much remains to be done to make them more readily accessible.

In addition, since the privileging of a natural science approach to patient care from the late 19<sup>th</sup> century onwards—an approach secured by socio-economic and political-legal dynamics—, traditional medicine has become increasingly marginalised (Borck, 2016; Coulter, 2007; Stolberg, 1998). Consequently, the usefulness of traditional therapeutics has often been questioned in academic circles or met with outright opposition and denigration, despite their longevity (Bruchhausen & Schott, 2008, p. 11; Coulter, 2004; Riddle, 1985, pp. xx-xxii). From the viewpoint of orthodox science, therapeutic claims for traditional medicines have no validity, and any healing effect that patients may have experienced from traditional medicines are seen as the result of a psychological ‘placebo effect’ or superstition (Holloway, 2000; Parker, 2007; Shapiro, 1959; Sneader, 2005). Cassidy, however, claims that such divergent views on the effectiveness of traditional medicine and its empirical knowledge base, which in literate societies was extensively codified in text, have more to do with paradigmatic preferences than they have to do with rules of science (Cassidy, 1995, p. 19). Existing research on European medical textbooks points to the likelihood that historically used taxa of medicinal plants exert a pharmacological activity beyond a placebo response (Leonti, 2011, p. 552; Moerman & Jonas, 2002). Therefore, this thesis aims to establish whether historical medical sources can provide sufficiently reliable pharmacological information that could be drawn on for regulatory purposes. It does so by comparing the transmission of pharmacological data over several hundred years and compares these data, where available, with evidence of efficacy from RCTs and data from experiential research. Historical data are further juxtaposed with approved health claims in contemporary official monographs as well as authoritative monographs by current experts on the traditional *materia medica*.

### 4.3 Research design

In formal European healthcare, there are five key bibliographic sources that document the medicinal uses of plants. These key sources are historical medical textbooks and their contemporary equivalents, regulatory pharmacopoeias, their commentaries, and official and authoritative herbal monographs:

- Historical medical textbooks on the botanical *materia medica* represent the body of knowledge on remedial substances as used and recommended by clinicians. Historically, medical textbooks were written by university-educated physicians and apothecaries. These clinicians possessed the formal professional education, expertise, and resources required for such an undertaking. Authoritative historical medical textbooks reflect formal medical care and represent the standard scientific knowledge of their times (Anton et al., 2012b). They progressed in the 20<sup>th</sup> century into normative textbooks on phytotherapy.
- Pharmacopoeias provide guidelines on essential medicines used in regular healthcare. Their drug specifications became legally binding in many European countries from the late 18<sup>th</sup> century onwards although official municipal pharmacopoeias already existed in the 16<sup>th</sup> and 17<sup>th</sup> century (Schmitz et al., 2005, pp. 195-196, 573-582; Vogelenzang, 1967, p. 348). Only the broad acceptance of a medicinal substance by a pharmacopoeia committee leads to its listing, a principle that is upheld today (Schanz, 2009, p. 44). Pharmacopoeias are important bibliographic sources for regulatory purposes because they confirm official use and provide conclusive botanical identification for a medicinal plant species and its official plant part(s). Over many centuries, pharmacopoeias also served as guidelines on therapeutic applications in patient care. In contrast to such earlier pharmacopoeias, those from the end of the 18<sup>th</sup> century onwards omit therapeutic information on clinical uses. Thus, pharmacopoeias transformed into official guidelines for medicine making only, focusing solely on the mandatory rules of quality control, drug identification, storage, and nomenclature of the medicines. Subsequently, commentaries took up the role of providing advice on clinical applications, and this body of bibliographic evidence will be included in this analysis.
- Herbal monographs systematically document therapeutic information on a plant species and its preparation(s). Monographs are either released as stand-alone

documents or as a series of monographs on several medicinal plants. Monographs can be official if released by a government, or non-official but authoritative and normative if released by experts. Monographs fulfil the role of official or authoritative therapeutic guidelines.

For this study, selected texts from these distinct categories are systematically investigated as potential sources of historical documentary evidence concerning empirically evaluated traditional plant medicines and their indications of use.

#### **4.4 Research methods**

To be considered admissible in the registration of a traditional herbal product, the assessment of historical data and evidence requires a critique. The research methods of this thesis are grounded in a historical research design (Saucier Lundy, 2008, p. 396). The study employs a longitudinal, comparative analysis of selected texts from the early modern period, defined as from the end of the 15<sup>th</sup> century (Richter, 1998, p. 302) to the 21<sup>st</sup> century. *Arnica montana* (Arnica) and *Hypericum perforatum* (St. John's Wort) are used as exemplars to identify the consistency of therapeutic information recorded in historical medical textbooks. In a first step, their tradition-of-use data will be extracted from selected medical textbooks according to criteria outlined below, and systematically recorded in tables using a pre-established therapeutic use-categories concept for coding as also explained below. In the juxtaposition of 400 years of clinical use, consistencies and differences can easily be recognised. This thesis terms this method as the “Historical Assessment Tool”. It will assist in the systematic collation and organisation of data on treatments that were deemed as effective in patient care over time. In addition, this tool will provide a framework for the collation of safety observations recorded in the literature. Observations of safety or adverse events documented from long-standing use in patient care might provide useful safety data.

##### **4.4.1 Process Map of the Historical Assessment Tool**

Following is the process map used for the systematic collation and analysis of raw data retrieved from historical sources. Particulars of the Historical Assessment Tool will be explained in further detail in subsequent sections.

- 1) Select representative medical textbooks based on pre-determined selection criteria;

- 2) Establish therapeutic use-categories for the coding of therapeutic information;
- 3) Translate therapeutic indications of a plant exemplar from German to English; For pre-modern texts: translate *early modern* German terminology into *modern* German before translating into English<sup>2</sup>;
- 4) Code: attribute each therapeutic indication of a plant exemplar from a selected medical textbook to a therapeutic use-category and record in a table as well as a designated Historic Data Excel spreadsheet (for independent validation); repeat for each selected medical textbook; and
- 5) Analyse the consistency of medical endorsement of indications over the analysed period, their reputed effectiveness, and assessments on safety.

Use of multiple sources of data collection or multiple methods of analysis have been recommended in various disciplines. Such an approach provides different angles for looking at the same phenomenon and adds credibility by strengthening confidence in conclusions drawn (Patton, 2014, p. 661). This method has been termed triangulation (Jick, 1979). The most robust approach is to integrate both qualitative and quantitative methods in mixed-method triangulation (Patton, 2014, p. 663). This thesis will first triangulate text sources from five key categories; medical textbooks, regulatory pharmacopoeias, their commentaries, regulatory monographs, and authoritative monographs. It will investigate consistencies and differences in various data sources at different time points within the same qualitative method. It will then analyse the data retrieved from this qualitative method with data from clinical and experimental research. Scientific trials of Arnica and St. John's Wort are retrieved via a systematic database research in Medline, Embase, AMED, Cochrane Library, Web of Science and Cinhal (to June 2014). Search strategies are recorded in Appendix 1. Evaluation of experimental research will help to explain possible mechanisms underpinning traditional therapeutic uses. Comparing qualitative and quantitative data elucidates complementary aspects of the same phenomenon (Patton, 2014, p. 663). Triangulation of data will assist the objective of this research to establish whether judiciously selected historical sources on the European *material medica* provide a pathway to substantiate therapeutic claims for traditional plant indications. The main purpose of the

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<sup>2</sup> The author is fluent in modern German and English and commands university entrance level of Latin. For the translation of text from early modern German to German, Dr. Heike Will, pharmacist and expert of the early modern period, University of Würzburg, provided linguistic expertise. The translations were further validated by Professor Gundolf Keil, linguist and Emeritus professor of History of Medicine, University of Würzburg.

triangulation is therefore to determine the extent to which traditional indications and safety aspects are documented in historical medical textbooks compared with contemporaneous regulatory pharmacopoeias, their commentaries, and herbal monographs.

#### **4.4.2 Libraries, archives and collections accessed**

Thousands of medical textbooks and pharmacopoeias await scientific exploration. First this study considered key historical sources that were reviewed by Verhoeven (2012), Mersi (2011), Schanz (2009), Freyer (1998), and Richter (1998). It then reviewed medical textbooks from the *Universitäts- und Landesbibliothek Düsseldorf* (University and State Library of Düsseldorf, Germany); the *Julius-Maximilians Universität Würzburg* (University of Würzburg); the *Germanisches Nationalmuseum* (German National Museum, Nürnberg, Germany); the museum of the township Bad Bergzabern, birthplace of Tabernaemontanus, Germany); the *Deutsches Apotheken-Museum* (German Museum of Pharmacy, Heidelberg, Germany); the *Medizinhistorisches Institut Universität Bern* (Institute of Medical History, University of Bern, Switzerland); the Swiss National Library; Swissmedic, Berne, Switzerland; the private library of Reinhard Saller, emeritus Professor and Director of the Institute of Complementary Medicine, University Hospital Zürich; and the private library of the author. Electronic copies of several historical textbooks were accessed via the History of Medicine division of the U.S. National Library of Medicine, via the Biodiversity Heritage Library, via Internet Archive, and via Google books. After key texts were preliminarily screened, a selection of the most salient texts was collated as displayed in Appendix 2. Of those texts a final selection was taken based on the criteria below.

#### **4.4.3 Selection criteria of medical textbooks**

Both historical and contemporary primary sources were selected according to the following three criteria:

1. Authors needed to be university-educated and qualified practitioners in the professional use of plant medicines with long-standing clinical experience treating patients. Experienced mainstream practitioners were selected because their written works reflect contemporaneous, medical practice at the time of publication of their textbook. As such they likely represent observed treatment outcomes as evaluated by formally educated clinicians made over the course of their professional careers. This supports the plausibility of their recorded data. Such evidence is rated higher

than data in textbooks copied down without the benefit of clinical evaluation from patient care. This selection criterion further aims at minimising idiosyncrasies. A body of medical literature authored by formally trained physicians may also be better accepted in the current regulatory environment than textbooks written by non-academic phytotherapists or texts categorised as advice literature for lay people or folk medicine, even though these may display the same clinical data and may be equally valid if they represent a clinically evaluated source.

2. The selected textbooks needed to reflect authoritative medical reference books. For the purpose of this thesis, an ‘authoritative’ book means one being used in conventional academic teaching, having been printed in multiple editions, or being referenced regularly as an authoritative source in subsequent medical textbooks. Such professional peer recognition suggests currency of the information presented.
3. A selected textbook needed to represent an authoritative source for a selected 25-year period, resulting in approximately four medical textbooks per century. This criterion helps to ensure that there are data for each successive generation of formally trained clinicians.

The starting point of this study is the 4<sup>th</sup> edition of *New vollkommen Kräuter-Buch* authored by the German physician, apothecary and botanist Tabernaemontanus (1664), originally published in 1588. It is the medical textbook recognised as the most comprehensive German language repository of clinical plant knowledge in early modern Europe (Bofinger, 2004). As it is written in early modern German, the succeeding selected texts are also in German language so that the comparative contextual analysis reflects transmission of medical knowledge in the same cultural area. Consequently, the contemporaneous medical literature published in English is not considered (apart from cross-checking of some information).

#### **4.4.4 Selection of pharmacopoeias**

This thesis selected two pharmacopoeias from the same cultural area and periods as the selected medical literature, namely the *German pharmacopoeia* and its predecessor, the *Prussian pharmacopoeia*, which was the legal and structural foundation of the German pharmacopoeia. The examination includes the supplements to this official body of literature as well as commentaries which provide normative guidelines on therapeutic uses. This inclusion is necessary because from the end of the 18<sup>th</sup> century onwards, pharmacopoeias only establish quality standards, not guidelines on therapeutic use, as noted above.

#### **4.4.5 Selection of official monographs**

Official monographs published by a regulatory authority provide official guidelines on a medicinal plant's formally accepted indications, information on dosage, and preparations. When a preparation fulfils the criteria laid out in an official monograph, it is granted market access in the associated territory.

Two official sets of monographs were selected for this study. One set was published by the German Ministry of Health during the 1980s and 1990s (*Commission E Monographs*) and one was published by the European Medicine Agency (*EU Herbal Monographs*) based on the EU Directive 2001/83/E. The latter represent the most recent regulatory monographs published in Europe. The two selected sets of regulatory monographs serve as a benchmark to contrast officially endorsed health claims with clinical uses contemporaneously published in the selected medical textbooks.

#### **4.4.6 Selection of authoritative expert monographs**

Professional bodies and international organisations also publish herbal monographs. They are not official, but they may be referenced in some jurisdictions as authoritative bibliographical sources when applying for regulatory approval of a herbal product.

This thesis chose three collections of monographs for analysis: the monographs published by the European Scientific Cooperation on Phytotherapy (ESCOP), the professional body that represents national herbal medicine organisations across Europe (edition 2013); the German pharmaceutical reference work *HagerROM. Hagers Enzyklopädie der Arzneistoffe und Drogen* (edition 2012); and the collection of herbal monographs of the WHO. The first two are authoritative expert monographs in Europe, and the third is a collection of monographs that the WHO offers to the international community as an authoritative source of scientific and traditional information on medicinal plants.

### **4.5 Organisation and processing of data**

The analysis of historical texts poses several methodological challenges relating to the conceptualisation and management of a large volume of data, to linguistic barriers, to the modern interpretation of historical nosologies, and to the identification of pre-Linnean plant taxonomy. These challenges are encountered predominantly in texts published before the 19<sup>th</sup> century and must be overcome before historical information on medicinal plant

applications can be coded for analysis. Thus, the primary data recorded in the 4<sup>th</sup> edition of Tabernaemontanus (1664) are first translated into contemporary language before being tabulated. The data from all other text sources are transferred directly into their respective data tables as well as the Historic Data Excel spreadsheet.

#### **4.5.1 Translation of pre-modern texts**

Translating pre-modern textbooks into modern terminology with exactitude is problematic because pre-modern concepts of health and illness differ from contemporary biomedical views (Stolberg, 2011). Translations may therefore contain interpretative elements. As widely discussed in medical anthropology, explanatory models of health and illness constitute a set of beliefs related to aetiology, symptoms, pathophysiology, course of sickness, and treatment strategies. They are cultural models of reality that are also influenced by political-legal and socio-economic factors which may transform over time (Hahn & Gaines, 2012; Kleinman, 1978, 1980; Oubré, 1995, p. 45; Whyte et al., 2002).

Until the 19<sup>th</sup> century, the scientific framework of European medicine was principally the natural philosophy (*Naturphilosophie*) of Hippocratic medicine with its key feature of humoralism, also termed humoral pathology or humoral theory. This medical concept stated that the human body can self-regulate, heal and restore (*vis medicatrix naturae*), and thus approached healthcare not only with medicines but also with guidelines on healthy living. Ill health was understood as a failure to adapt to the internal or external environment. Even though certain aspects of humoralism started to be questioned by findings from dissections in gross anatomy in the early modern era, it was not until the middle of the 19<sup>th</sup> century when natural sciences such as chemistry, physics, and biology seriously challenged the humoral explanatory model of illness (Bruchhausen & Schott, 2008, pp. 11-15). The vitalistic Hippocratic medicine principles that underpinned European medicine over the past millennia were eventually replaced by cellular pathology as the paradigmatic foundation of Western biomedicine. The new medical paradigm primarily focused on cells, body tissues, external germs, receptors, and man-made synthetic drugs. Biomedicine became the dominant form of mainstream medicine in Europe. Despite this reorientation, plant medicines, the focus of this thesis, continued to exist alongside their synthetic analogues.

The shift in medical theories from humoralism to biomedicine causes some difficulties when trying to correlate historical indications with contemporary body system categories

and nosologies. Leven (1998) and Karenberg (2009) have drawn attention to the complexities of identifying diseases in pre-modern texts. Such challenges arise because, as already mentioned, medical descriptions for illnesses are not ahistorical, independent elements; rather, they are an expression of a given culture at a given time and therefore will change as culture and its expressions evolve (Rothschuh, 1978). Despite these difficulties, the translation of herbal monographs from the early modern period onwards is aided by the fact that medical textbooks during pre-modern times are focused less on categorising specific diseases and more on the treatment of signs and symptoms based on observed pharmacological actions of plants. Moreover, during the early modern period, some physicians started to depart from Galen's classification of medicinal plants, which since antiquity guided the choice of drugs according to their attributed primary humoral qualities of warming, cooling, drying, and moistening (Goehl, 1984). Instead, in the spirit of humanism, physicians complemented and sometimes corrected the information in antique Greek and medieval Arabic herbals with their own clinical observations (Klerk, 2014). Such empirical observations on therapeutic effects of drugs formed the practical basis of physicians, particularly since the Renaissance, to describe the remedial actions of medicinal plants on human physiology. In their pragmatic approach, they used organoleptic information, colour, smell, taste, and sensation (termed 'secondary plant qualities') as well as observed pharmacological actions such as pain relieving, wound healing, or laxative effects (termed 'tertiary plant qualities') to inform their treatment approach (Crellin & Philpott, 1990; Stille, 2004, pp. 19-20; Van Asseldonk, 2007, October). Whereas the concept of primary humoral qualities is intrinsically linked with medical theory, documented empirical observations can be more easily attributed for this research project. It is interesting to note that organoleptic observations continue to inform therapeutic uses of medicinal plants in indigenous communities where archetypical chemosensory cues have shown to correlate with nosological units (Geck, Cabras, Casu, Reyes Garcia, & Leonti, 2017). Recently, an analysis of historically attributed humoral qualities to medicinal plants has suggested that such attribution may be less foreign than thought and may have a pharmacological basis. Plants that have been historically classified as cold and wet have relatively high levels of water or mucilage with an emollient effect. Cold and dry plants have astringent compounds like tannins and parasympatholytic alkaloids. Hot and wet plants commonly have compounds like fatty oils, sugar, and starch. Hot and dry plants contain aromatic compounds like essential oils or glycosylates, sometimes combined with tannins (Van Asseldonk, 2007, October, p. 9). Botanical constituents such as tannins, saponins, and

mucilage are archetypal phytochemicals; their humoral classifications are also found in diverse medical traditions (Bao, Li, Zheng, & Li, 2015; Chen, 1995; de la Cruz, Malpartida, Santiago, Jullian, & Bourdy, 2014; Messer, 1987; Rezadoost et al., 2016).

#### 4.5.2 Translation resources

As detailed in the Process Map of the Historical Assessment Tool, the translation of indications from early modern German to contemporary German and subsequently to English requires a three-step process. After the botanical exemplars are correctly identified, the text passages will be first electronically transcribed from the original source and then translated into contemporary German. The resulting approximation will be subsequently translated into English before the pharmaceutical and pharmacological data will be tabulated.

The following etymological and medical reference resources were used to overcome linguistic barriers encountered in the translation of the 17<sup>th</sup> century source:

- *Ein Neuwes Arzney Buch* by German physician and anatomist Christoph Wirsung (1500-1571) is one of the most detailed early modern texts on human pathology in German language. The attached ‘dictionary on incomprehensible words’ (*dictionario der unverständlichen Wörter*) is particularly useful. The text was first published in 1568 and used by the medical profession as an authoritative medical encyclopaedia. It was later translated into English (Wirsung & Mosan, 1654). Tabernaemontanus revised and edited the edition published in 1577 (Wirsung & Tabernaemontanus, 1577). This pathology textbook is a fitting compendium to Tabernaemontanus’ *New vollkommen Kräuter-Buch* (Tabernaemontanus, 1664) for elucidating medical terminology.
- Höfler (1899), Metzke and Heydemann-Metzke (1995), Genaust (1996), Mildenerger (1997), Kluge (2002), and Haubrich (2003) provide extensive etymological references for the translation of early modern medical terms.
- Francia and Stobart (2014) and Goehl (1984) offer translation aids on humoral concepts of pathologies.
- Ten glossaries further facilitated translation:
  - *Glossarium Latino-Germanicum Mediae et Infimae Aetatis* (Dfg) (Diefenbach, 1857)

- *Novum Glossarium Latino-Germanicum Mediae et Infimae Aetatis* (Dfng) (Diefenbach, 1867)
- *Deutsches Wörterbuch von Jacob und Wilhelm Grimm* (DWB) (DWB, 1854-1960)
- *Enzyklopädie Medizingeschichte* (EnzMedGesch) (Gerabek, Haage, Keil, & Wegner, 2005)
- *Frühneuhochdeutsches Wörterbuch* (FrnhdWb) (Goebel & Reichmann, 1989-2013)
- *Handwörterbuch des Deutschen Aberglaubens* (HWdAgl) (Hoffmann-Krayer & Bächtold-Stäubli, 1927-1942)
- *Lexikon des Mittelalters* (LexMA) (Keil, 1980-1998)
- *Mittelhochdeutsches Handwörterbuch* (LEXER) (Lexer, 1872-1878)
- *Reallexikon der Germanischen Altertumskunde* (RGA) (Reallexikon der Germanischen Altertumskunde, 1973-2008)
- *Die Deutsche Literatur des Mittelalters: Verfasserlexikon* (VL) (Keil, Ruh, Schröder, Wachinger, & Worstbrock, 1978-2008).

#### 4.5.3 Selection of exemplars

In an initial step, 13 medicinal plants were selected from the 4<sup>th</sup> edition of Tabernaemontanus (1664) and translated into modern German. This selection helped to gauge both the level of therapeutic information on medicinal plants presented in this early modern period text as well as the appropriateness of the early modern period as a starting point for this longitudinal, comparative textual analysis. The 13 medicinal plants were chosen from the viewpoint of contemporary use where they provide key therapeutics in the treatment of 12 body systems (as listed at the end of this subsection).

The vetting of these preliminary 13 plant monographs pointed to consistencies between therapeutic uses of medicinal plants in the early modern period and contemporary phytotherapy in the main areas of use, but also to some differences where early modern applications tended to be broader than those of contemporary phytotherapy for most but not all exemplars. The early modern period was confirmed as a fruitful starting point for this research based on the comprehensive clinical information presented in the selected text. Accordingly, Arnica and St. John's Wort were selected as the two exemplars for the final comparative analysis. They are two of the most popular medicinal plants used as OTC

remedies in New Zealand (Nicholson, 2006, p. 5), a popularity which is mirrored in Europe (Dal Cero, 2016, p. 22). They therefore hold contemporary relevance. St. John's Wort reflects a rich medical tradition that spans millennia. Today it is also one of the most scientifically researched medicinal plants. Arnica is a ubiquitous medicinal plant in European healthcare for the treatment of musculo-skeletal injuries and ailments. It had a wider range of applications in the past than today, and so provides a useful case study.

<b>12 body systems</b>	<b>Medicinal plant</b>	<b>Tabernaemontanus 4<sup>th</sup> edition 1664</b>
bones	<i>Symphytum officinalis</i> (Comfrey)	pp. 949-951 2 <sup>nd</sup> volume
digestion	<i>Achillea millefolium</i> (Yarrow)	pp. 371-379 1 <sup>st</sup> volume
gynaecology	<i>Alchemilla vulgaris</i> (Lady's mantle)	pp. 248-251 1 <sup>st</sup> volume
cardio-vascular system	<i>Crataegus</i> spp. (Hawthorn)	pp. 1448-1449 3 <sup>rd</sup> volume
kidneys	<i>Solidago virgaurea</i> (Goldenrod)	pp. 1259-1260 2 <sup>nd</sup> volume
liver / gallbladder	<i>Silybum marianum</i> (St. Mary's Thistle)	pp. 1078-1079 2 <sup>nd</sup> volume
lungs	<i>Thymus vulgaris</i> (Thyme)	pp. 741-744 2 <sup>nd</sup> volume
muscles	<i>Arnica montana</i> (Arnica)	pp. 714-715 2 <sup>nd</sup> volume
nerves (restoration)	<i>Hypericum perforatum</i> (St. John's Wort)	pp. 1249-1252 2 <sup>nd</sup> volume
nerves (pain)	<i>Papaver somniferum</i> (Poppy)	pp. 961-968 2 <sup>nd</sup> volume
skin / mucous membranes	<i>Calendula officinalis</i> (Calendula)	pp. 710-714 2 <sup>nd</sup> volume
stomach	<i>Matricaria chamomilla</i> (Chamomile)	pp. 58-68 1 <sup>st</sup> volume
uro-genital tract (andrology)	<i>Urtica dioica</i> / <i>Urtica urens</i> (Nettle)	pp. 920-924 2 <sup>nd</sup> volume

#### **4.5.4 Definition of use-categories**

The attribution of indications from historical texts to biomedical disease categories requires the development of a coding framework that can capture the varied therapeutic uses of medicinal plants in historical medical texts. The therapeutic use-category concepts of Heinrich et al. (2006, p. 158), Will (2009, p. 20), Dal Cero (2016, p. 25), and Staub et al. (2016, p. 1045) provided a fitting starting point. The use-categories defined in this study refer to body systems and to anatomical sites, except for the use-categories cancer and infection, and for two use-categories that reference a therapeutic action, apotropaic and tonic. A tonic is understood here as an agent that is able to support, restore, or maintain the physiological functioning of an organ system, leading to the subjective feeling of well-being (Götti, Melzer, & Saller, 2014).

The use-categories are defined as follows:

<b>Use-categories <i>abbreviation</i></b>	<b>Contemporary terminology</b>
Apotropaic <i>apotrop</i>	antidote, against poisons, against external threats, talisman
Cancer <i>cancer</i>	malignant growths and knots, cancer
Cardio-vascular system <i>card-vasc</i>	heart, arteries, veins, and vessels, circulation, shock
Digestion <i>gastro-intest</i>	stomach and intestines: weak digestion, diarrhoea, constipation, parasites, worms, gastro-intestinal infection
Endocrine system <i>hormonal</i>	glands, hormones, metabolism
Gynaecology <i>gyn</i>	menstruation, fertility, abortion, obstetrics, puerperium, maternity, menopause
Head <i>head</i>	eyes, ears, teeth, brain, cognition, memory
Infection (systemic) <i>infection</i>	systemic infections: malaria, blood poisoning / septicaemia, fever
Liver / Gallbladder / Spleen <i>liver-spleen</i>	liver and gall bladder complaints: gallstones, nausea, dyspepsia, liver detoxification; blood building (in humoralism) spleen: digestive issues, humoral detoxification
Musculo-skeletal system <i>musc-skel</i>	muscles, bones, tendons, ligaments, joints
Nervous system <i>nerve</i>	pain, neuralgia, headache, injuries, sleep, dreams
Respiratory tract <i>respiratory</i>	upper respiratory tract: nose, sinuses, throat lower respiratory tract: bronchi, lungs
Sexual function <i>sex</i>	sexual function, sexual dysfunction, aphrodisiac, anaphrodisiac
Skin / mucous membranes <i>skin-mucous</i>	wounds, burns, ulcers, skin inflammation, mucous membranes of the mouth and gastro-intestinal tract
Skin / mucous membranes <i>skin-mucous cleanse</i>	topical drainage, cleansing of tissues
Somatoform disorders <i>somatoform</i>	state of mind: mood, sadness, depression, melancholy, dysphoria, anxiety, courage, drive
Tonic <i>tonic</i>	systemic effects: invigoration, euphoria, to alleviate exhaustion
Urinary tract <i>uro</i>	kidney and bladder complaints, oedema, gravel and stones, infection, voiding disorders, enuresis (bed wetting)

#### 4.5.5 Explanatory notes to the use-categories

- Spleen disorders are attributed to the liver-spleen category and not to a separate lymphatic category because in ancient Greek medicine the spleen was co-responsible for humoral balance of digestive processes (Staub et al., 2016, p. 1045).
- In pre-modern times, biliary disturbances were seen to cause both indigestion and

melancholy (Francia & Stobart, 2014, p. 301; Wirsung & Tabernaemontanus, 1577, p. 297). Therefore, the attribution of a complaint to either the liver-spleen category or to the somatoform disorders category can only be interpreted through context. For example, the indication to chase excess black (bile) as discussed by Tabernaemontanus references a humoral concept and relates to the elimination of melancholy; *melas* is Greek for black and *kholē* is Greek for bile. In humoralism, fear, sadness, gloom, and fright were seen as typical symptoms of ‘melan-cholic’ illnesses (Zimmermann, 1975, pp. 91-96). Such mental and emotional afflictions are today commonly referenced as depression (Tschupp, 1998, pp. 44-47). Consequently, this indication is attributed to the somatoform category. In contrast, when Tabernaemontanus describes the liver cleansing benefit of *reiniget Leber*, this phrase probably relates not only to the liver as an organ but also to its humoral blood building function (Stolberg, 2003, p. 121). Liver indications are attributed to the liver-spleen category.

- The term *Ader* references *strangförmiges Gebilde* (strand-like formation) (Mildenberger, 1997, p. 38). *Ader*, *Sehnader*, *Sennader* or *Geäder* may include ligaments, tendons, fascia, nerves, and muscles (DWB, 1854-1960, pp. Band 16, Sp. 148; Mildenberger, 1997, pp. 38-40, 665). By extension, the term *Nerven* could possibly have had a wider application than the contemporary biomedical definition of ‘nerves’ and could have included tendons and ligaments depending on context (Haubrich, 2003, p. 156).

#### 4.5.6 Attribution of historical indications to use-categories

For the purpose of this thesis, the German term *Anwendungsnennung* is translated as ‘indication of use’ or ‘indication’ for short. This translation aligns with the terminology used in other research projects (Mayer-Nicolai, 2009; Tobyn et al., 2011, p. ix; Will, 2009), and reflects the term ‘therapeutic indication’ used in herbal monographs authored by the EU. An ‘indication’ covers the reason for or situation in which a medicinal plant is used. Therefore, the term is interchangeable with ‘use report’. In this thesis, the word ‘indication’ does not imply its contemporary biomedical meaning which refers to the use of a specific drug for treating of a biomedical disease as approved by a regulatory authority; although it may relate to such a specific biomedically defined indication when an indication is used in the context of clinical trials. This biomedical sense will be noted when it occurs.

As noted, the attributions of historical indications to use-categories predominantly reflect the anatomical site of the discussed complaint or, alternatively, the affected body system. Although most indications are attributed to one use-category only, an indication may in some instances span over two or more categories. For example, if an author explains the anatomical site of a complaint as well as the pharmacological action of the plant chosen for treatment, this pharmacological action is additionally noted under the corresponding use-category. The following are some explanatory examples of attributions made in this way:

- Muscle pain is attributed to the musculo-skeletal use-category (musc-skel) as the anatomical site of complaint as well as to the nervous system (nerve) use-category since the plant is discussed as a pain-relieving remedy.
- Bleeding is categorised under the respiratory tract use-category (respiratory) if the indication references spewing blood from the chest, under the muscular-skeletal system use-category (musc-skel) if the text references an anti-ecchymotic action (reabsorption of blood in bruises), to the skin-mucous membrane use-category (skin-mucous) if a styptic action on an externally bleeding wound is discussed, or to the gynaecology use-category (gyn) if the reference is to menstrual bleeding. Bleeding of the eye or brain is referenced to the anatomical location (head) as well as to the cardiovascular (card-vasc) use-category to reflect systemic styptic action.
- Headaches can span across two or more use-categories. The anatomical site is the head (head). If an explanation is given (e.g. headaches due to menstruation), the indication is also noted under gynaecology (gyn). If nervous tension is described as the cause, the indication is also noted under nervous system use-category (nerve).
- If the text discusses infections of a specific body system, the indication is listed under that use-category. For example, the treatment of an infection of the digestive tract is listed under gastro-intest or the treatment of an infection of the respiratory tract under respiratory. If an infection is referenced as systemic in nature without a reference to a specific body part or system, its indication is allocated to the generic category of infections (infection), as is the case with malaria.
- Strokes are attributed to the cardio-vascular use-category (card-vasc) if the author discusses a plant's circulatory effect, to the nervous system use-category if the stroke was said to have been caused by nerve injuries, and/or to the head use-category if the author discusses the anatomical location.

#### 4.5.7 Botanical nomenclature

The establishment of the scientific nomenclature of a medicinal plant is a prerequisite for valid research outcomes (Bennett & Balick, 2014; Heinrich & Verpoorte, 2014; Rivera et al., 2014). To avoid ambiguities and errors, and so that related information on indications and safety can qualify for regulatory purposes, the botanical nomenclature of medicinal plants described in historical medical textbooks must therefore be established unequivocally.

The following resources were selected to validate and check botanical nomenclature. This selection was based on and expands previous research that successfully identified historical plant species with a similar approach (Will, 2009, pp. 13-14):

- a) the plant can be identified with reference to the historic plant dictionaries of Marzell and Wißmann (2000) and Mildenerger (1997)
- b) synonyms listed in Tabernaemontanus, together with the plant illustration, can be identified via Marzell and Wißmann (2000) or (Mildenerger, 1997)
- c) the plant has been conclusively identified by Marzell and Wißmann (2000) in other medical textbooks of the same historical period such as in Fuchs (1543), Bock (1577), Brunfels (1532)
- d) the plant has been conclusively identified by Baumann in Fuchs under reference to Linnaeus, Schinz, Sprengler, Dierbach, Kirschleger, Hatton, Sprague & Nelmes, Rytz, Marzell and Meyer (Baumann, Baumann, & Baumann-Schleifhauf, 2001, pp. 51-56)
- e) the plant has been conclusively identified by Will in Brunschwig (Will, 2009)
- f) the historical plant name conclusively corresponds with the botanical name mentioned in a contemporaneous German or English language medical textbook such as in Fuchs (1543), Bock (1577), Brunfels (1532), Gerard (1633), or Turner (1562)
- g) the historic plant name conclusively corresponds with the contemporary name
- h) the plant name can be identified via deductive reasoning, but
- i) a plant name that can only be guessed by deductive reasoning must be discounted.

In a further step, a plant name is cross-referenced with a botanical nomenclature database, the International Plant Names Index (IPNI), to align the historical name with the most up-to-date contemporary botanical name of the plant. IPNI is a collaboration between The

Royal Botanic Gardens, Kew, The Harvard University Herbaria, and The Australian National Herbarium.

#### **4.5.8 Organisation of Historic Data Excel spreadsheet**

The primary data were collated into the Historic Data Excel spreadsheet as a reference for independent verification. They underpin the tables constructed via the Historical Assessment Tool. Each indication was recorded by year of listing, author, type of textbook, page number, botanical identity (taxon, species name in German, English, Latin, vernacular or foreign plant names), plant part used, harvest advice, cautions, preparation (mode of administration), method of plant preparation (fresh or dry), application (topical and/or systemic), dosage, use-category, type of medical system where applied (regular, traditional or folk medicine), and original text (for independent cross-reference). The following sections establish the labels used for the recording of this primary data.

##### **4.5.8.1 Labels for plant parts**

Plant parts parts corresponding to the descriptions in the sources:

flores	folium	radix
flores con receptaculis	folium, flores	rhizome
flores sine receptaculis	herba	semen
flores (summitates)	herba, folium	
flores, herba (summitates)	planta tota cum flores	

#### 4.5.8.2 Labels for plant preparations

Pharmaceutical preparations corresponding to the descriptions in the sources, as translated from German to English:

ash (salt)	extract – wine	poultice
bath	food	powder
capsules/tablets	fumigation	rub
compress	gargle	rub with fresh plants
cream / ointment / gel	honey preparation	smoking
distillate	hydrosol	snuff
drug	injection	spiritus/schnapps
electuary	juice of fresh plants	steam bath (inhalation)
enema	mead	syrup
essential oil	oil	tincture
extract	paper/charta	wash
extract – beer	peccary	water extract/tea

#### 4.5.8.3 Labels for source type

Types of bibliographic sources used for the analysis:

<b>Advice Literature</b>	Practical health advice written by physicians or non-physician herbal experts for lay people (not in the final selection)
<b>Medical Textbook</b>	A medical text written by a university-educated practising physician or apothecary (authoritative)
<b>Com Ph</b>	An academic commentary to a pharmacopoeia (authoritative)
<b>Monograph</b>	A comprehensive text on a single medicinal plant (official or authoritative)
<b>Ph</b>	Pharmacopoeia (official)
<b>Ph - Hom</b>	Pharmacopoeia for homeopathic, traditional, and anthroposophical preparations (official)
<b>Ph Supplement</b>	Pharmacopoeia supplement (authoritative)

#### 4.5.8.4 Conversion of weights

The selected text from the early modern period, *New vollkommen Kräuter-Buch* (Tabernaemontanus, 1664), was printed at a time before measurements and weights were standardised across central Europe and when regions, cities, and even different professions implemented their own standards (Schmitz, 1998, pp. 446-447). In this study, the

conversion of weights is based on the official apothecary weights of the city of Basel, Switzerland, where the *New vollkommen Kräuter-Buch* was printed (Mildenberger, 1997).

#### **4.6 Background and selection of medical textbooks as sources of evidence**

Medicines derived from plants have dominated the medical landscape for most of human history and are also a vital part of European medical and cultural history (Kyrou et al., 2017; Stille, 2004; Tshongo Muhindo, Ahn, Rousseau, Dierckxsens, & Hermans, 2017). To understand the regulatory situation in Europe, it is necessary to appreciate the central role of professional transmission of empirical knowledge on medicinal plants in regular European healthcare. This section first contextualises the historical significance of the botanical *materia medica* literature and then provides a summary of each of the textbooks selected for this study of the period from the 16<sup>th</sup> to the 21<sup>st</sup> century. The following short synopsis focuses on written transmission, but this thesis recognises that such written transmission co-existed alongside various forms of oral traditions and that those traditions influenced each other (Touwaide & Appetiti, 2015). The oral transmission of knowledge is, however, outside of the scope of this thesis.

Documentary evidence on the therapeutics used by European physicians confirms that medical, pharmaceutical, and botanical knowledge of therapeutic substances has been consistently recorded for more than 2500 years. Medicinal plants provided mainstream medicines well into the middle of the 20<sup>th</sup> century (De Vos, 2010; Schmitz, 1998; Schmitz et al., 2005). Influences on the European medical tradition can be traced back to Mesopotamia and later to Egypt with its pharmacopoeia of *Ebers Papyrus* (1500 BC). However, the basis of European medicine was laid down in classical Greece and during the Roman Empire, being grounded in the natural philosophy of Aristotle. Influential physicians and philosophers started to build written consensus about what was considered efficacious medicine (Leonti & Verpoorte, 2017, p. 162). Pharmacological and pharmacobotanical knowledge was presented in monographs and transmitted over the following millennia (Heinrich & Anagnostou, 2017). The most eminent classical authors were Hippocrates of Kos (ca. 460-370 BC) and his successors who wrote the *Corpus Hippocraticum*, a collection of medical treatises (Uehleke & Kraft, 2001, p. 246). The ensuing medical texts by the Roman army physician Pedanios Dioscorides (1<sup>st</sup> century AD) and those authored about a century later by the Greek physician Galen of Pergamon became the most influential classical herbals ever written. They profoundly shaped European

medicine through their continuous dissemination of empirical knowledge on medicinal plants until the end of the 18<sup>th</sup> century (Leonti & Verpoorte, 2017, p. 162). Dioscorides, who systematically described in his *De Materia Medica* around 500 medical plant species as well as 90 mineral and 35 animal drugs, documented the medical, pharmaceutical, and botanical knowledge in the style of a medical encyclopaedia (Dal Cero, Saller, & Weckerle, 2014, p. 255; Riddle, 1985). From then on, the term *materia medica* was applied to all medical textbooks where medical experts systematically authored in-depth monographs on therapeutic substances.

Over the centuries educated physicians integrated local, foreign, or experientially-gained knowledge on the pharmacological effects of medicinal plants into a formal scientific framework of explanation, which reflected the theoretical understanding of their time (Touwaide, 2005, pp. 169-170). Translations of this Greek and Byzantine medical knowledge into Syriac, a dialect of Middle Aramaic, facilitated the transmission of the classical body of knowledge into Arabic and thus into the medieval Islamic world where it was not only preserved but developed further and transmitted back to the West through the pioneering work of Avicenna (1000 AD), the School of Salerno (ca. 1000-1300 AD), and the body of work created during the period of al-Andalus (711-1492 AD) (Russell, 2009). During the Middle-ages, Benedictine monks were directed by monastic rule to duplicate herbals, thus preserving the European tradition. The invention of a mechanised printing press in the 15<sup>th</sup> century by the German goldsmith Johannes Gutenberg (ca. 1400-1468) enabled the mass production of medical textbooks and their wide dissemination. From the 16<sup>th</sup> century onwards, such texts were predominantly authored by university-educated physicians (Pugliano, 2017, p. 238).

The early modern period marks a new approach to the documentation of medical knowledge and healthcare. Practitioners no longer relied solely on written texts or library medicine, a common feature of medieval medicine; rather, they moved towards systematic, clinical observation such as bedside medicine and epidemiology (Ackerknecht, 1992, pp. 96, 146). The spirit of the Renaissance fostered empirical science and rekindled interest in classical scholarship and ancient Graeco-Roman medical knowledge under the motto *ad fontes* (Dilg, 2001; Porter, 2003, p. 171). Thus, Renaissance-inspired authors of medical compendiums and pharmacopoeias presented themselves as both reenactors of the ‘true’, classical knowledge as well as creators of new knowledge (Pugliano, 2017).

From the end of the Middle Ages and beginning of the early modern period, the European *materia medica* was recorded in opulent, elaborate, and magnificently illustrated herbals. The medical information was systematically presented following scientific rules similar to those displayed in today's textbooks. The logical, systematic framework provides an alphabetical index of medicinal plants, their botanical description and synonyms for identification, clinical indications, and ailments in humans and animals (Clair, 2011; Schmitz, 1998, pp. 403-418). The era is regarded as the pinnacle of clinical plant knowledge. Medical texts from the early modern period incorporated empirical scholarship of ancient Greek, Roman, Byzantine, medieval Islamic, and European oral and written medical tradition alongside new insights and plant monographs from central and northern European medicine, complementing the Mediterranean flora discussed in the antique Greek herbals. They added new genera and species from newly discovered territories (Adams, Alther, et al., 2011; Adams et al., 2009; Adams, Gschwind, et al., 2011; Adams et al., 2010; Bofinger, 2004; Dal Cero, Saller, & Weckerle, 2013). For example, the medical commentary to Dioscorides' *De Materia Medica* (1544) by Andrea Matthioli (1501-1578) described an additional 600 medicinal plant species (Leonti & Verpoorte, 2017, p. 164). The influential *New Kreüterbuch* (1543) by the German professor of medicine and botany Leonhart Fuchs (1501-1566) lists around 100 new medicinal plants not previously described in Germany (Heide, 2001). These comprehensive herbals from the early modern period became the predecessors of today's official pharmacopoeias and modern herbal monographs. They are rooted in the Graeco-Roman and Arabic tradition. Consequently, this analysis starts with a text from that period. The therapeutic applications recorded in the ensuing medical textbooks reflect the ongoing transmission of clinical knowledge on medicinal plants across the paradigmatic, socio-economic and political-legal changes of over 400 years. This body of literature falls under the WHO description of a codified system of traditional medicine. It has been disclosed in writing in ancient scriptures, is fully in the public domain, and has been passed on from generation to generation (Intergovernmental Committee on Intellectual Property and Genetic Resources Traditional Knowledge and Folklore, 2010, Annex, p.7).

#### **4.6.1 17<sup>th</sup> century: Tabernaemontanus *New vollkommen Kräuter-Buch* (1664)**

Humanism, the intellectual exploration of human nature freely and critically, laid the scholarly foundations for the work of the Protestant physician, apothecary, and professor of

medicine and botany Theodorus Jacobus Tabernaemontanus, born Jakob Theodor (1520-1590), and his systematic vetting of the European *materia medica* with clinical observation (Clair, 2011). Despite his lasting influence, Tabernaemontanus received relatively late historical attention (Schanz, 2009, p. 42). Medical historians and archivists, namely Sprengel (1817), Sachs (1875), Leyser (1881), Roth (1898), Buttman (1898), Hoffmann (1940), Figala (1974), Becker (1984), Carlé (1964a, 1964b), and Künkle and Lorenz (1988) recovered fragments of original data about his life and work, but it was not until the research of Müller-Jahncke (1982), Reiser (1989), Bergdolt (1990, 1992), and most importantly Bofinger (2004; Müller-Jahncke & Bofinger, 2003) that more comprehensive insights into his impact in the transmission of the European *materia medica* emerged (Clair, 2011). His lasting influence on medicine and botany is not only evident in central Europe (Sachs, 1875; Sprengel, 1817; Tillmann, 1988; Übel, 1990; Volz, 1990) but also in Great Britain via his professional and personal exchanges with the English physicians, botanists and medical authors William Turner (1508-1568) (Turner, Chapman, Tweddle, & McCombie, 1995) and John Gerard (1545-1612). Gerard made liberal use of information published in Tabernaemontanus' *New vollkommen Kräuter-Buch* and of his illustrations from *Icones stirpium* (1590) (Gerard, 1633; Schanz, 2009, p. 43). 18<sup>th</sup> century Swedish botanist Carl von Linné (Linnaeus) named the pan-tropical genus *Tabernaemontana* with its exquisitely flowering shrubs and small trees in his honour. The English literature on early modern herbals is yet to acknowledge his contribution to botanical pharmacy, as exemplified in Arber's incomplete appraisal of early modern herbals or Pavord's selective cultural history of botany (Arber, 1912/1938, p. 76; Pavord, 2005).

Tabernaemontanus' *opus magnum*, the *Neuw Kreuterbuch*, later called *New vollkommen Kräuter-Buch*, was first published in 1588 (vol 1), with volumes 2 and 3 posthumously published in 1591 in Frankfurt, Germany. After further editions in 1613 and 1625, the tomes were subsequently edited and published in Basel, Switzerland (Tabernaemontanus, 1588, 1591, 1613, 1625, 1664, 1687, 1731). The updated edition of 1664, which includes addenda by two physicians and botanists from the University of Basel, was re-printed unchanged until 1731 and is selected as *pars pro toto* for medical practice in the early modern period. This textbook fulfils all selection criteria as laid out.

While humoral concepts still influenced Tabernaemontanus, his medical textbooks represent a new era of medical writing, one that integrates evaluated clinical advice from an

experienced physician, detailed botanical information including precise graphic plant representations, and guidelines on pharmaceutical compounding. Comparing the first volume solely authored by Tabernaemontanus with the second and third volumes that the German professor of medicine Nikolaus Braun (1558-1639) completed after the author's death using printing blocks and notes left behind, it is evident that Tabernaemontanus added more detailed observations than contemporaries who continued to follow more closely the medical paradigm formalised by Galen (Baumann, 1998, pp. 105-108, 175, 237). With his practical medical, pharmaceutical and botanical experience, Tabernaemontanus documented insightful observations in great detail. In this respect, his approach to medicine was closer to Dioscorides who, unlike Galen, wrote his influential medical text *De Materia Medica* as a practical pharmacopoeia without linkage to transitory medical theories (Riddle, 1985, p. xix). This practical approach to the European *materia medica*, the clinical vetting of what works and what does not, may explain why, despite fluctuations in medical concepts over time, plant indications have enjoyed remarkable longevity, as validated by modern science.

Tabernaemontanus advocated the use of local medicinal plants instead of exotic ones and described local species not described by Dioscorides (Tschirch, 1909a, p. 21). His interest in local plants did not preclude him from writing extensive monographs on imported drugs such as Cinnamon, Cardamom, and Nigella. As a student of two of the three 'fathers of modern botany' (Bergdolt, 1992)—the German physicians Otto Brunfels (1488-1535) and Hieronymus Bock (1498- 1554)—, Tabernaemontanus also advanced the classification of plants, thus contributing in crucial aspects to the development of the botanical binary nomenclature formalised later by the Swedish physician and botanist Carl von Linné (1707-1778) (Bofinger, 2004). The scientific approach and systematic arrangement of monographs, the comprehensive register of medicinal plants in 10 languages, and the register for ailments and preparations allow a logical way to navigate the large tome that incorporates the description of over 3000 medicinal plants over 1500 pages. The preface references 111 ancient, medieval, and contemporary authors, and more authors are referenced in the text itself. The *materia medica* expands on ancient Greek, Arabic, and European medieval sources. It includes customary medicinal plants from central Europe and floras that are largely absent in Dioscorides' classical *De Materia Medica* and subsequent European herbals (Adams et al., 2012, p. 11). Tabernaemontanus' description of *Arnica montana* is such an instance. Furthermore, he provides descriptions of galenic preparations that were not previously explained in other herbals (Richter, 1998, pp. 220-221, 233-234).

His medical encyclopaedia on European therapeutics became recognised by both physicians and lay practitioners as the most comprehensive and reliable summary of medical knowledge of the preceding two millennia (Steinke & Meier, 2003, pp. 31-32). It surpasses earlier and later herbal treatises regarding the number of medicinal plants discussed, precision of indications, and practical advice (Heilmann, 1973, p. 35). Written and published shortly before the Thirty Years War (1618-1648) devastated much of Europe's bibliographic reference collections, it remains the most comprehensive repository of European botanical therapeutics (Bofinger, 2004).

The author's clinical approach to the *materia medica* influenced the academic medical education and practice of European physicians for the next 200 years (Friedrich & Müller-Jahnke, 2005, p. 115). Additionally, the plant monographs in *New vollkommen Kräuter-Buch* were integrated in Johann Heinrich Zedler's *Grosses, vollständiges Universal-Lexicon* (universal dictionary) (Zedler, 1732-1754), the largest German language encyclopaedia of the 18<sup>th</sup> century. It served as a clinical guide for priests extending their spiritual care to the physical health of their parish such as the Bavarian pastor Sebastian Kneipp or Swiss pastor Johann Künzle. Additionally, it was used as a reference for lay self-care (Bergdolt, 1990, 1992; Clair, 2011; Mägdefrau, 1992; Schmid, 1939). Apart from its multiple editions, the popularity of this medical textbook is demonstrated, for instance, by the Vester Sammlung, a large repository of significant historical-pharmaceutical textbooks hosted at the *Universitäts- und Landesbibliothek Düsseldorf* that has 108 medical textbooks and encyclopaedias referencing Tabernaemontanus. Most quotations are recorded in 18<sup>th</sup> and 19<sup>th</sup> century sources with some also in 20<sup>th</sup> century texts.

#### **4.6.2 18<sup>th</sup> century: Löseke and Plenck**

Tabernaemontanus' textbook was last printed in 1731 so this data analysis continues with a subsequent text from the late 18<sup>th</sup> century: the 6<sup>th</sup> and last edition of the teaching textbook of Johann Ludwig Leberecht Löseke's *Materia medica* (Löseke & Gmelin, 1790). This textbook aligns with the publication of the 1<sup>st</sup> edition of the Prussian pharmacopoeia which will be explored in a later section.

##### **4.6.2.1 Löseke (1724-1757)**

Johann Ludwig Leberecht Löseke was a practising physician and lecturer at the Prussian university of Halle, now in Saxony-Anhalt. Luminaries at the newly founded University of

Halle (1694), such as Georg Ernst Stahl (1660-1734) and Löseke, defended the vitalistic principles said to underpin human physiology against the upcoming speculative theories of iatrochemists and iatrophysics (Ackerknecht, 1992, pp. 128-129). The first edition of Löseke's *Materia medica oder Abhandlung von den auserlesenen Arzneymitteln: Nach derselben Ursprung, Güte, Bestandtheilen, Maße und Art zu wirken nebst Vorschriften wie dieselben aus der Apotheke zu verordnen sind* was printed in Berlin in 1754. By the 4<sup>th</sup> edition published in 1776, it is said to have become an important reference text for surgeons and physicians. It was also used as a lecture script at several universities (Löseke & Zückert, 1776, p. Vorwort). After Löseke's early death, the textbook continued to be published by medical colleagues, initially by Johann Friedrich Zückert, and later by Johann Friedrich Gmelin, who in addition to practising medicine was also a chemist. Löseke's *Materia medica* was extensively quoted for the next 100 years, including in the English medical literature (D.V., 1829; Pereira, 1854).

Löseke emphasises the importance of empirical knowledge for science. This approach aligns with other influential contemporaries such as the German physician Friedrich Hoffmann (1660-1742), who proclaimed the slogan “reasoning plus experience” (Ackerknecht, 1992, p. 129). Löseke is not concerned with why a drug works, being satisfied with repeated clinical observation that it did in fact work, as for example with opium for pain relief or Cinchona bark for the treatment of malaria (Löseke & Zückert, 1776, Vorbericht des Verfassers). The author references a wide-ranging collection of medical literature and experimental and academic research, mainly by authors from the 16<sup>th</sup> to the 18<sup>th</sup> century. Tabernaemontanus and Matthioli are two of his key medical references, and Linnaeus (1707-1778) provides the ultimate compendia for ensuring botanical accuracy in Löseke's *Materia medica*.

Löseke expresses fascination towards the chemical discoveries made during his lifetime and lauds the endeavours of chemists in discovering presumed active principles and modes of actions of medicinal plants. Yet the main therapeutics in his *Materia medica* remain whole plant medicines, reflecting mainstream medical practice of his time (Löseke & Gmelin, 1790, p. 5; Schmitz, 1998, pp. 403-406). Each plant monograph provides information on therapeutic actions as well as contraindications where required. In a time when Paracelsus inspired heroic drug therapies with toxic heavy metals such as mercury, lead, and arsenic—which then became fashionable (Ackerknecht, 1992, p. 144)—and when physicians aspired

to be seen as modern scientists (Wulle, 1999, pp. 94-95), the author warns colleagues against the use of “*heftige und neuerfundene Arzneyen*” (violent and invented medicines) (Löseke & Zückert, 1776, p. Vorbericht des Verfassers). Both his fascination with and concern about the influence of chemistry on medicine illustrate the interplay between old medical paradigms of that time such as humoralism, and the emerging natural science-based ones. 18<sup>th</sup> century physicians faced many uncertainties with the rapid changes in medical theory and pharmaceutical practice that led European medicine to the era of chemical laboratory medicine (Ackerknecht, 1992).

#### 4.6.2.2 Plenck (1735-1807)

For the analysis of St. John’s Wort, it was necessary to include one extra text from the late 18<sup>th</sup> century. A cross-validation with other medical textbooks revealed that the shortness of Löseke’s *Hypericum perforatum* entry is not mirrored in other contemporaneous medical textbooks which originate from warmer climate zones of Europe where St. John’s Wort grows more prolifically, for example in Switzerland or Austria. This highlights the fact that traditions may also be defined across the 12 global climate zones with their various habitats and those may influence the selection of medicinal plants discussed in regional medical textbooks. For example, the influential Swiss physician, botanist, anatomist, and natural scientist Albrecht von Haller (1708-1777) (Steinke, Boschung, & Pross, 2009) references St. John’s Wort in his seminal but unofficial first edition of the *Pharmacopoeia Helvetica* on no less than 24 different pages (Haller, 1771, pp. 85-86, (II) 38-40, 67, 106-108, 110-111, 150-151, 155, 201, 203, 235, 274-275, 280-281, 306, 315, 334). This quantity of references on medical uses highlights the continued significance of St. John’s Wort in some regions of Europe, even when under the experimental scrutiny of natural science during the Age of Enlightenment. Likewise, the *Icones Plantarum Medicinalium* by Josephus Andreas Jacobus Plenck (1735-1807), an Austrian physician, surgeon, obstetrician pharmacologist, chemist, and lecturer at the University of Tyrnau correspondingly lists multiple medical uses of St. John’s Wort (1794, p. 57). Plenck was an influential medical authority of the 18<sup>th</sup> century, and his clinical teaching textbook was widely used and quoted (De Santo, Aliotta, De Santo, & Aliotta, 2002). It fulfils the selection criteria established in 4.4.3 and is thus selected for this analysis. Plenck’s medical writing highlights how the therapeutic indications of this period were informed both by tradition and by novel natural science (Richter, 1998, pp. 303-306).

### 4.6.3 19<sup>th</sup> century: Richter, Strumpf, and Hager

The first quarter of the 19<sup>th</sup> century exhibits the widening paradigmatic divide in medical theory. There were now numerous divergent approaches to clinical medicine and its *materia medica*, all grounded in different methodologies influenced by historical, theoretical, philosophical, empirical, and experimental considerations (von Engelhardt, 2000, pp. 144-145).

#### 4.6.3.1 Richter (1778-1832)

Georg August Richter (1778-1832), physician and professor of *Praktische Heilkunde* (practical medical science) at the Prussian University of Königsberg, authored the influential teaching series for clinicians *Ausführliche Arzneimittellehre. Handbuch für praktische Aerzte* in 6 volumes (Richter, 1826, 1827, 1828, 1829, 1830, 1832). Richter based his textbook series on a synthesis of clinical notes from his surgeon father, on influential physicians such as Christoph Wilhelm Hufeland (1762-1836), on his own repeated empirical observations, and on his collection of scientific research that he systematically recorded from 1812 onwards. His academic teaching text stands out for the detailed explanations of pharmacodynamic properties of medical plants on the human organism, providing a deeper understanding about how physicians at that time saw the actions of plant drugs beyond specific medical indications.

Richter highlights the “*Verwirrung*” (confusion) and “*Widersprüche*” (contradictions) amongst opposing medical theories and movements at the time (Richter, 1826, pp. V-XII). His stated motivation for the textbook series is to synthesise medical information for practising physicians as an aid during a time of paradigmatic upheaval, where ‘passions, authorities, egotism, blind empiricism, speculative philosophies and hair-splitting dogmatism’ caused significant confusion in medicine (Richter, 1826, pp. V-VI). In this period, long-standing whole plant drugs increasingly competed with isolated actives such as morphine, emetine, quinine, piperine, gentianin, lupulin, and atropine (Richter, 1998, p. 308). Like Löseke before him, Richter defends the inclusion of traditional medicines and states that the proposed exclusions of such well-established drugs by some have more to do with individual preferences than with the actual usefulness of a drug.

#### 4.6.3.2 Strumpf (no biographical dates)

Prussian physician Ferdinand Ludwig Strumpf, a Hofrath (civil service title roughly

equivalent to privy councillor) and town physician of Strassfurt before working in private practice in Berlin, produced the two-volume pharmacology textbook *Systematisches Handbuch der Arzneimittellehre* (Strumpf, 1848, 1855). These volumes continue to highlight efforts during the middle of the 19<sup>th</sup> century to hold onto a complete and trustworthy *materia medica* while also being open to new chemical discoveries. The scholarly structured academic teaching text is dedicated to Karl Gustav Mitscherlich, professor of pharmacology at the Friedrich-Wilhelm University in Berlin, and claims to comprehensively reflect contemporaneous pharmacology (Strumpf, 1848, p. VIII). Its aim is to provide physicians with a wide choice of medicines and rehabilitate what the author sees as the unjustifiable dismissal of traditional medicines by illustrating their therapeutic worth in practical patient care (Strumpf, 1848, p. VII). Strumpf's clinical observations and case reports provide insight into the dynamics of a mid-19<sup>th</sup> century clinical practice.

The textbook includes all official medicinal substances listed in the *Prussian pharmacopoeia*, as well as recently classified 'obsolete' medicines, alongside a small number of newly synthesised chemical drugs. It provides an extensive scientific literature review and information on historical medical uses, taxonomy, botany, chemical properties, preparations, pharmacodynamics effects, indications, clinical observations, and side effects. The author quotes Tabernaemontanus in the historical section, confirming the lasting influence of his medical authority (Strumpf, 1855, p. 47).

#### **4.6.3.3 Hager (1816-1897)**

Hermann Hager's three-volume pharmacology textbook *Handbuch der pharmaceutischen Praxis. Für Apotheker, Ärzte, Drogisten und Medicinalbeamte* is selected to represent the last third of the 19<sup>th</sup> century (Hager, 1876, 1878, 1883c). The Prussian author (1816-1897) was a prominent practising apothecary, pharmacologist, and chemist. He was also one of the most prolific and influential authors of pharmaceutical and botanical works in the 19<sup>th</sup> century (Kerstein, 1966, pp. 470-471). Apart from his serial translations and commentaries on the Prussian and German pharmacopoeias (Hager, 1865, 1873, 1874, 1883a, 1883b, 1884, 1892; Hager, Fischer, & Hartwich, 1891, 1892, 1895), his standard textbook *Hagers Handbuch der pharmaceutischen Praxis* left a legacy that reaches into the 21<sup>st</sup> century. This pharmaceutical reference text has been continuously updated and is available electronically as *HagerROM*. *Hagers Handbuch der Drogen und Arzneistoffe* (HagerROM, 2016).

The wide selection of chemical drugs discussed alongside traditional plant medicines in Hager's textbooks makes evident that the natural science-based medical paradigm is becoming strongly present for the first time. Trade in medicinal plants declined by the end of the industrial revolution when industrially mass produced synthetic drugs became widespread (Richter, 1998, p. 362). Natural science orientated physicians now exhibited strong scepticism against traditionally endorsed medicinal plants if their effectiveness could not be experimentally explained—to the extreme that this attitude led to therapeutic nihilism by some medical schools (Richter, 1998, p. 362; Schott, 2000). Nonetheless, Hager discusses numerous traditionally used medicinal plants in line with their listings in official pharmacopoeias and their demand in apothecaries, albeit in an abbreviated fashion.

#### **4.6.4 20<sup>th</sup> century: Schulz, Madaus, Kroeber, Weiss, and Saller et al.**

While at the beginning of the 20<sup>th</sup> century medicinal plants still provided the majority of drugs in European medicine, they became rapidly displaced by synthetic drugs, despite some increased use during war times. The textbooks selected for this period illustrate the effects of the modern natural science paradigm and its regulatory framework on the traditional *materia medica*.

##### **4.6.4.1 Schulz (1853-1932)**

Hugo Paul Friedrich Schulz (1853-1932), professor of chemistry and pharmacology at the Prussian University of Greifswald, north-eastern Germany, published his university lecture notes on the therapeutic effects and applications of German medicinal plants under the title *Vorlesungen über Wirkungen und Anwendung der deutschen Arzneipflanzen. Für Ärzte und Studierende* (Schulz, 1919). This work achieved 'great recognition' (Madaus, 1938b, p. 56) and became a reference text on the pharmacological actions of medicinal plants (Kroeber, 1948; Saller, Reichling, & Hellenbrecht, 1995). The teaching text by Schulz (1919, p. Vorwort) was aimed at educating physicians and medical students on official plant drugs listed in pharmacopoeias and on plant-based therapeutics commonly used by diverse medical training institutes and by patients. Even though academic medicine at the turn of the century was now moving fast towards the adoption of synthetic drugs as its key therapeutics, Schulz endorses the use of medicinal plants in healthcare by physicians and patients. He claims that this is justified even when a plant's mechanism of action and effectiveness could not yet be explained experimentally (Schulz, 1919, pp. 1-3). Schulz's

defence of folk medicine indicates a widening gap between physicians who were academically grounded in new medical theories and the use of synthetic drugs and many of their patients who adhered to customary medical practices. This division became increasingly obvious after the last quarter of the 19<sup>th</sup> century (Steinke & Meier, 2003, p. 31).

#### **4.6.4.2 Madaus (1890-1942)**

Leading up to WW2, the German physician, mathematician, scientist, and drug company owner from Lower Saxony, Gerhard Madaus (1890-1942), wrote the comprehensive and thoroughly researched three-volume textbook *Lehrbuch der Biologischen Heilmittel* (Madaus, 1938a, 1938b, 1938c). It is still in print today. The aim of his research was to translate extensive traditional knowledge into modern science by drawing from the disciplines of botany, chemistry, pharmacy, pharmacology, and toxicology. This encyclopaedic medical resource aimed to improve the knowledge of his fellow physicians on the effects and applications of 444 local and imported medicinal plants. Based on an ethnomedical approach, on surveys of physicians working in clinics, hospitals, and private practice, on modern scientific research, and on historical appraisals including Tabernaemontanus, he presents systematically collated evidence on medicinal plants of Europe and, to a lesser degree, of other continents (Madaus, 1938b).

The context of Madaus' textbook is the experience of pressures on the medical system in WW1 and the scarcities of synthetic drugs experienced in the period leading up to WW2, which prompted a renewed official focus on plant drugs for mainstream healthcare (Richter, 1998, pp. 350-351). This situation coincided with the realisation that synthetic 'wonder drugs' such as aspirin were linked to serious side effects such as gastritis, gastric bleeding, and Reye syndrome in children (Desborough & Keeling, 2017), hurting the reputation of newly-developed pharmaceutical drugs. Modern medicine was experiencing somewhat of a crisis, prompting cohorts of medical doctors to defer to a natural, constitutional, and neo-Hippocratic approach to patient care (Aschner, 1931, 1937).

#### **4.6.4.3 Kroeber (1872-1951)**

The analysis of how plant medicine was clinically applied in the post-war period focuses on the seminal phyto-pharmacological textbook by the leading German pharmacist Ludwig Kroeber (1872-1951) *Das neuzeitliche Kräuterbuch. Die Arzneipflanzen Deutschlands in alter und neuer Betrachtung* (Kroeber, 1948). It was published shortly after WW2.

Although the selection of this text means that there are only 10 years between Madaus' textbook and this one, Kroeber's work was chosen for two reasons: firstly, it can indicate if the consequences of war impacted the way medicinal plants were used in patient care; and secondly, it endured as an important text for decades and thus merits evaluation. Until the 1970s this three-volume medical compendium (Kroeber, 1947, 1948, 1949b) was consulted as an academic reference for phytotherapeutic courses that were offered as complementary courses alongside academic medical education at some German universities (Professor Dr. med. Reinhard Saller, personal communication, 26.08.2014).

Kroeber was director of the large hospital pharmacy in München Schwabing and a member of the German pharmacopoeia committee. He collaborated with clinicians, chemists, and pharmacologists to write a comprehensive phytotherapeutic textbook aimed at practising physicians, apothecaries, and 'friends of natural healing' (Kroeber, 1949b, p. 477). In this textbook, Kroeber discusses 298 plants and provides a wide range of clinical, experimental, and historical information. Kroeber references Tabernaemontanus and other 16<sup>th</sup> century 'physician-botanists' for their precise and detailed observations, which he says were continuing to 'fertilise' modern medical practice (Kroeber, 1948, p. 21). It is evident that healthcare in the immediate post-war period remained pluralistic and provided a variety of therapies and preparations, including traditional plant medicines, their modern isolates, synthetic drugs, homoeopathic remedies, and other medicines (Flamm, Kroeber, & Seel, 1948, p. 20).

#### **4.6.4.4 Weiss (1885-1991)**

The medical textbook *Lehrbuch der Phytotherapie* (1974) authored by Rudolf Fritz Weiss (1895-1991) heralds a new era of phytotherapy (Weiss, 1974). Weiss was a prominent lecturer on phytotherapy in German postgraduate medical curricula for natural therapies at the *Berliner Akademie für ärztliche Fortbildung* (Berlin Academy for post-graduate medical education), and later in life an honorary professor for the same subject at the University of Tübingen. His academic teaching text is written from the perspective and experience of a practising physician and was initially published in 1944 under the title *Die Pflanzenheilkunde in der ärztlichen Praxis. Vorlesungen an der Berliner Akademie für ärztliche Fortbildung* (Weiss, 1944). From the beginning of his clinical teaching career in 1937, Weiss approached phytotherapy as a scientific and specialised branch of medicine. He claimed that the scientific thoroughness and practical usefulness of phytotherapy did not

lag behind other specialised branches of medicine, and he promoted its permanent inclusion in the medical curriculum (Weiss, 1985, p. 8). His goal was to formulate a modernised representation of traditional plant medicine—phytotherapy—that fits into the context of contemporary mainstream pharmaceutical medicine. Unlike the medical textbooks of his predecessors who presented clinical data in the context of individual plant monographs, Weiss organised the information around organ systems and conditions, thus allowing conventional medical doctors to easily integrate plant-based medicines into their treatment plans. Weiss' distilled clinical experience is highly practical, drawing on his decade-long grounding as an internist.

The 3<sup>rd</sup> edition of Weiss' textbook reflects the position of plant medicine in the 1970s. The 6<sup>th</sup> and last edition Weiss updated and released as the sole author (1985) was translated into English (Weiss, 2001) and continues to be used in academic phytotherapeutic training of English speaking countries, including New Zealand and Australia as witnessed by the author. The ensuing editions, heavily revised and rewritten by the internist Volker Fintelmann, were less well received by clinicians because they lacked some of the previous practical usefulness. Subsequently, it is the 6<sup>th</sup> edition, now referred to as the classic edition, that continues to be reprinted.

#### **4.6.4.5 Saller (1947- ), Reichling (1943- ), and Hellenbrecht (1939-1994)**

Twenty years later, the *Phytotherapie. Klinische, pharmakologische und pharmazeutische Grundlagen* meets the challenge of delivering a rounded picture of scientific evaluation alongside traditional, historical, and regulatory endorsed plant medicine applications in the context of a modern healthcare system (Saller et al., 1995). The three authors bring to this textbook pharmacological and pharmaceutical academic rigor, as well as long-standing expertise with clinical patient work. Reinhard Saller (1947-) is a practising physician and emeritus Professor and Director of the Institute of Complementary Medicine, Department of Internal Medicine, University Hospital Zürich. Jürgen Reichling (1943-) is a practising pharmacist, pharmacologist, and emeritus Professor at the Institute of Pharmacy and Molecular Biotechnology, University of Heidelberg. Dieter Hellenbrecht (1939-1994) was a practising physician and Professor at the Institute of Pharmacology at the Goethe University of Frankfurt, Main. Their comprehensive introduction to phytotherapy for students and health professionals is an original synthesis of the philosophical underpinning of traditional plant medicine, up-to-date pharmacology, and the regulatory realities of modern Western

healthcare systems.

With their firm foundation in patient care, the authors emphasise that the use of traditionally grounded phytotherapy is a paradigmatic decision where evidence from the newly developed RCTs plays an ancillary rather than a leading role in the clinical decision making process (Saller et al., 1995, p. 9). They emphasise that cultural aspects, individual requirements, spiritual needs, and symbolism may play as much a role in a patient's desire for traditional medicines as might the pharmacological effect of the medicinal plant itself (Saller et al., 1995, p. 9). In the authors' view, phytotherapy is particularly well suited for a constitutionally-orientated, personalised medicine that addresses the pathophysiology of a disease as well as the individual situation or terrain that is at the core of the patient's health and illness (Saller et al., 1995, pp. 22-24). As such, the use of plant medicines is not an alternative to conventional, biological science-based medicine, but a distinct-yet-regular part of it. They claim that plant medicines address gaps of care and complement biomedicine in the prevention and treatment of acute and chronic illness (Saller et al., 1995, p. 11).

#### **4.6.5 21<sup>st</sup> century medical textbook: Bäumler (no biographical dates)**

The analysis on clinical uses of plant medicines by practising physicians closes with the textbook *Heilpflanzen Praxis heute. Porträts, Rezepturen, Anwendungen* (Bäumler, 2007), a medicinal plant compendium that was reprinted in quick succession in 2010, 2012 and 2013. Siegfried Bäumler is a senior internist and clinician in both conventional and natural medicine who practises at the Kneippianum, Bad Wörishofen (Munich), a well-frequented German hospital and health resort specialising in natural healing. This textbook aims to provide a practical plant medicine compendium by expanding a science-focused phytotherapy with 'empirical phytotherapy', incorporating repeated observations by generations of practising physicians and long-standing therapeutic uses in folk medicine (Bäumler, 2007, p. VII). The author deems this approach necessary since some medicinal plants have not yet been investigated with contemporary scientific methodologies but have been validated in clinical practice. Bäumler's textbook provides data on botany, pharmacology, and pharmacy, as well as information on traditional, historical, social, philosophical, and mythological context. There are practical treatment recommendations, formulas, and a comprehensive list of indications for easy reference, as well as caveats throughout the text, making it a practical compendium for clinicians.

## 4.7 Pharmacopoeias and their compendiums as sources of evidence: The examples of the Prussian and German pharmacopoeias

Exemplifying the official representation of medicinal plants and attributed indications from the end of the 18<sup>th</sup> century onwards, this thesis investigates all editions, supplements, and commentaries of the *Pharmacopoea Borussica* (the forerunner and most influential pharmacopoeia in pre-unified Germany), the ensuing *Pharmacopoea Germanica* (the official pharmacopoeia of Germany), and the current *Deutsches Arzneibuch* (the German pharmacopoeia named so since 1910). The *Ergänzungsbuch* (supplement) and *Kommentar* (commentary) were two additional necessary texts to support practising physicians and apothecaries because since the end of the 18<sup>th</sup> century pharmacopoeias became reference works for pharmaceutical drug specifications only. This situation reflects the rapidly increasing influence of academically-orientated pharmacists in defining this novel purpose of pharmacopoeias during this time (Tschirch, 1915, p. 497). The section below expands on the Prussian and German pharmacopoeias, their commentaries and supplements.

### 4.7.1 Context of the Prussian pharmacopoeia

The Prussian pharmacopoeia (*Ph. Borussica*) is a regulatory text which exemplifies the official position on plant medicine in northern Germany some 200 years after the first publication of Tabernaemontanus' *New vollkommen Kräuter-Buch* (Tabernaemontanus, 1588). It was the committee of the 1<sup>st</sup> edition of the *Ph. Borussica* which made the far-reaching decision to transform this legal text into a reference work for pharmaceutical drug specifications and manufacturing only. This new structure, which now excluded therapeutic information, became the prototype of all Central European pharmacopoeias up to the present day (Schmitz et al., 2005, pp. 573-574). The preface to the 1<sup>st</sup> Prussian Pharmacopoeia (*Pharmacopoea Borussica*, 1799) reveals that the text is the expert consensus of a group of seven authors, which represents a relatively small-but-influential committee dealing with drug appraisals. The size of the committee appears limited in comparison to the large body of therapeutic substances used in clinical practice up to the end of the 18<sup>th</sup> century. Earlier pharmacopoeias were predominantly written by physicians, but the 1<sup>st</sup> edition of the Prussian pharmacopoeia is co-authored by three apothecaries who significantly shaped this new type of pharmacopoeia (Schmitz et al., 2005, pp. 573-574). For the first time, the influence of natural science becomes apparent not only in the new structure of the *Ph. Borussica*, but also in the introduction of a new nomenclature for

chemical medicines and the vigorous elimination of traditional therapeutics (Schröder, 1960, p. 11). The committee considered many of them as “*überflüssig*” (redundant) (Preussische Pharmacopöe: aus der lateinischen Urschrift übersetzt, 1813, p. VII). As a result, over 300 medicines were removed from the preceding reference text *Dispensatorium Regium Electorale Borusso-Brandenburgicum* (1781), which only 18 years earlier had listed over 1,000 medicines (Schmitz et al., 2005, pp. 574-576). The elimination of long-established medicines reflects the rapid developments in chemistry which led to a desire to ‘modernise’ medicine to align this field with what the authors perceived as the peak of modern science (Tschupp, 1998, pp. 121-122).

All seven editions of the *Ph. Borussica* (1799, 1804, 1813, 1827, 1829, 1847 and 1862) are written in Latin. Subsequently, these editions were translated into German and annotated by commentators to make them more linguistically and technically accessible to the professionals who were mandated to follow these guidelines (Straberoh, 1829, pp. VI-VII). From its 1<sup>st</sup> edition in 1799 to its 7<sup>th</sup> and last edition in 1862, the Prussian pharmacopoeia fundamentally influenced the development of other regional German pharmacopoeias and asserted its dominance by serving as the foundational text for the German pharmacopoeia of the unified Germany. The 7<sup>th</sup> edition of the *Ph. Borussica* was adopted ahead of the unification by most of German States except for Hannover, Bayern, and Württemberg, which maintained their own regional pharmacopoeias until the publication of the *Ph. Germanica* (1872) that superseded all regional German pharmacopoeias.

#### **4.7.2 Context of the German pharmacopoeia / Deutsches Arzneibuch**

The German pharmacopoeia exemplifies the official position of plant medicine in Germany after the unification of the German States in 1871, almost 300 years after the first publication of Tabernaemontanus’ *New vollkommen Kräuter-Buch* (Tabernaemontanus, 1588). The *Pharmacopoeia Germanica* (1865) was the first attempt at forming a national German pharmacopoeia that harmonised the independent regional equivalents of the German States (Schneider, 1966, pp. 195-196). However, it was not until the political unification of Germany in 1871 that a common, legally-binding pharmacopoeia was introduced on June 1, 1872, to replace all regional variants. It was modelled on the 1867 update of the German pharmacopoeia from 1865, which in turn was modelled on the Prussian pharmacopoeia.

The need to prepare a unified pharmacopoeia for the German Empire suggests that regional medical customs were widespread in 19<sup>th</sup> century German States. Despite efforts to integrate such diversity—as highlighted in the preface of the first edition of *Ph. Germanica* (Hager, 1872)—the preceding Prussian pharmacopoeia had a decisive influence on the content of the unified German pharmacopoeia and significantly reduced the listings of customary medicines used in other regions. The preface clarifies that even though the listed medicines were compulsory pharmacy stock items, neither were individual states precluded from adding further medicines to it, nor were local pharmacies hindered in the manufacturing and selling of local medical specialities (Hager, 1872, p. VII).

In the latter part of the 20<sup>th</sup> century the position of the German pharmacopoeia as the sole reference standard for drug specifications in Germany changed. Binding agreements amongst EU Member States to develop a common European pharmacopoeia meant that national pharmacopoeias lost their place as the primary reference source for drug standards (Böhme & Hartke, 1981, p. VII). The 1<sup>st</sup> European pharmacopoeia was published in 1974 and was initially binding in eight European countries (Schanz, 2009, p. 45). The integration of the *Deutsches Arzneibuch* with the *Europäisches Arzneibuch* into one German language edition was concluded by 1986 with the publication of *DAB 9* (DAB 9, 1986, p. 3). Consequently, medicines are regulated in Germany by three complementing standard reference texts: the *Deutsches Arzneibuch DAB* (German pharmacopoeia), the *Homöopathisches Arzneibuch HAB* (Homoeopathic pharmacopoeia for homeopathic, traditional, and anthroposophical medicines), and the *Europäisches Arzneibuch* or *Ph. Europea* (European pharmacopoeia). All three pharmacopoeias are legally binding.

#### **4.7.3 Commentaries**

Commentaries to the Prussian and German pharmacopoeias were printed as authoritative repertoires for practising physicians and apothecaries, but were not officially ratified (Schmitz et al., 2005, pp. 582-584). They are included in this study as academic appraisals of the traditional *materia medica*. Their endorsement of indications will be analysed and compared with indications recorded in contemporaneous clinical textbooks. This comparison is to establish how comprehensively commentaries reflected contemporaneous medical praxis. Commentaries were popular reference works for clinicians and compounding pharmacists. At the turn of the 20<sup>th</sup> century, thousands of copies were sold, highlighting their necessity (B. Fischer & C. Hartwich, 1901, p. Vorrede; Schneider & Süss,

1902, pp. V-VI). The last commentary to the *Deutsches Arzneibuch* (DAB) was printed in 1993 (Hartke, 1993). Since the harmonisation with the European pharmacopoeia there are now ongoing commentaries to this pan-European legislative text.

#### 4.7.4 Supplements

As did the Prussian pharmacopoeia beforehand, the German pharmacopoeia significantly reduced the list of essential medicines, in particular plant-based medicines. Consequently, the supplements to the German pharmacopoeia released by the *Deutscher Apotheker-Verein* (the professional organisation of German apothecaries) became important reference texts from the 1870s onwards. These supplements aimed to provide authoritative drug standards on those medicinal plants, plant parts, and preparations that were absent in the official German pharmacopoeia but required for clinical practice, as trade items between pharmacies, and to meet patient demand. Just how many traditional medicines were removed from the German pharmacopoeia becomes obvious when considering that the *Deutscher Apotheker-Verein* evaluated for its first supplement 2400 medicines, of which 800 were selected for a monograph entry (Deutscher Apotheker-Verein, 1891, pp. III-IV). The monographs in these supplements set quality standards and mirror the structure of official pharmacopoeias; they too do not provide guidance on therapeutic use. Their practical usefulness to compounding apothecaries and pharmacists meant that they quickly went out of print. Updated editions were reprinted in quick succession (Deutscher Apotheker-Verein, 1891, 1897, 1906, 1916, 1930a, 1930b). The last supplement was printed in 1948, which was a reprint of the 6<sup>th</sup> supplementary text from 1941 [Erg.-B. 6] (Deutscher Apotheker-Verein, 1948). Subsequently, many of their listings became formally integrated into the main body of the German pharmacopoeia. Supplements are included in this analysis because they reflect contemporaneous use of medicinal plants in regular German healthcare.

#### 4.8 Official monographs as sources of evidence

Official herbal monographs on legally sanctioned indications of use became necessary once such information was absent from pharmacopoeias. This study evaluates the *Kommission E Monografien* (*Commission E Monographs*), which were authored in the 1980s and 1990s by the Kommission E (Commission E), the scientific advisory board of the former Bundesinstitut für Arzneimittel und Medizinprodukte (the German equivalent of Ministry of

Health). In addition, it evaluates the *European Union Herbal Monographs (EU Herbal Monographs)* authored by the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA). They provide the regulatory guidelines in EU Member States for registering herbal medicinal products for self-medication.

#### **4.8.1 Commission E monographs**

The Commission E was formed in 1978 as part of the enactment of the updated Second Medicines Act 1976 (*Arzneimittelgesetz 1976* or AMG 76) which provided a framework for registering the non-pharmaceutical medicines of phytotherapy, anthroposophical medicine, and homoeopathy (Hügel, Fischer, & Kohm, 1995). The new law mandated the explicit acknowledgement of pluralism in medicine in order to prevent a monopoly of natural science modalities as the exclusive benchmark for decisions on the registration of medicines (Deutscher Bundestag, 1976, p. 7). By law, empirical evidence and unique features of plant medicines were thus required to be permissible. These stipulations were informed by European guidelines for the harmonisation of medicines in the EU market (EWG Richtlinien 65/65, 75/318 and 75/319) that authorised alternative evidence for all categories of medicines (Müller, 2001, pp. 252-253). Consequently, the remit of the Commission E was to evaluate scientific and empirical knowledge on plant drugs. It pioneered the assured regulatory acceptance of plant medicines in conventional healthcare.

The work of Commission E became known beyond Germany for publishing 380 monographs that evaluated the safety and effectiveness of plant medicines (*pflanzliche Arzneimittel*) so that they could be licensed and medically prescribed in Germany (Bundesinstitut für Arzneimittel und Medizinprodukte, 2002). The monographs were published between 1984 and 1994 in the German *Bundesanzeiger* (Federal Gazette). They are accepted as supporting evidence for the registration of plant medicines in many jurisdictions, including Australia and Canada. The *Commission E Monographs* were listed in the formerly proposed New Zealand Natural Products Bill in New Zealand as a permitted source of evidence for therapeutic claims.

#### **4.8.2 European Union herbal monographs**

The objectives of the Directive 2001/83/EC of the European legislative framework are to allow European citizens access to medicines of their choice by ensuring the continued availability of plant medicines in the European market, and that their particular

characteristics are considered when assessing their quality, efficacy, and safety (Knöss, 2014a, p. 30; Knöss & Chinou, 2012). The regulations pertain to plant-based drugs only. The addition of drug material of animal origin including honey and propolis, chemical compounds, isolated plant constituents such as menthol, or amino acids are not permitted, although vitamins and minerals are if they are ancillary to the herbal formula (Keller, n.d., p. 12). The indications must be appropriate to the traditional herbal medicinal product with minor, self-limiting conditions only, and suitable for use without supervision. Such remedies must be of a specific strength and posology (dosage), and used orally, externally, or through inhalation. The main meaning of external use relates to topical applications to the skin; however, if the traditional use of a herbal medicinal product relates to oral, nasal, rectal, vaginal mucosae, ocular, or auricular delivery, such delivery is accepted if no safety concerns exist (Keller, n.d., p. 14). The simplified registration procedure (Acceptance Criteria Article 16a) applies if there is sufficient data on traditional use of the product to prove safety and plausible pharmacological effects based on long-standing use and experience (Keller, n.d., p. 14).

There are two different types of monographs: one for “well-established medicinal use” and one for “traditional use” (European Medicine Agency, n.d.-a). As per Directive 2001/83/EC of the European Parliament and of the European Council, monographs on well-established medicinal use are based on scientific literature that embed two criteria: first that there are sufficient safety and efficacy data available for its registration, and second that the active substance of the medicinal product has been used within the EU for a minimum of 10 years. Efficacy is established with at least one RCT or a well-documented observational study. A monograph based on traditional use provides a pathway for a simplified registration where empirical data, but no clinical trials exist. Claims are accepted on the basis of plausible effectiveness and sufficient safety data (Europäisches Parlament, 2004). However, before product registration is granted, a product must demonstrate that it has been used for at least 30 years including at least 15 years within the EU, is intended to be used without supervision of a medical practitioner, and is not administered by injection.

The quality requirements for herbal medicinal products on the European market are contained in the EU pharmaceutical legislation and are the same for all herbal medicinal product licences in both traditional or well-established use categories (Kroes, 2014). They are also the same quality requirements laid down for conventional synthetic OTCs. As per

31 December 2016, 1719 traditional use and 859 well-established use registrations have been granted across the 28 Member States (European Medicines Agency, 2017, p. 2).

Regarding monographic assessment, the EMA states on its official website (European Medicine Agency, n.d.-a) that “[a] European Union (EU) herbal monograph (formerly known as Community herbal monograph) contains the scientific opinion of the Committee on Herbal Medicinal Products (HMPC) on safety and efficacy data about a herbal substance and its preparations intended for medicinal use. The HMPC evaluates all available information, including non-clinical and clinical data, but also documented long-standing use and experience in the EU.” Accepted sources of evidence for a traditional use monograph include medicine, pharmacy, pharmacology, phytotherapy, and herbal medicine textbooks; pharmacopoeia entries; and official expert committee reports (Fan et al., 2012, p. 570). Specifically, ESCOP, WHO, and Commission E monographs are accepted as bibliographic evidence by HMPC, as are national formularies and compendia. Additionally, a listing in a pharmacopoeia can be used as proof of medicinal use of a plant and its preparations during the years a monograph has been valid (Committee on Herbal Medicinal Products (HMPC), 2016, lines 273-281). A product dossier additionally requires any records that reflect the existence of a product in the market place over a period of 30 years, although a definite template for a simplified application via bibliographic proof is not available due to the varied nature of herbal medicinal products in the market place (Stolte & Knöss, 2014, pp. 64-65).

EU herbal monographs provide all information necessary for the registration of a product for sale, namely approved indications, suitability of use, and safety information, such as information regarding undesirable effects and interactions with other medicines. These EU monographs aim to support the harmonisation of the European herbal market by enabling national competent authorities to refer to one unique set of information on a herbal substance or preparation when evaluating marketing applications (Knöss, 2014a, p. 30). EMA states that even though Member States are not obliged to follow the monographs, any decision by a Member State not to accept the content of a monograph as adopted by the HMPC is seen as contradicting that Member State’s role in harmonising a simplified registration procedure (Commission of the European Communities, 2008, p. 3). The Mutual Recognition Procedure (MRP) which is based on Article 16d of the EU Directive 2004/24/EC (as amended) provides the pathway for traditional herbal medicinal products

(THMPs) to be registered and sold across Europe (Fan et al., 2012, pp. 570-571). According to Directive 2001/83/EC of the European legislative framework, all traditional herbal medicinal products require pre-marketing authorisation, including documentation of quality, safety, and efficacy before gaining access to the market (Steinhoff, 2002, p. 572). Thus, the EU herbal monographs provide a regulatory starting point towards the integration of THMPs into mainstream medicine across the EU. They afford the regulatory assurance that preparations adhering exactly to these monographs fulfil the quality, safety, and efficacy requirements for registration. Conversely, EMA does not prohibit other types of preparations or indications; however, for those preparations or indications, additional proof of effectiveness and safety must be provided before they are accepted for registration.

References for medicinal plants that are published as a List Entry by the European Commission and not by the European Medicine Agency via HMPC provide another pathway for harmonisation of the European herbal market. These entries are legally binding for all Member States and a safety summary to support a product application is removed (Quintus & Schweim, 2012, p. 379). By April 2018, HMPC has published 154 monographs of which 13 are for well-established use; the European Commission published 12 List Entries. Only two List Entries relate to a combination formula of medicinal plants (Knöss & Wiesner, 2017, p. 13). The low number of List Entries predominantly relates to the lack of modern genotoxicity data on medicinal plants rather than actual risk concerns (Knöss, 2018, p. 374).

#### **4.9 Authoritative expert monographs as sources of evidence**

This section discusses three key authoritative monographs as sources of evidence for plant medicines, two published in Europe (the *ESCOP Monographs* and *HagerROM. Hagers Handbuch der Pharmazeutischen Praxis*) and one published by the WHO for its Member States and the international community.

##### **4.9.1 ESCOP monographs**

The *ESCOP Monographs* represent authoritative texts on herbal medicinal products. They are permissible references for numerous regulatory authorities, such as the European Medicines Evaluation Agency, the Australian TGA, and Health Canada. They were also listed as approved evidence in the proposed New Zealand Natural Health and Supplementary Products Bill. The *ESCOP Monographs* are a continuation of the pioneering

work of Commission E which concluded in the mid-1990s. The initial funding for the enterprise was provided by the European Commission.

ESCOP was founded in 1989 and represents national phytotherapy associations from fifteen European countries in their discussions with European medicines regulators. Their aim is “to advance the scientific status of herbal medicinal products and to assist with the harmonisation of their regulatory status at the European level (Kemper & Bruhn, 2005, p. 702). The organisation collaborates with external herbal medicine experts and with a board of supervising editors who contribute to the writing of *ESCOP Monographs*. From 1997-2010, this umbrella organisation published 108 authoritative monographs on medicinal plants which are continuously updated (Calvo & Cavero). Since 2011, new and revised monographs are published electronically (Krenn, Steinhoff, & Escop, 2014, A1). *ESCOP Monographs* list indications, dosage, contra-indications, interactions, and undesirable effects together with summaries of pharmacological, clinical, and toxicological data. These monographs claim to be a step in the development of harmonised scientific standards for herbal medicinal products in Europe (ESCOP, 2003b, p. VII).

#### **4.9.2 The HagerRom. Hagers Handbuch der Drogen und Arzneistoffe**

*HagerROM. Hagers Handbuch der Drogen und Arzneistoffe* (until recently known as *Hagers Enzyklopädie der Arzneistoffe und Drogen*) is the continuation of the pharmaceutical encyclopaedia authored by Hermann Hager who wrote the seminal 19<sup>th</sup> century text series *Handbuch der pharmaceutischen Praxis. Für Apotheker, Ärzte, Drogisten und Medicinalbeamte* (Hager, 1876). It has been continuously updated over the past 130 years and is now electronically published with regular updates (HagerROM, 2016). The text integrates the *Commission E Monographs*, several European pharmacopoeias, and the *HAB* compendium. It further provides information from scientific research, enduring clinical textbooks, and folk medicine. Recent editions of this pharmaceutical reference textbook reflect the exponential increase in experimental and clinical research into plant medicine. Of the five selected legal and authoritative monographs, this monograph contains the most comprehensive body of knowledge and has the advantage that it is continuously updated. It provides a comprehensive evaluation of existing clinical knowledge combined with modern insights.

### 4.9.3 WHO monographs

The internationally authoritative *WHO Monographs* are published in the context of the WHO's long-standing strategy to support systems of traditional medicine that have global importance in serving an estimated 80% of the world population for their primary health needs (World Health Organization, 2012, 2013). From the 1990s onwards the WHO developed monographs to support the "assurance of the safety, quality and efficacy of medicinal plants and herbal products" (World Health Organization, 1999, p. 1). The *WHO Monographs* provide Member States with expertise and quality standards for the incorporation of traditional medicines into their regular healthcare systems and may be considered by a national authority on this basis (World Health Organization, 1999, p. 4).

Over a period of 11 years, the WHO published 116 medicinal plant monographs in four volumes (1999, 2004, 2007 and 2009), plus an additional regional volume published in Russian (World Health Organization, 2010). This additional volume was specifically authored for the Newly Independent States (NIS) and Countries of Central and Eastern Europe (CCEE). It comprises monographs on medicinal plants commonly used in that region. As the national drug regulatory authorities were fully involved in the development of these monographs, they serve as official guidelines.

WHO (1999, p. 2) states that the purpose of the monographs is to:

- provide scientific information on the safety, efficacy, and quality control/quality assurance of widely used medicinal plants, to facilitate their appropriate use in Member States;
- provide models to assist Member States in developing their own monographs or formularies for these or other herbal medicines; and
- facilitate information exchange among Member States.

Much work remains to develop further monographs on key medicinal plants from diverse biospheres and to update existing monographs with new research. All *WHO Monographs* are freely available on the official WHO website.

## 4.10 Summary

This chapter discussed the methods applied in this thesis and introduced the Historical Assessment Tool as a systematic tool for the collation of the large amount of

pharmacological data on medicinal plants recorded in historical and contemporary textbooks. It further explained the purpose of the triangulation of such data across both qualitative and quantitative sources to strengthen conclusions drawn from the data analysed. It then proceeded to contextualise the historical significance of the botanical *materia medica* literature in European healthcare before providing a summary of each of the selected medical textbooks of the period from the 16<sup>th</sup> to the 21<sup>st</sup> century. The purpose of this was to provide the rationale for and context of the selected textbooks. This chapter also briefly described the historical background of the selected pharmacopoeias, their commentaries, and their supplements before explaining the selection of the official and authoritative monographs analysed in this study. The next two chapters of this thesis will now apply the described methods to cross-analyse pharmacological data on Arnica and St. John's Wort and their transmission over the past 400 years.

## 5 ARNICA: THERAPEUTIC INDICATIONS FROM THE EARLY MODERN PERIOD (1588/1664) TO CONTEMPORARY PHYTOTHERAPY (2007)

This chapter discusses the therapeutic significance of *Arnica montana* in European healthcare. A botanical, etymological, and historical introduction is followed by a longitudinal textual analysis of Arnica's medicinal uses as recorded in medical textbooks, pharmacopoeias and their compendia, and monographs over the past 400 years. An additional review of scientific research provides contemporary clinical and experimental evidence on *Arnica montana*.

The research questions under investigation are twofold. Is this professionally documented medical knowledge about the effectiveness and safety of traditional European plant medicines a reliable and verifiable source of evidence that can be incorporated into a regulatory framework? Secondly, do such historical documentary sources adequately and accurately describe medicinal plants, their uses, therapeutic effects, and safety to support the regulatory acceptance of traditional medicines? In other words, could these sources contribute to an evidence-based framework for New Zealand's evidence-based policies on NHPs?

### 5.1 Introduction to *Arnica montana* in European healthcare

#### 5.1.1 Botanical profile

*Arnica montana* is an alpine herbaceous perennial herb in the daisy family (*Asteraceae*). It belongs to the genus *Arnica*, a genus which includes about 30 different species (Mabberley, 2017). Native to Europe, it grows in alpine meadows and open coniferous forests 600-2800 meters above sea level from Scandinavia to the Balkans, and from Spain across central Europe to the Ukraine and central Asia (Engels & Brinckmann, 2015, p. 1). It can also grow in sandy, humic, or peaty lowlands (Info Flora, n.d.), resulting in different active constituent profiles (Willuhn, 1972b). *Arnica* reaches a height of about 30-60 cm with a horizontally growing



Figure 2. *Arnica montana* in Kroeber, 1948, p.37

rhizome and bright yellow-orange tubular flowers. It establishes best in moist swampy areas with slightly acidic soil deficient in lime. It disappears quickly in areas that have been fertilised for farming purposes.

Since the 18<sup>th</sup> century Arnica grew markedly in popularity, owing to traditional use, positive experimental research (Stirnadel, 1959), and literary praise in works such as *Ode sur les Alpes* (1773) by the Swiss physician Albrecht von Haller, and by the German poet, statesman, and natural scientist Johann Wolfgang von Goethe (Faber, 1953b, p. 179; Pelikan, 1975 (1958), pp. 247-249). In the 19<sup>th</sup> century it became increasingly sought after but subsequently endangered (Mayer & Czygan, 2000). In the 20<sup>th</sup> century, Arnica became subject to various regional and EU policies, habitat directives, and wildlife trade regulations (Allen et al., 2014; Bundesamt für Naturschutz, p. 3; Engels & Brinckmann, 2015, p. 5; May, 2013, p. 2). Romania is currently the main provider of wildcrafted Arnica, which is predominantly used for medicinal and cosmetic purposes (Engels & Brinckmann, 2015, p. 4). Due to its high demand and endangered status, some European phytotherapy companies undertake their own cultivations.

### 5.1.2 Historical and etymological profile

Arnica is an old folk remedy prevalent in alpine areas of German speaking countries. It holds both medical and cultural significance (Zörnig, 1909, p. 111). Its unique applications made it an important remedy in both professional and folk medicine (Tschirch, 1909a, pp. 1174-1184). Arnica first appears in European medical textbooks during the Middle Ages. It was not known by classical Greek physicians, including Hippocrates, Theophrastus, and Plinius, who commonly did not describe alpine flora (Faber, 1953b, p. 181; Kreitmair, 1952, p. 441). The “Alisma” of Dioscorides, which was interpreted by Mattioli as “Arnica”, was more convincingly *Alisma plantago* since Dioscorides describes “Alisma” as displaying plantago like leaves with white, *not* yellow, flowers (Faber, 1953b, p. 181). Apart from its role in healthcare, Arnica in alpine areas of German speaking areas was one of nine sacred herbs selected to celebrate summer solstice and other regional customs (Faber, 1953b, p. 180).

The German name *Arnika* may be derived from the Greek *arnakis* (lamb fur), in reference to the plant’s soft, hairy leaves, or *ptarmika* (sneeze herb), which relates to the unique property of Arnica dust to induce sneezing (Zörnig, 1909). Other authors speculate on its Arabic origin (Madaus, 1938b) or the possibility that the name was coined in central Europe

during the medieval period when the names Arcinca, Arnica, Artinca, and Arnich first appeared (Faber, 1953b, p. 179). In the 17<sup>th</sup> century, Arnica established such a phenomenal reputation that it was bestowed the name *Panacea lapsorum* (Willuhn, 1991), referring to Panazee, the goddess of the universal remedy and daughter of the Greek god of medicine, Asclepius. The old German name *Wohlverlei* or *Wolferlei* may refer to its use in the treatment of *Intertrigo perinealis*, colloquially called wulf (wolf) (Wijnsma, Woerdenbag, & Busse, 1995, p. 51). The species' epithet *montana* relates to its endemic presence in alpine regions.

Obon recognises that it is common in traditional medicine to refer to medicinal plants of different species with shared vernacular names when they have shared morphological and aromatic characteristics (Obon et al., 2012). This makes the positive botanical identification of medicinal plants discussed in historical medical textbooks both challenging and a high priority, being the prerequisite for a sound analysis. It is unclear when Arnica was unequivocally cited for the first time, because the plant had various Latin and vernacular names in pre-Linnaean times. The German apothecary and pharmaceutical author Heinrich Zörnig claims that Arnica was first referenced in Hildegard von Bingen's 12<sup>th</sup> century medical textbook *Physica* where it is said to have gone under the name of "Wolvisgelegena" (Zörnig, 1909, p. 111). The first unequivocal citation, however, is in the 14<sup>th</sup> century medical encyclopaedia by Mathaeus Sylvaticus, who referred to Arnica as "arnic" (Mayer & Czygan, 2000).

The term "arnic" did not immediately have universal currency; 15<sup>th</sup> and 16<sup>th</sup> century physician-botanists continued to use varied Latin nomenclature such as *Doronicum*, *Caltha alpina*, *Calendula alpina*, *Nardus celtica altera*, *Chrysanthemum latifolium*, and *Damasonium primum Dioscoridis*, or German terms such as *Lucianskraut*, *Mutterwurz*, and *Fallkraut* (Geiger, Nees von Esenbeck, & Dierbach, 1839, p. 808; Saller et al., 1995, p. 50; Tschirch, 1909a, p. 34). There are several other regional names, such as *Johannisblume* or *Johanniskraut* (not to be confused with the other *Johanniskraut* which refers to St. John's Wort), *Stichkraut*, *Wolferley* or *Wohlverleih*, *Bergwegebreit*, and *Bergwohlverlei* (Tschirch, 1909a, pp. 1174-1175).

Tabernaemontanus (1664) confirmed that "Wolferley" is the "Arnica" of the *medici* (medical doctors), thus creating a definite link between the noted vernacular and Latin names (Tabernaemontanus, 1664, pp. 714-715). In the English medical literature, *Arnica*

*montana* is also known under various vernacular names such as mountain daisy, mountain tobacco, leopard's bane (Mayer & Czygan, 2000), or mountain marigold (Gerard, 1633, pp. 740-741). Only since the establishment of the classical binominal taxonomy introduced by Swedish physician and botanist Carl von Linné (1707-1778) has *Arnica* consistently been identified in medical textbooks as *Arnica montana*.

### 5.1.3 Official status

*Arnica montana* is currently the only officially approved species of the genus *Arnica* in the European pharmacopoeia, regulations that are legally binding for European Member States. *Arnica chamissonis* LESS. ssp. *foliosa*, an *Arnica* species native to North America, was official in the German pharmacopoeia for a short time from 1987 (*DAB 9*) to 1993 (*DAB 10*) to provide an alternative crop to *Arnica montana*, a plant which is difficult to cultivate. Historically, other species from the genus *Arnica* were also used in medicine (Obon et al., 2012). For example, *Arnica alpina*, *Arnica foliosa*, *Arnica longifolia*, and *Arnica sachalinensis* (REGL.) have all been used for therapeutic purposes (Willuhn, 1972b; 1981, p. 3). *Arnica fulgens*, *Arnica sororia*, and *Arnica cordifolia* were official in the US National Formulary VIII (Willuhn, 1972b), but did not achieve official status in Europe. It is plausible that these species also have medicinal properties.

## 5.2 *Arnica montana* in medical textbooks

The longitudinal textual comparison of medicinal uses of *Arnica montana* as recorded in authoritative medical textbooks from the 17<sup>th</sup> to the 21<sup>st</sup> century highlights that despite changes in paradigmatic explanatory models of health and illness, key indications remained remarkably consistent. Table 1 (below) provides an overview of the use-categories addressed by the listed indications. Indications relating to the use-categories musc-skel, nerve, skin-mucous, and tonic were consistently cited over the past 400 years, whilst indications relating to card-vasc and respiratory use-category were consistently endorsed from the late 18<sup>th</sup> century onwards. The remainder of use-categories show intermittent listings.

**Table 1. Use-categories addressed in medical textbooks.**

Use-categories	Tabernaemontanus 1664	Löseke 1790	Richter 1827	Strumpf 1855	Hager 1876-1878	Schulz 1919	Madaus 1938	Kroeber 1948	Weiss 1974	Saller et al 1995	Bäumler 2007
card-vasc	0	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
gastro-intest	✓	✓	✓	✓	✓	0	✓	✓	0	0	0
gyn	✓	✓	✓	✓	0	(✓)	✓	0	0	(✓)	(✓)
head	0	✓	✓	✓	✓	✓	✓	✓	0	0	0
infection	0	✓	✓	✓	✓	0	✓	0	0	(✓)	✓
liver-spleen	✓	✓	0	0	0	0	0	0	0	0	0
musc-skel	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
nerve	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
respiratory	0	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
skin-mucous	✓	0	✓	✓	✓	✓	✓	✓	✓	✓	✓
tonic	✓	✓	✓	✓	(✓)	✓	✓	✓	✓	(✓)	✓
uro	✓	✓	✓	0	✓	0	✓	0	0	0	0
<p><i>Dark green rows refer to continued use</i>  <i>Light green rows refer to intermittent but present-day use</i>  <i>White rows refer to present-day discontinuation</i>  <i>Brackets (✓) reference historical medicinal uses or folk medicine use</i></p>											

The prefaces to the evaluated medical textbooks reveal that Arnica was a plant drug highly esteemed by the medical profession until the 1850s, after which time its fame, in contrast to folk medicine, started to wane. During WW1 and WW2, it was extensively employed again in injury recovery, which boosted its medical status (Stirnadel, 1959, p. 1518). Today, Arnica is mainly applied in complementary healthcare and in self-medication. Conventional healthcare relies predominantly on synthetic drugs and advances in trauma care to deal with issues traditionally addressed with Arnica. The most striking change in medicinal use of Arnica over the past 400 years, however, is its documented systemic and topical use until the mid-1980s, when European regulators approved topical use of Arnica only, taking a more conservative approach to benefit-risk ratios for plant medicines.

The following sections discuss the pharmacological and pharmaceutical profile of Arnica in the European medical literature in more detail. When historical indications are summarised for the sole purpose of delivering bibliographic evidence for regulatory requirements, such

an analysis would not be required. However, in the context of this thesis, observations on medical trends provide supplementary insights on continuities and discontinuities of plant indications. The analysis of this first exemplar delivers therefore some explanatory context on plant applications over the past 400 years in addition to the tabulated data on recorded historical and contemporary indications.

### **5.2.1      *Arnica montana* in Tabernaemontanus (edition 1664)**

Tabernaemontanus (1664, pp. 714E-715A ) discusses Arnica and its therapeutic applications under *Chalta [Caltha] alpina*, in German termed “Mutterkraut” and “Mutterwurz”, which the author identifies as the ‘Arnica of the physicians’. This passage is a reprint of the original Arnica manuscript from the 1<sup>st</sup> edition (1588) of the *Neuw Kreuterbuch*, where Tabernaemontanus accurately refers to the Arnica taxonomy of Rembert Dodoens (1516 – 1585), Dutch imperial physician and botanist, and that of Conrad Gessner (1516-1565), Swiss physician and botanist. The approximation of the translation is provided in Appendix 3, and the English translation of the pharmaceutical and pharmacological data is tabulated in Appendix 4.

#### **5.2.1.1          Annotations to the 1664 edition**

The 4<sup>th</sup> edition of *New vollkommen Kräuter-Buch*, which is used in this analysis, contains annotations by the Bauhin editors Caspar and Hieronymus Bauhin, both physicians, botanists, and successive professors at the University of Basel, Switzerland. All annotations attributed to *Arnica* itself are included in this analysis. As noted in Appendix 4, the Bauhin annotations relate to general uterine complaints, to inducing menstruation, to stopping diarrhoea, and to detoxifying animals. A cross-reference check with Gerard’s *The Herbal or General History of Plants* (Gerard, 1633, pp. 740-741) confirms a contemporaneous documentation of Arnica’s therapeutic uses in gynaecological issues, in infections, and for detoxification. This matches the Arnica annotations by the Bauhin editors to the 1664 Tabernaemontanus edition. Thus, Gerard’s monograph on Arnica validates the inclusion of the Bauhin editors’ addendums to the Arnica monograph from 1664. The annotated list of indications recorded in the 4<sup>th</sup> edition of the *Neu vollkommen Kräuter-Buch* for Arnica therefore addresses eight use-categories: gastro-intest, gyn, liver-spleen, musc-skel, nerve, skin-mucous, tonic, and uro.

It is surprising that gynaecological indications were initially left out of Tabernaemontanus' 1588 edition, as the vernacular name for Arnica, "Mutterkraut" and "Mutterwurz", refers to the uterus. Records for Arnica in gynaecology were known at least since medieval times. For example, Italian physician and botanist Matthaeus Sylvaticus (c. 1280- c. 1342) listed Arnica for abortive purposes in his influential medical encyclopaedia (Mayer & Czygan, 2000). Tabernaemontanus was well aware of the usage of Arnica for gynaecological purposes since he had edited Wirsung's pathology book (Wirsung & Tabernaemontanus, 1577). Here, Arnica is listed as "Mutterwurz" to be used for infertility due to amenorrhoea (p. 239), for inducing menstruation (p. 382), and for unspecific complaints of the uterus (p. 380, 382). Tabernaemontanus may have distinguished between information suitable for the medical profession only (Wirsung's pathology book), and what was appropriate for an encyclopaedia also used in lay healthcare (*Neuw Kreuterbuch*).

The editors of the 4<sup>th</sup> edition of Tabernaemontanus' *Neu vollkommen Kräuter-Buch*, mistakenly attribute further indications to *Arnica* that relate to a different species. This mistaken botanical attribution was caused by the Dioscorides commentary of Pietro Andrea Mattioli (Matthiolus, 1501-1577), an influential Italian physician and botanist who claimed the "Groß Lucians Kraut" to be the same plant as the "Mutterkraut" thus combining the therapeutic uses of two distinctly different plants (Tabernaemontanus, 1664, p. 1116). This conflation was an incorrect (pre-Linnean) attribution as already noted by Dodoens in his *Cruydt-boek* from 1554 (Mayer & Czygan, 2000). In contrast to Mattioli, the German physician Adam Lonitzer (1528-1586) attributes in 1573 "Groß Lucians Kraut" to "Wasserwegerich" or "Froschlöffel" (*Alisma plantago*). This is plausible as they share identical botanical characteristics (Mayer & Czygan, 2000). Therefore, all indications of "Groß Lucians Kraut" that the Bauhin editors claim for Arnica are excluded in this analysis and only those that genuinely pertain to Arnica are listed.

### **5.2.1.2 The understanding of heart and circulation in the early modern period**

Neither the original 1<sup>st</sup> edition (1588) nor the 4<sup>th</sup> edition (1664) of Tabernaemontanus' *Neu vollkommen Kräuter-Buch* refer to the use of Arnica in heart conditions or as a circulatory stimulant. These indications were, however, acknowledged by later authors, for instance the English physician John Gerard, who translated and copied significant portions of the text. In reference to the monograph of *Caltha*, Gerard describes the plant "Mountaine Marigold" and "wilde Marigold", explaining:

The floure of the Marigold is of temperature hot, almost in the second degree, especially when it is dry: it is thought to strengthen and comfort the heart very much, and also to withstand poyson, as also to be good against pestilent Agues, being taken any way. Fuchsius hath written, That being drunke with wine it bringeth downe the termes, and that the fume thereof expelleth the fecondine or after-birth...Conserue [conserve] made of the flouers [flowers] and sugar taken in the morning fasting, cureth the trembling of the heart, and is also given in time of plague, or pestilence, or corruption of the aire. (Gerard, 1633, pp. 740-741).

Gerard's reference to Arnica's indication as a heart tonic may have owed to his early exposure to William Harvey's experimental confirmation of the circulation of blood (Harvey, 1628), a physiological fact which was not yet known when Tabernaemontanus first published his Arnica monograph (1588). The discovery of Arnica as a heart tonic illustrates that a medical tradition is not static but can expand with new medical insights.

### **5.2.2      *Arnica montana* in medical textbooks from 1790 to 2007**

This section analyses the pharmacological and pharmaceutical profile of Arnica recorded in authoritative medical reference textbooks from the late 18<sup>th</sup> century to current phytotherapeutic textbooks by practising physicians in the 21<sup>st</sup> century. Appendix 5 provides an overview of all therapeutic indications listed for Arnica in these sources over this period.

#### **5.2.2.1      Arnica in Löseke (1790)**

The 6<sup>th</sup> edition of the medical textbook *Materia Medica*, authored by Löseke and annotated by Gremlin (Löseke & Gmelin, 1790), reveals that Arnica was used more expansively in patient care than in the early modern period. From the 1700s onwards, a significant amount of experimental research into the pharmacology of Arnica expanded its medicinal applications (Stirnadel, 1959) as did new insights into human anatomy and pathophysiology (Erley, 1965, p. 232).

The Arnica monograph published in the *Materia Medica* covers indications belonging to 12 use-categories (see Appendix 5). Eight therapeutic actions align with actions already discussed in Tabernaemontanus. In an approximation to modern terminology, they are:

- analgesic

- anti-bacterial
- anti-ecchymotic
- bitter tonic
- detoxifying
- diuretic
- emmenagogue / uterine tonic
- tissue healing.

In contrast to Tabernaemontanus' *Neu vollkommen Kräuter-Buch*, the 18<sup>th</sup> century text notes three new treatment areas: indications relating to the cardio-vascular system, based on insights from experimental research into the circulatory stimulant actions of Arnica; the treatment of eyes, an anatomical area previously not specifically mentioned; and infection, specifically the treatment of malaria. These indications expand on the traditional medicinal uses of Arnica.

The *Materia Medica* lists three different extraction methods, all accomplished with fresh Arnica flowers. The water and beer extracts were already noted by Tabernaemontanus, while the wine extract is newly noted in relation to Arnica (Löseke & Gmelin, 1790, p. 171). The 18<sup>th</sup> century textbook lists for the first time an enema preparation, compounded with Arnica and mucilage drugs for those who cannot tolerate Arnica preparations *per oral* (Löseke & Gmelin, 1790, p. 171). Arnica enema is subsequently listed in Richter (1827) and Strumpf (1855); it is last mentioned in the 4<sup>th</sup> edition of the commentary to the German pharmacopoeia by Schneider & Süss (1902, pp. 421-422). Other preparations noted in Löseke were not found elsewhere and were therefore considered speciality preparation of an individual practitioner. They were discounted as traditional preparations.

#### **5.2.2.2 Arnica in Richter (1827)**

The second volume of Richter's *Ausführliche Arzneimittellehre. Handbuch für praktische Aerzte* (Richter, 1827, pp. 140-153) classifies Arnica under *Scharfe Mittel*, a term which refers to acrid remedies. Richter (1827, p. 141) describes Arnica as an 'extremely important remedy' which cannot be replaced by another drug. As displayed in Appendix 5 the indications match Löseke's indications to a very high degree, meaning that the recommended clinical applications of Arnica did not significantly change despite increasing paradigmatic dissonance in medical theories at the time. The only differences are that

Richter more precisely describes the beneficial circulatory actions of Arnica on the brain, and he introduces its cleansing effect on wounds and infected ulcers. At the same time, he discontinues the indication of urinary gravel, whilst still listing Arnica as a diuretic (uro use-category), and its use as a bitter tonic (liver-spleen category). This illustrates that physicians in clinical practice did not simply copy other peer's recommendations but evaluated them with their own empirical observations.

Richter (1827, p. 141) explains that Arnica activates the veins, arteries, lymph vessels, and nerves, and also primes their 'irritability' (*Irritabilität*) and 'sensitivity' (*Sensibilität*). The author references capillaries, mucous membranes and connective tissues, sinews, tendons and ligaments, synovial skin, the periosteum, pleura and peritoneum, and outer skin as areas where actions are noted. The author also highlights Arnica's therapeutic effect against processes of putrefaction. In addition, he describes Arnica's invigoration of nerves, muscles, and vessels, all of which are beneficial to congestion of the brain and abdomen. He notes that in small doses Arnica increases the ability of the skin, lungs, and kidneys to both reabsorb and secrete fluid.

Richter (1827, p. 148) argues that Arnica is best used immediately after an injury and states that in the treatment of after-effects of stroke it may only be effective in the first six weeks. The author summarises the following therapeutic effects of Arnica:

- anti-ecchymotic
- anti-haemorrhagic (after an injury or in passive bleeding from various organs)
- anti-inflammatory (in rheumatism)
- tissue healing.

Richter (1827, pp. 141-143) cautions that excessive doses can cause inner agitation, heart pressure, stomach and digestive troubles, vomiting, diarrhoea, colic, tightening of the chest, and issues with urination. The documentation of safety warnings shows that the medical profession was aware of the dose-dependent side-effects of Arnica.

### **5.2.2.3 Arnica in Strumpf (1855)**

The Arnica entry by Strumpf (1855, pp. 46-56) is detailed and it highlights the continued importance of Arnica in medical care. The emerging divergent value judgments on medicinal plants in the context of a shifting medical theory had little effect on Strumpf's textbook as the indications and preparations match closely those of Richter (see Appendix

5). One difference is that the author no longer recommends the use Arnica as a diuretic (uro use-category). Strumpf demonstrates his clinical expertise and pharmacodynamic understanding of Arnica by including mucous membrane soothing plants such as Licorice in a recipe to counteract Arnica's potential acrid effects, and by offering various organ-specific recipes where Arnica is used as a synergist to support circulatory stimulation.

#### **5.2.2.4 Arnica in Hager (1876)**

Despite shifts in medical theory now clearly evident by the end of the 19<sup>th</sup> century, the evaluation by Hager (1876, pp. 462-467) of Arnica's therapeutic applications in patient care does not reveal fundamental changes. Except for discontinuing indications relating to gynaecology, rheumatism, and to the stopping of passive bleeding, the author lists complaints belonging to all use-categories recorded twenty years earlier by Strumpf (Strumpf, 1855, pp. 46-56). Hager focuses, however, on the most important clinical uses, all of which reflect long-standing clinical practice. He restores Arnica's indication for the promotion of diuresis after Strumpf de-listed it 20 years earlier.

Hager (1876, p. 463) describes the stimulant effects of Arnica on nerves, blood vessels, respiration, blood circulation, and the excretion of urine and sweat. The listed systemic uses are as follows:

- circulatory stimulant
- paralysis from brain and spinal illnesses
- cerebral concussion
- infections affecting the gastro-intestinal system
- infections causing putrefaction (*Nerven- und Faulfieber*)
- external and internal trauma
- epilepsy
- acceleration of respiration.

The listed topical uses are as follows:

- sprains and strains
- haematoma
- wounds
- ulcers.

The author lists several commercial preparations containing Arnica for the treatment of chest ailments, wounds, eye issues, sciatica, nerve injuries, and cancer.

Unlike Richter and Strumpf, Hager no longer groups plants with the same pharmacological actions under the same class and order but organises his textbook into alphabetically sequenced monographs. This aligns with the presentation of the *materia medica* in the German and its preceding Prussian pharmacopoeia. Hager also does not reference antique or medical authorities from the early modern period. For the first time, a medical textbook recounts a case report of accidental poisoning with Arnica tincture (Hager, 1883c, p. 115). The tincture was not unequivocally identified, but if it was indeed an Arnica tincture, the dose of 60-80g of a 1:3 tincture (the extraction ratio of Arnica flower extract listed in Hager) would have represented 20-26g of drug material compared to the 0.3-1g therapeutically recommended. This case report served as an important warning against overdosing with Arnica.

#### **5.2.2.5 Arnica in Schulz (1919)**

Schulz (1919, pp. 293-299) also discusses Arnica at length, listing indications belonging to seven use-categories (card-vasc, head, musc-skel, nerve, respiratory, skin-mucous, tonic (Appendix 5). His listings reflect the same use-categories as the previous authors. The majority of indications are discussed in the card-vasc, musc-skel, and skin-mucous use-categories.

Indications noticeably decrease in Schulz's (1919) text compared with indications listed in medical textbooks up until the latter part of the 19<sup>th</sup> century. This points to a decline in importance of Arnica in regular medicine during this period. The omitted indications relate to the gastro-intestinal tract (diarrhoea and infections), to gynaecology (to promote menstruation and to cleanse the uterus after birth), to the head (concussion and its after effects), to the musculo-skeletal system (gout and rheumatism), to the head (epilepsy), and to the urinary tract (diuresis). The de-listing of Arnica in the treatment of rheumatism and gout may be linked to the 3<sup>rd</sup> commentary to the *Ph. Germanica* which also discontinued these indications (Hager et al., 1891). Schulz still mentions, however, previous medicinal uses of Arnica to reabsorb cerebral bleeding in strokes and as a strengthening stimulant, especially for the elderly with pneumonia.

The author also reports that in the previous century Arnica was still an important wound, heart, and circulatory remedy. He notes the medical profession's increasing lack of interest in the therapeutic use of Arnica owing to perceived overuse, and a shift in benefit-risk considerations. Schulz (1919, pp. 293-295) highlights, however, that Arnica remained a popular remedy in German households, where Arnica tincture was said to be commonly stocked in first aid cabinets for self-medication. He discusses the contemporaneous use of Arnica in veterinary clinics to treat sprains in animals from overexertion, to treat overworked vocal cords in singers, and to induce abortion (an illegal folk medicine application). He elaborates both on the therapeutic benefits of Arnica and on its side-effects when the plant drug is not used appropriately. As a pharmacologist, he emphasises that as a matter of course all strongly acting drugs must be taken with safety considerations in mind.

#### **5.2.2.6 Arnica in Madaus (1938)**

Madaus (1938b) reverses the trend towards reduction of clinical uses documented in medical textbooks and presents a more comprehensive list of indications for *Arnica montana* than was common in the previous 60 years. Published before WW2, this monograph re-lists ailments that became absent in medical textbooks from the last quarter of the 19<sup>th</sup> century onwards (see Appendix 5). Madaus' Arnica monograph is significant because it is informed by a survey of therapeutic plant uses by German medical practitioners. This textbook covers indications in 11 use-categories and complements the monograph by Schulz (1919), published 20 years earlier, with traditional indications belonging to three use-categories (gastro-intest, infection, and uro). All were listed previously by Hager in the last third of the 19<sup>th</sup> century. Madaus further lists coronary insufficiency, specifically *Angina pectoris*, atherosclerosis *Adipositas cordis*, and cyanosis as modern indications.

Two novel preparations are discussed in this text; an injection of Arnica solution and Madaus' innovative "Teep" (a trituration of fresh plants in a milk sugar base). While the latter continues to be listed as an official preparation in the compendium to the German pharmacopoeia (the *Homöopatisches Arzneibuch*), these preparations are not listed in the German or European pharmacopoeia.

### 5.2.2.7 Arnica in Kroeber (1948)

The Arnica monograph by Kroeber (1948, pp. 37-42) published in his seminal textbook *Das neuzeitliche Kräuterbuch. Die Arzneipflanzen Deutschlands in alter und neuer Betrachtung* records indications across eight use-categories (card-vasc, gastro-intest, head, musc-skel, nerve, respiratory, skin-mucous, and tonic). Apart from specific discussions of injury treatments which were more prevalent during war times, this clinical textbook closely reflects the main indications for Arnica as recorded by Madaus before WW2. Kroeber's text, however, streamlines indications relating to the same cluster of complaints, and did not continue with the re-uptake of traditional pre-WW2 indications relating to gynaecology, infections, and urinary tract issues (see Appendix 5).

In response to the necessities of war, Kroeber (1948, p. 40) focuses on the use of Arnica in the treatment of war injuries and wounds; for example, he recommends Arnica to stop bleeding in cerebral concussions and in the eye. These treatments are consistent with the usage of Arnica during WW1 when it had reclaimed its place in restorative care for injuries and bleeding wounds (Spaich, 1978, p. 87). Not least because of the scarcity of other drugs during times of war, Arnica remained an important plant in European healthcare with an estimated yearly harvest by the general population of around 50,000kg of dried Arnica (Faber, 1953b, p. 187).

### 5.2.2.8 Arnica in Weiss (1974)

In his *Lehrbuch der Phytotherapie*, Weiss (1974) lists therapeutic uses of Arnica under different body systems and medical problems rather than under a dedicated plant monograph as presented by previous authors. He streamlines the indications previously recorded by Kroeber to the most frequent clinical problems. They relate to six use-categories (cardio-vasc, musc-skel, nerve, respiratory, skin-mucous, and tonic) (see Appendix 5). He expands on the internal uses of Arnica for coronary and general blood circulation, for *Angina pectoris*, and for the ageing heart. He de-lists, however, the long-standing usage of Arnica for the treatment of gastro-intestinal infections, perhaps due to the availability of effective antibiotic treatments, and for head injuries, an area where trauma treatment had exponentially developed since WW2 (gastro-intest and head use-categories). While there was little change in clinical usage of Arnica before and after WW2, there was a reduction of indications in this 1970s textbook compared with indications listed during the 1940s.

### 5.2.2.9 Arnica in Saller, Reichling, and Hellenbrecht (1995)

The Arnica monograph by Saller, Reichling, and Hellenbrecht (Saller et al., 1995) is based on long-standing medicinal uses, clinical experience, and scientific evaluation of clinical studies and experimental research. All sources are clearly referenced with the pertinent literature for independent cross-validation. Indications are discussed across three areas of therapeutic usage: traditional, clinical and official as approved by the regulatory *Commission E Monograph Arnicae flos*. The scientifically endorsed indications relate to five use-categories; card-vasc, musc-skel, nerve, respiratory, and skin-mucous. These are consistent with those of previous authors who based their texts predominantly on empirical evidence (see Appendix 5). The biggest distinction between this medical textbook and previous textbooks is in the card-vasc use-category. Until Weiss (1974, p. 177), internal uses of Arnica to support heart function and blood circulation were clinically discussed and endorsed, but Saller et al. (1995, p. 50) newly list them under folk medicine. This distinction may have arisen from changes in German regulations during the 1980s which implemented a new approach to healthcare based on preventative measures of health and safety. These regulations restrict the use of Arnica to external use only.

The Arnica monograph by Saller et al. (1995, pp. 49-55, 405) incorporates all approved claims of the *Commission E Monograph*, a monograph which confirms Arnica's anti-inflammatory, analgesic, and antiseptic properties (Kommission E, 1984a). The authors quote experimental and rodent research. It points to Arnica's antiseptic, antibiotic, anti-bacterial, anti-fungal, anti-inflammatory, anti-rheumatic, lipid- and cholesterol-reducing, anti-sclerotic, blood-pressure lowering, immune stimulant, cytotoxic, antitumor, diuretic, cholagogue, and granulopoiesis stimulant actions (Saller et al., 1995, p. 52). These interpretations, deduced from basic science methodologies, may elucidate the empirical use of Arnica preparations in TEM.

In contrast to the *Commission E Monograph* (1984a) which exclusively refers to Arnica flowers, the authors list both officially and traditionally recognised active parts of Arnica, as folk medicine continues to use Arnica herb (aerial parts of the plant) and root (rhizome). These are the same plant parts that were officially sanctioned in the German pharmacopoeia until the end of the 19<sup>th</sup> century. It is noteworthy that in 1978 the supplementary text to the German pharmacopoeia, the *Homöopathisches Arzneibuch (HAB)* (1978, p. 205) restored Arnica rhizome as an officially endorsed plant part. Saller et al. (1995, p. 54) state that Arnica preparations can be made with both fresh or dry plant materials, except for Arnica

oil which must be made with dry flowers. Formally approved preparations are tincture, infusion, and oil of Arnica, as well as topical creams.

#### **5.2.2.10 Arnica in Bäumler (2007)**

In Bäumler's (2007) clinical textbook the therapeutic applications of Arnica come full circle. Grounded in the experiences of a seasoned physician of both conventional and natural medicine, the Arnica monograph in *Heilpflanzenpraxis heute: Porträts, Rezepturen, Anwendung* reflects traditional indications based on repeated clinical observations complemented with insights from newer scientific methodologies. Bäumler (2007, pp. 61-63) recommends therapeutic preparations of Arnica in seven use-categories; card-vasc, infection, musc-skel, nerve, respiratory, skin-mucous, and tonic (see Appendix 5). In line with previous medical authors pre-1980, he describes the internal use of Arnica at low doses of 3-10 drops (1:10 tincture) for weakness of the heart, for *Angina pectoris*, and as a tonic in exhaustion from overexertion (Bäumler, 2007, pp. 63, 646). Bäumler notes that allergic reactions are rare and further states that when Arnica is taken correctly side-effects in patients are minimal (Bäumler, 2007, pp. 640-641).

#### **5.2.3 Summary results of empirically endorsed medicinal uses of *Arnica montana* listed in the medical literature: What remained, what changed**

The following section provides the results from triangulating qualitative data recorded in independent medical textbooks on the medicinal uses of *Arnica montana* over a period of 400 years. The data show several indications that were consistently endorsed over this period. When comparing historic with present-day therapeutic uses of Arnica, the results displayed in Appendix 5 demonstrate uninterrupted consistency of empirical evidence on two clusters of therapeutic indications.

Based on repeated and professionally evaluated clinical observations, practising physicians over this period considered Arnica to be beneficial for complaints of the musculo-skeletal and nervous systems. Clinical usage over several centuries means that these treatments fulfil the tradition-of-use criteria well beyond the suggested definition of tradition by the WHO of three generations (75 years) or by the EU of 30 years.

**Table 2. Empirically endorsed medicinal uses of *Arnica montana* listed in medical textbooks over at least 400 years.**

Use-category	Indications
<b>musc-skel</b>	injuries, sprains and strains, torn muscles and ligaments; bruises, oedema, haematoma
<b>nerve</b>	pain related to musculo-skeletal system and nerves

In the 18<sup>th</sup> and 19<sup>th</sup> centuries, insights from experimental research expanded prior use of Arnica thus demonstrating that tradition is not static. The following are additional therapeutic indications noted over the past 200 years; they relate to four use-categories:

**Table 3. Medicinal uses of *Arnica montana* listed in medical textbooks since the end of 18<sup>th</sup> century.**

Use-category	Indications
<b>card-vasc</b>	circulatory insufficiency (since Löseke 1790) varicose veins, phlebitis (topical) (since Kroeber 1948)
<b>respiratory</b>	breathing difficulties / catarrh (since Löseke 1790 until Weiss 1974) sore throat (infection) (since Madaus 1938)
<b>skin-mucous</b>	ulcers, wounds (since Richter 1827) boils (since Schulz 1919) mouth and throat inflammation (since Strumpf 1855)
<b>tonic</b>	heart tonic in exhaustion and debility (since Schulz 1919)

The indications of Arnica for circulatory insufficiency, varicose veins, phlebitis, sore throat, ulcers, wounds, boils, mouth and throat inflammation, and as a heart tonic in exhaustion and debility, meet the EU tradition-of-use criteria of 30 years of continued medicinal use.

However, the therapeutic claims for Arnica as an internal tonic and as a circulatory and coronary stimulant, including for the improvement of breathing, pose a regulatory challenge. These indications fulfilled the tradition-of-use criteria until the 1980s when the Commission E departed from tradition and exclusively authorised external uses of Arnica. Internal uses became re-classified as historical uses, causing a gap in the legal transmission of medicinal knowledge about the correct internal uses of Arnica. Remarkably, despite regulatory cautions since the 1980s, Arnica tinctures and infusions continue to be discussed for internal use in some medical textbooks, for instance in Bäumler (2007, pp. 63, 646). Traditional internal uses of Arnica are also noted in textbooks by European phytotherapists who endorse a low-dose internal use of Arnica in clinical practice (Vonarburg, 1993, pp.

26-27; Willfort, 1975, pp. 53-54; Zizmann, 1996, pp. 218-220). Similarly, such low dose application is evident in customary practice (Mességué, 1977, pp. 31-32). Based on this continued internal use of Arnica in clinical practice, the indications ‘tonic’ and ‘circulatory stimulant’ would benefit from a renewed regulatory benefit-risk assessment to determine their regulatory status since toxicity concerns of Arnica are dose-dependent.

A detailed discussion on indications recorded in the evaluated medical textbooks is provided in Appendix 6. This deeper data analysis serves the purpose of illustrating the initial steps undertaken in the development of the Historical Assessment Tool as a method for the systematic organisation of tradition-of-use data of medicinal plants. It is conducted for the first exemplar (Arnica) only.

### **5.2.3.1 Dosage range recorded in medical textbooks**

Physicians noted a dosage regime between 200mg and 2g of dried flowers or roots, commonly prepared as a medicinal tea taken 3x per day. The lower end of the dosage lines up with the commentary to *DAB 8* (Böhme & Hartke, 1981, p. 165) that recommends an infusion of 200mg of flowers in 200ml hot water, taken by tablespoon full 10ml at a time. Most medical textbooks (see Historic Data Excel spreadsheet), limited the maximum recommended dosage to 1g of flower or root, as exemplified in Hager (1876, pp. 463, 465). Regarding extracts, medical textbooks recommend a dosage range of a 1:10 tincture between 0.12ml and 1.2ml (10 to 30 drops) taken 3 times per day. This dosage also lines up with the recommended safe dosage range listed in the commentary to *DAB 8*, which is 0.3-0.5g (20-30 drops) of tincture (Böhme & Hartke, 1981, p. 165). Since the 19<sup>th</sup> century, medical textbooks caution against overdoses with Arnica due to toxic side-effects.

### **5.2.4 *Arnica montana* in the Prussian and German pharmacopoeias**

This section examines official guidelines on *Arnica montana* listed in the Prussian and German Pharmacopoeias and their unofficial but normative compendiums. The purpose of analysing this body of literature is twofold; firstly, to triangulate their data with the data of the evaluated medical textbooks, and secondly to investigate their suitability as bibliographic evidence to substantiate claims on traditional uses of medicinal plants. It does so by contrasting the data recorded in this body of literature with data recorded in the medical literature.

### 5.2.5 The Prussian pharmacopoeia

Analysis of the Prussian pharmacopoeia, published in seven editions between 1799 and 1862, reveals a fundamental change in the regulatory approach to the European *materia medica*. As said before, up to the end of the 18<sup>th</sup> century guidelines on pharmaceutical preparations and their related therapeutic applications appeared together, but the committee of the 1<sup>st</sup> edition of the *Ph. Borussica* transformed the pharmacopoeia structure into a reference work for drug specifications and pharmaceutical manufacturing only.

Consequently, the sole purpose of the Prussian pharmacopoeia was to provide regulatory guidelines on which plant parts were mandatory pharmacy stock items, their preparations, and quality standards.

The preface to the 4<sup>th</sup> edition of the *Ph. Borussica* (Staberoh, 1827, p. IX) highlights the emerging competing interest between pharmacists and practising physicians. Whilst the authors state that a pharmacopoeia must meet the wishes of both healthcare professions, it is interesting to note that physicians are reprimanded for expecting too many customary medicines to be available. No doubt, in the context of pharmacopoeias, the trend towards emphasising technical over clinical viewpoints was made easier with the separation of technical manufacturing guidelines from therapeutic considerations for patient care. This increasing influence of natural science on the medical repertoire available to European physicians proved to have long-lasting consequences (Tschirch, 1909b, p. 4). The 7<sup>th</sup> and last edition of the *Ph. Borussica* (1862) confirms the upsurge of industrially mass-produced pharmaceutical drugs in place of traditional plants and their applications (Völcker, 1862).

The regulatory separation between drug standards and therapeutic applications remains in Europe and other Western countries to this day. It is also reflected in New Zealand where Medsafe<sup>3</sup>, a business unit of the Ministry of Health, is the authority responsible for the regulation of technical aspects of therapeutic products, while PHARMAC and ACC are responsible for judging their therapeutic suitability for funding (Ministry of Health).

#### 5.2.5.1 Official plant parts in the Prussian pharmacopoeia

The *Arnica montana* monograph published in the 1<sup>st</sup> edition of the Prussian Pharmacopoeia lists flower, herb, leaf, root, and whole plant as mandatory official plant parts (1799, pp. 21,

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<sup>3</sup> Further information on the scope of Medsafe can be found under <https://medsafe.govt.nz/>.

29, 49). They were deemed essential drugs until the 5<sup>th</sup> edition published in 1829 (Dulk, 1847). The 6<sup>th</sup> edition removed the mandatory availability of Arnica leaves and Arnica herb. Arnica flowers *without* receptacle became the official drug from the 6<sup>th</sup> edition onwards. The 7<sup>th</sup> edition removed the mandatory availability of Arnica root. Therefore, by 1862 Arnica flowers *without* receptacle remained the only official drug (Völcker, 1862, p. 80). Commentaries to the 2<sup>nd</sup> (Juch, 1808), 3<sup>rd</sup> (Juch, 1817), and 4<sup>rd</sup> (Juch & Raab, 1830) editions of the *Ph. Borussica* provide some insights into the rationale for changing the official plant drug from Arnica flower *with* receptacle to Arnica flower *without* receptacle. It is noteworthy that the commentator is from southern Germany which highlights the far reach of the Prussian pharmacopoeia. Carl Wilhelm Juch, Bavarian Professor of Chemistry, Natural Science and Nutrition, notes that the receptacles of Arnica flowers are commonly contaminated with eggs or larvae of the Arnica fly (*Tephritis arnica*) when harvested well past flowering (Juch, 1817, p. 246). So that the Arnica flowers avoid contamination, he recommends harvesting them just as they open. However, in line with other commentators he points out that such contaminations are not the real reason for potential irritation in the gastro-intestinal tract; rather, the cause can be found in the acrid active constituents of the plant itself (Dulk, 1833c, pp. 109-112; Juch & Raab, 1830, pp. 24-25). Nonetheless, the 6<sup>th</sup> (1847) and 7<sup>th</sup> (1862) editions of the Prussian pharmacopoeia mandate the use of Arnica flowers without receptacle (Hager, 1865; Mohr, 1849).

#### **5.2.5.2 Official preparations in the Prussian pharmacopoeia**

The Prussian pharmacopoeia endorses three Arnica preparations; hot water infusion, ethanol-water extract, and powder. The 4<sup>th</sup> edition discontinues the ethanol-water extract made with the whole Arnica plant and replaces it with an extract made with Arnica flowers only (Juch & Raab, 1830; Straberoh, 1829, p. 244). Whilst there are no specific references as to how to manufacture an *Arnica* tincture or extract from its drug, there are general directions on the manufacturing of tinctures (Völcker, 1862, p. 199), extracts, and powders (Völcker, 1862, pp. 57-58). It is noteworthy that with each pharmacopoeia edition and related commentaries, the analytical section expands with reports on new discoveries of active constituents and analytical methods (Dulk, 1828, pp. 89-94; 1848; Hager, 1865; Mohr, 1848).

### 5.2.5.3 Listed therapeutic indications in commentaries to the Prussian pharmacopoeia

Analysis of commentaries to the Prussian pharmacopoeias reveals that different commentators provide different therapeutic appraisals, or none at all. Friedrich Mohr, an apothecary and pharmaceutical assessor at the Royal Prussian Medical Association, omits all information relating to therapeutic applications of Arnica preparations and thus limits the clinical usefulness of his annotations (Mohr, 1848, p. 443; 1849, pp. 245, 411). In contrast, the commentary of the Prussian apothecary and pharmaceutical author Hermann Hager (1816-1897) comprehensively discusses therapeutic applications, making his a useful clinical text (Hager, 1865). Unlike other commentators, this author also includes information from pharmacopoeias of two other German states, the kingdom of Hannover and the electorate of Hessen, providing an expanded picture of the regulatory status of Arnica in German states at the time.

**Table 4. Use-categories of *Arnica montana* addressed in the commentaries to the Prussian pharmacopoeia.**

Use-categories	Tabernaemontanus 1664	Dulk 1808 comm. to 2 <sup>nd</sup> Ph. Borussica	Dulk 1813 comm. to 3 <sup>rd</sup> Ph. Borussica	Dulk 1828 comm. to 4 <sup>th</sup> Ph. Borussica	Dulk 1829 comm. to 5 <sup>th</sup> Ph. Borussica	Mohr 1847 comm. to 6 <sup>th</sup> Ph. Borussica (no indications)	Hager 1865 comm. to 7 <sup>th</sup> Ph. Borussica
card-vasc	0	0	0	0	0		✓
gastro-intest	✓	✓	✓	✓	✓		0
gyn	✓	0	0	0	0		0
head	0	0	0	0	0		✓
infection	0	✓	✓	✓	✓		✓
liver-spleen	✓	0	0	0	0		0
musc-skel	✓	✓	✓	✓	✓		✓
nerve	✓	✓	✓	✓	✓		✓
respiratory	0	0	0	0	0		✓
skin-mucous	✓	✓	✓	✓	✓		✓
tonic	✓	✓	✓	✓	✓		(✓)
uro	✓	0	0	0	0		✓
<p style="text-align: center;">Dark green rows refer to continued use            Light green rows refer to intermittent but present-day use            White rows refer to discontinuation            Brackets (✓) reference historical medicinal uses or folk medicine use</p>							

Discrepancies in annotations on recommended therapeutic uses of official plant drugs illustrate that the separation of manufacturing guidelines from officially approved

therapeutic applications opened room for divergent assessments. Commentaries therefore need to be analysed in conjunction with clinical textbooks to understand how comprehensively they reflect contemporaneous medical practice. The two main commentators of the Prussian pharmacopoeia are Friedrich Philipp Dulk (1788-1851) (on the 2<sup>nd</sup> to 5<sup>th</sup> edition) and the aforementioned Hager (on the 7<sup>th</sup> edition). Dulk, like Hager, was a pharmacist. He also lectured in chemistry at the influential Albertus University, Königsberg, and was a practising apothecary in that same East Prussian city.

Table 4 (above) provides an overview of the use-categories covered by the therapeutic indications of *Arnica montana* endorsed by Dulk and Hager in their commentaries to the Prussian pharmacopoeia in comparison to use-categories covered by Tabernaemontanus in the 17<sup>th</sup> century.

#### **5.2.5.4 Dulk's series of commentaries (1808 – 1829)**

Dulk's series of commentaries (1808, 1813, 1828, and 1829) endorses Arnica preparations in treating injuries, bruises, and rheumatism (muscle-skel), for activating nerves in instances of paralysis (nerve), and for diarrhoea (gastro-intest). Moreover, the powder with comminute Arnica flowers is recommended as a snuff for sneezing (tonic and skin-mucous cleansing action) (Dulk, 1828, pp. 89-94; 1833a, pp. 106-107; 1833b, pp. 109-112; 1847, pp. 716-718). The author recommends Arnica leaves for the same indications but recognizes that they are less potent than the flowers. The indications listed by Dulk belong to the same use-categories as those by Tabernaemontanus, but he expands traditional uses by additionally listing Arnica for the treatment of bruises and in rheumatism. Moreover, he expands on tradition by listing Arnica as an antiseptic remedy and as a care for wounds (infection and skin-mucous category). Such applications became prevalent in the 19<sup>th</sup> century on the back of experimental research that was not available when Tabernaemontanus wrote the *Neuw Kreuterbuch*. In contrast to Tabernaemontanus, Dulk discontinues the listing of Arnica as a bitter for humoral detoxification in poisoning (liver-spleen category). This is the only indication in the first half of the 19<sup>th</sup> century where a change in medical theory from humoralism to natural science led to the discontinuation of an indication in the use of Arnica.

Dulk lauds Arnica root for its antiseptic properties, which he attributes to tannins. He claims it to be a more potent antiseptic than other remedies, having the ability to combat sepsis in wounds as well as in internal putrefaction, an action he says surpasses that of Peruvian bark

(*Cinchonae cortex*). Due to its antibacterial properties, he recommends Arnica root over Arnica flowers to stem diarrhoea. Research in the 1970s confirmed that Arnica rhizome and root contain higher levels of essential oils than Arnica flower and petals, thus having a stronger antiseptic action than the above ground plant parts (Willuhn, 1972b, pp. 225-226). Aromatic hydrocarbons are the main group of essential oil constituents in Arnica root; they are thymol derivatives (Pljevljakušić et al., 2012, p. 177).

#### **5.2.5.5 Hager's commentary (1865)**

Hager's (1865, pp. 582-583, 691-692, 1133-1134) commentary discusses therapeutic indications relating to eight use-categories. That is, he expands Dulk's (1828) commentary with indications relating to an additional three use-categories; card-vasc, head, and uro. The use of Arnica to activate diuresis was already discussed by Tabernaemontanus. However, the use of Arnica as a circulatory stimulant, diaphoretic, and treatment for cerebral concussions is an expansion of traditional medical use based on experimental investigations. Like Dulk, Hager recommends Arnica's stimulating and antiseptic effects in the treatment of septicaemia (*atonische Nerven- und Faulfieber*), for the external treatment of bruises due to falls and blows, and for watery ulcers of the skin. These three areas of treatment are also an expansion on traditional indications listed by Tabernaemontanus.

#### **5.2.5.6 Summary results of medicinal uses of *Arnica montana* listed in commentaries to the Prussian pharmacopoeia**

This section analysed commentaries to the Prussian pharmacopoeia as an independent qualitative data source on indications of *Arnica montana* endorsed for regular patient care. The results of this evaluation were used to cross-validate indications listed in the contemporaneous medical literature. Appendix 7 provides the tabulated summary of indications listed in the commentaries to the Prussian pharmacopoeia. A comparison amongst Tabernaemontanus (1664), Dulk (1828), and Hager (1865) shows that all three authors list indications belonging to the musc-skel, nerve, and tonic use-categories; although Hager references the tonic use of Arnica snuffs and tobacco for the first time as a customary rather than regular medicinal application (Hager, 1865, p. 692). Unlike Hager, both Tabernaemontanus and Dulk record the treatment of diarrhoea with Arnica (gastro-intest use-category). Hager's de-listing of this indication is due to the discontinuation of *Arnica radix* from the list of essential drugs in the 7<sup>th</sup> edition of the Prussian

pharmacopoeia, the plant part traditionally used for the treatment of gastro-intestinal ailments (Hager, 1865). Hager disagrees with this regulatory de-listing. He remarks that Arnica flower and root have distinctly different medicinal properties since the root is said to contain high levels of tannins which are not present in the flowers. For this reason, he argues that preparations made from these two different plant parts cannot be interchanged. The distinct properties of Arnica root may be why the contemporaneous *Ph. Hannoverana* and *Ph. Hassia* continue to list Arnica root (Hager, 1865, p. 583). Consequently, Hager (1876, p. 465) lists the use of *Arnica radix* for the treatment of gastro-intestinal complaints in his separate clinical textbook *Handbuch der pharmaceutischen Praxis*.

Comparison of Hager's and Dulk's commentaries with the medical literature of the first half of the 19<sup>th</sup> century (Appendices 5 and 7) reveals that Hager's commentary more closely mirrors clinical applications of Arnica in patient care. Apart from indications relating to the gastro-intest and gyn use-categories, nine use-categories listed by Hager are congruent with those listed in the contemporaneous medical textbooks. As already mentioned, the discontinuation of the indication 'diarrhoea' is due to the removal of *Arnica radix* from the list of essential drugs. Why Hager stopped recommending the use of Arnica to promote menstruation and to cleanse the uterus during the *puerperium* is unknown.

In conclusion, analysis of the Prussian pharmacopoeia shows that this body of literature provides evidence of how official plant parts and their preparations were officially permitted in a European country in the first half of the 19<sup>th</sup> century. It is a legal source of bibliographic evidence concerning an officially endorsed medicinal plant and its preparations. The corresponding authoritative commentaries independently validate the main indications of Arnica recorded in the contemporaneous medical literature. In contrast to medical textbooks, this body of evidence does not, however, encompass the broader long-standing applications recorded in the medical literature. The usefulness of commentaries as a sole body of evidence for therapeutic claims is complicated by the fact that there are several different commentators, each providing a slightly different appraisal of endorsed therapeutic applications for patient care. Therefore, this thesis recommends that commentaries to the Prussian pharmacopoeia are used as *complementary* sources of evidence for therapeutic claims alongside judiciously selected authoritative medical textbooks. These have been shown to represent more comprehensively long-standing clinical uses of Arnica, raising the possibility that they represent more comprehensively long-standing clinical uses of other medicinal plants too.

## 5.2.6 The German pharmacopoeia

This section discusses *Arnica montana* in the regulatory context of the German pharmacopoeia (*Ph. Germanica*), starting with its 1<sup>st</sup> official edition published in 1872 after the formation of the *Deutsches Reich* (German Empire) and continuing to its renamed present-day equivalent *Deutsches Arzneibuch* (*DAB*) (named so since 1926). The first two sections below discuss the official plant parts and official preparations as listed from the 1<sup>st</sup> edition of the *Ph. Germanica* to the 10<sup>th</sup> edition of the *DAB* 2012 (1926; 1968; 1978; 1986; 1993; 2012; 1999; 1910; Hager, 1872; 1890, 1900; 1882). The third section discusses the indications listed in the commentaries to the German pharmacopoeia. The results exemplify consistency in official guidelines on some plant parts and preparations over a 140-year period, but also significant changes in the official scope of *Arnica* from the turn of the 20<sup>th</sup> century, and then again from the 1980s.

### 5.2.6.1 Official *Arnica* plant parts in the German pharmacopoeia

*Arnica montana* is listed consistently in the German pharmacopoeia since its 1<sup>st</sup> edition (Hager, 1872), reflecting *Arnica*'s ongoing significance in professionally delivered healthcare. An analysis of official plant parts reveals consistencies in the recommendation of *Arnica* flower as an official drug as well as an elimination of all other initially official plant parts until their reuptake at the end of the 20<sup>th</sup> century. Their temporary omission over the course of the 19<sup>th</sup> and 20<sup>th</sup> century contrasts with the full range of plant parts used by Tabernaemontanus (aerial parts, flowers, and root) as well as the plant parts referenced in the medical literature published parallel to the German pharmacopoeia. The reduction of official plant parts in the *Ph. Germanica* influenced the recommended indications for *Arnica* in the corresponding commentaries.

*Arnica* flower is the official plant part listed in all editions of the German pharmacopoeia; however, until the 7<sup>th</sup> edition the *Deutsches Arzneibuch* (1968, p. 343), this listing related to *Arnica* flower *without* receptacle only. This requirement was to help avoid potential contamination issues of *Arnica* receptacles with eggs and larvae from the *Arnica* fly, a constraint questioned by commentators ever since its adoption by the German regulator (Anselmino & Gilg, 1911c, pp. 537-539; 1928, pp. 604-607; Bernhard Fischer & C. Hartwich, 1901, pp. 290-291; Hager, 1872, p. 22; 1883a, pp. 750-752; Hager et al., 1891, pp. 663-664; Hirsch & Schneider, 1891, p. 306; Schlickum, 1883, pp. 178-179; Schneider & Süss, 1902, pp. 421-422). Experimental research in the 1970s established that the

receptacle of Arnica contains higher levels of essential oils than the flower, justifying the clinical request for including the receptacle as part of the official drug (Willuhn, 1972b, pp. 225-226).

Arnica root is listed in the inaugural edition of the *Ph. Germanica* (1872) but was discontinued as an essential pharmacy item from the 2<sup>nd</sup> edition onwards (1882). This discontinuation contrasts with nine other European pharmacopoeias, all of which retained the listing of Arnica root, including those of Austria, England, Italy, and Spain (Tschirch, 1909a, p. 1174). The supplements to the German pharmacopoeia, published by the *Deutscher Apotheker-Verein* (German Apothecary Association), also list Arnica root as a drug commonly requested by physicians, traded between pharmacies, or purchased directly by patients for self-medication (Deutscher Apotheker-Verein, 1891, pp. VI, 219; 1906, p. 300). The reason for discontinuing Arnica root as an essential medicine is not discussed in the 2<sup>nd</sup> edition of the German pharmacopoeia, but it may have been due to conservation issues or a re-assessment of various treatment options for diarrhoea and gastro-intestinal infections, the key indications for Arnica root. By de-listing Arnica root, indications relating to the gastro-intestinal tract also became de-listed in the commentaries to the 2<sup>nd</sup> edition of the German pharmacopoeia (Hager, 1883a). Almost one hundred years later, Arnica root was re-introduced as an official plant part in the 1<sup>st</sup> edition of the compendium to the German pharmacopoeia, *HAB I* (1978). Advances in plant science now enable the cultivation of *Arnica montana* for commercial use, mitigating conservation issues associated with Arnica (Jurkiewicz et al., 2010; Pljevljakušić et al., 2014).

From *DAB 9* (1986) to *DAB 1999*, the German regulator permitted a second interchangeable subspecies, *Arnica chamissonis* Less. spp. *foliosa* (Nutt.), with similar active constituents. However, when the German pharmacopoeia harmonised with the European pharmacopoeia, only *Arnica montana* remained as the official species.

#### **5.2.6.2 Official preparations in the German pharmacopoeia**

The Arnica flower as a drug and two preparations derived from it, water infusion and tincture, have consistently been official from the 1<sup>st</sup> edition of the German pharmacopoeia (Hager, 1872) to the 10<sup>th</sup> edition (*DAB 10*, 1993). Arnica preparations were either recommended for internal use or as an external compress. From 1999 onwards, the 1:10 strength tincture prepared from dry flower of Arnica remained the only official extract listed in the German pharmacopoeia (*DAB 1999*, 1999).

*DAB 7* lists for the first time a modern 20-25% Arnica cream prepared with a 1:10 dry plant Arnica tincture, and thus this preparation expands traditional preparations (*DAB 7*, 1968). In addition, *HAB 1*, the official compendium to the German pharmacopoeia, reintroduces preparations that were omitted in the German pharmacopoeia from the end of the 19<sup>th</sup> century. They are mother tinctures prepared with either fresh whole plant or with dry root and rhizome (1:10 extraction ratio) (*HAB 1*, 1978, pp. 198-210). In parallel to *DAB*, the *HAB* compendium also lists a mother tincture with dry Arnica inflorescence. Mother tinctures can be used directly as traditional phytotherapeutic preparations or as a starting preparation for homeopathic compounding (Leivers, 2005). Furthermore, *HAB 1* lists an oil preparation with dry Arnica inflorescence (extraction ratio 1:10) (1978, pp. 202-205).

### **5.2.6.3 Preparations in the commentaries to the German pharmacopoeia**

Analysis of the commentaries and supplements to the consecutive editions of the German pharmacopoeia reveals that the official drug and its extracts were applied in a variety of ways, including the tincture for bath preparations. The drug as a 5-20% water infusion could be applied either as a compress or as an enema, the diluted tincture for a compress, a bath preparation or as a rub, and the drug prepared as a powder or pill for internal use (0.3g - 1g per dose) (Schlickum, 1883; Jehn & Crato, 1901; Schneider & Süß, 1902). However, such preparations were de-listed in the 20<sup>th</sup> century. For example, the medicinal use of compresses was last recommended in the commentary to the 10<sup>th</sup> edition of the *DAB* (1991).

Up to the 4<sup>th</sup> commentary of the German Pharmacopoeia published in 1902, commentators describe two formerly official but by then customary preparations, Arnica snuff and tobacco (Schneider & Süß, 1902). They were commonly applied for their stimulating, toning, and mucous membranes cleansing effects. This custom is reflected in Arnica's Bavarian vernacular name *Schnupftabaksbleum* (Sneeze wort) (Tschirch, 1909a, p. 1175). A preparation that is also absent in the German pharmacopoeias and its commentaries, but listed in its supplementary text, is a *charta*, a medicated paper saturated with Arnica tincture then air dried (Deutscher Apotheker-Verein, 1891, 1897, 1906). These were ready-made stock items stored in pharmacies and hospitals for the swift topical treatment of injuries. They were replaced during the 20<sup>th</sup> century with more convenient topical preparations such as medicated creams and gels. A further unofficial but professionally dispensed preparation was an alcohol distillate made with Arnica flowers to be used as an external disinfectant or

as an internal tonic at a dose of 0.5g (Deutscher Apotheker-Verein, 1930b, 1948). Even though this preparation was dropped as a pharmacy item after WW2, Arnica distillate (or *Schnapps*) remains a customary home preparation in alpine areas of Switzerland, Austria, France, and Germany.

In contrast to these de-listings, the commentary to *DAB 7* newly records a gargle with the official 1:10 dry-plant tincture in a 5-10x dilution (1969, p. 512). This preparation was previously described in medical textbooks for the treatment of strained, inflamed, or infected vocal cords of professional singers (Fischer, 1941, p. 59; Schulz, 1919, p. 298). It is last listed in the commentary to *DAB 8* (1981). In contrast to *DAB*, the *Commission E Monograph* on Arnica (Kommission E, 1984a), a monograph that more closely reflects clinical applications in patient care compared to pharmacopoeia listings and commentaries, approves mouthwash as an officially sanctioned Arnica preparation. This official endorsement enabled the release of such preparations into the market place.

#### **5.2.6.4 Summary results of medicinal uses of *Arnica montana* listed in the commentaries to the German pharmacopoeia**

This section analysed commentaries to the German pharmacopoeia as an independent qualitative data source on indications of *Arnica montana* endorsed for regular patient care. The data was used to cross-validate indications listed in the contemporaneous medical literature. Table 5 below presents the synopsis of all use-categories addressed by indications recorded in the commentaries to the German pharmacopoeia or *Deutsches Arzneibuch (DAB)*. This summary shows that indications relating to the musc-skel and nerve use-categories were consistently cited in all commentaries. Indications relating to the tonic use-category (excitant action and in shock) and uro use-category (diuresis) were listed until the beginning of the 20<sup>th</sup> century when the first major reduction on endorsed indications becomes apparent (Anselmino & Gilg, 1911a, 1911b, 1928). Indications relating to the card-vasc and skin-mucous use-categories were referenced until the 8<sup>th</sup> commentary (Böhme & Hartke, 1983), but de-listed thereafter when the second major reduction on endorsed indications occurred. The remainder of use-categories show intermittent listings based on divergent views of the commentators.

The deletion of indications pertaining to the gastro-intest use-category is connected to the de-listing of the plant part responsible for the therapeutic action in gastro-intestinal infections. Arnica root was listed in the inaugural edition of the *Ph. Germanica* (1872) but

was discontinued as an essential pharmacy item from the 2<sup>nd</sup> edition onwards (1882). Consequently, the listing of the treatment of diarrhoea with Arnica root was also omitted from then on. All indications recorded in the commentaries to the German pharmacopoeia are tabulated in Appendix 8.

Appendix 9 provides an additional appraisal of these indications. The purpose of this in-depth evaluation was to additionally gauge the potential of commentaries as a bibliographic body of evidence for health claims. For this, Appendix 9 provides a comprehensive evaluation of indications endorsed by these commentaries and the context in which they were embedded. Such detailed evaluation is provided only once for the first exemplar.

**Table 5. Use-categories of *Arnica montana* addressed in the commentaries to the German pharmacopoeia editions 1<sup>st</sup> -10<sup>th</sup>.**

Use-categories	Tabernaemontanus 1664	Hager 1874 1 <sup>st</sup> ed.	Hager 1883 2 <sup>nd</sup> ed.	Schliekum 1882 2 <sup>nd</sup> ed.	Hager 1891/1892 3 <sup>rd</sup> ed.	Hirsch & Schneider 1891 3 <sup>rd</sup> ed.	Fischer & Hartwich 1901	Jehn & Crato 1901 4 <sup>th</sup> ed.	Schneider & Süß 1902 4 <sup>th</sup> ed.	Anselmino & Gilg 1911 5 <sup>th</sup> ed.	Anselmino & Gilg 1928 6 <sup>th</sup> ed.	Böhme & Hartke 1969 7 <sup>th</sup> ed.	Böhme & Hartke 1981 8 <sup>th</sup> ed.	Hartke & Mutschler 1986 9 <sup>th</sup> ed.	Hartke 1993 10 <sup>th</sup> ed.
card-vasc	0	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	0	0
gastro-intest	✓	✓	0	0	0		0	0	0	0	0	0	0	0	0
gyn	✓	0	0	0	0		0	0	0	0	0	0	(✓)	0	0
head	0	✓	✓	0	✓		✓	0	✓	0	0	0	0	0	0
infection	0	✓	✓	0	✓		✓	0	✓	0	0	0	0	0	0
liver-spleen	✓	0	0	0	0		0	0	0	0	0	0	0	0	0
musc-skel	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
nerve	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
respiratory	0	✓	✓	0	✓		✓	0	0	0	0	0	0	0	0
skin-mucous	✓	✓	✓	0	✓		✓	0	✓	✓	✓	✓	✓	0	0
tonic	✓	✓	✓	0	✓		✓	0	✓	✓	✓	0	0	0	0
uro	✓	✓	✓	0	✓		✓	0	✓	0	0	0	0	0	0
<p><i>Dark green rows refer to continued use</i>  <i>Light green rows refer to intermittent but present-day use</i>  <i>White rows refer to present-day discontinuation</i>  <i>Brackets (✓) reference historical medicinal uses or folk medicine use</i></p>															

The most consistently endorsed indications in scholarly commentaries to the German pharmacopoeia from 1874 until 1981, as listed either in *all* commentaries (card-vasc, musc-skel, and nerve use-categories) or in *most* commentaries (skin-mucous use-category), are as follows:

**Table 6. Endorsed indications for *Arnica montana* in the commentaries to the German pharmacopoeia 1874-1981.**

Use-category	Indications
card-vasc	circulatory insufficiency
musc-skel	blunt injuries, sprains, strains; bruises, oedema, haematoma
nerve	nerve and muscle pain
skin-mucous	ulcers / wounds

Commentaries after the mid-1980s departed from a favourable benefit-risk assessment for internal uses of Arnica as a cardio-vascular stimulant and as a topical disinfectant in wound care (1993; Hartke, Bertram, Mutschler, & Althoff, 1987). This assessment was in line with regulatory guidelines that permitted external uses of Arnica only. However, it contrasted with the Austrian pharmacopoeia *ÖAB 90* and *HAB* which permit the internal use of Arnica preparations at a low dose (Blaschek et al., 2012, pp. 12, 16). This recent regulatory-driven reduction in the scope of *Arnica montana* is the biggest shift of Arnica’s regular medicinal uses in Germany over the past 400 years. The 1980s were a watershed in Europe for the risk assessment of medicinal plants. This period now stands out for its noticeable regulatory low tolerance for any potential risks in relation to plant derived medicines (Zepernick, Langhammer, & Lüdcke, 1983). It is a context in which endorsement of internal and topical disinfectant applications of Arnica was omitted from *DAB 9* and its commentaries onwards; no information could be found in the German pharmacopoeia itself or in its commentary on a dose-dependent risk assessment in relation to these changes. This new regulatory approach to plant medicines coincided with emerging themes of danger and risk, which became prominent features of the biomedical discourse on herbal medicine (Lewis, 2011). *DAB 9* (1986) and its commentary (1987) exemplify this shift by displaying an increased focus on plant toxicology, potential risks, and side-effects. While this shift was aimed at protecting the public, it is significant that very few clinical herbal experts were selected to co-author the more recent monographs in *DAB*, as evident in the author list of the preface to *DAB 9*. It is noteworthy that commentaries to the 9<sup>th</sup> (1986) and 10<sup>th</sup> (1991) editions of *DAB* record

fewer indications than were *legally* permitted by the *Commission E Monograph* on Arnica (Kommission E, 1984a). In this official monograph, Arnica was additionally approved as a topical disinfectant to treat boils, inflammation of mucous membranes in the mouth and throat, and inflammation caused by insect bites.

By the end of the 20<sup>th</sup> century, the remaining entries in the commentary to *DAB 10* (1993, p. 190), compared with entries in medical textbooks, are as follows:

**Table 7. Indications for *Arnica montana* endorsed in the commentary to *DAB 10* (1993) compared with indications listed in the medical literature.**

Use-category	Indications listed in the 10 <sup>th</sup> commentaries to the German pharmacopoeia	Indications <i>consistently</i> listed in medical literature >30 years	Indications <i>consistently</i> listed in medical literature >150 years:
<b>musc-skel</b>	blunt injuries, sprains, strains; bruises, oedema, haematoma	injuries, sprains and strains, torn muscles and ligaments; bruises, oedema, haematoma	injuries, sprains and strains, torn muscles and ligaments; bruises, oedema, haematoma
<b>nerve</b>	muscle and joint pain	pain related to musculo-skeletal system and nerves	pain related to musculo-skeletal system and nerves
<b>tonic</b>		heart tonic in exhaustion and debility	tonic
<b>card-vasc</b>		varicose veins / phlebitis (topical)	circulatory insufficiency (since 1790)
<b>respiratory</b>		sore throat (infection)	breathing difficulties / catarrh (until Weiss 1974)
<b>skin-mucous</b>		mouth and throat (inflammation); boils	ulcers, wounds (since Richter 1827)

These remaining indications recorded in the commentaries to the German pharmacopoeia are in line with the main indications consistently listed in the evaluated medical literature over the past 400 years. Yet indications relating to the cardio-vascular and respiratory systems, and those relating to the skin and mucous membranes, became de-listed despite consistent clinical use.

In conclusion, Pharmacopoeias provide a legal source of bibliographic evidence on an officially endorsed plant drug and its preparations and should be permitted as a verified reference. The corresponding authoritative commentaries independently validate all main indications of Arnica applied in regular medicine during this time as recorded in the medical literature. A comparison of commentaries to the German pharmacopoeia and medical textbooks highlights that the commentaries are a less comprehensive source of data

on actual clinical use of medicinal plants than contemporaneous medical textbooks. As with the commentaries to the Prussian pharmacopoeia, the usefulness of commentaries as a body of evidence for claims is complicated by the fact that there were at times several different commentators to a pharmacopoeia edition, each providing a slightly different appraisal of recommended therapeutic applications for patient care. This thesis proposes that commentaries to the German pharmacopoeia could be used as *complementary* sources of evidence for therapeutic claims alongside judiciously selected authoritative medical textbooks. The evaluated medical textbooks have shown to represent more comprehensively long-standing clinical uses of Arnica compared to those listed in the contemporaneous commentaries to the German pharmacopoeia. This raises the possibility that they represent more comprehensively long-standing clinical uses of other medicinal plants too.

### **5.2.7 *Arnica montana* in regulatory and authoritative expert monographs**

The following section investigates how 20<sup>th</sup> century official and authoritative herbal monographs represent Arnica. It then triangulates the endorsed therapeutic indications listed in those monographs with therapeutic indications listed in medical textbooks.

This study analyses the following two official Arnica monographs:

- The *Kommission E Monografie (Commission E Monograph) Arnicae flos* by the German Ministry of Health (1984)
- The *European Union (EU) Herbal Monograph Arnicae flos* by the European Medicine Agency (2014).

These assess and sanction officially the therapeutic scope and safety of Arnica, therefore creating a regulatory pathway for Arnica products to be sold in the marketplace if those products adhere to the monograph's approved claims and guidelines.

Additionally, this study evaluates three authoritative expert monographs on Arnica:

- The *ESCOP Monograph Arnica flos* (2003)
- The *WHO Monograph Flos Arnicae* by the World Health Organisation (2007)
- The Arnica monograph in the pharmaceutical reference work *HagerROM. Hagers Enzyklopädie der Arzneistoffe und Drogen* (2012).

These latter three have no legal status but represent expert evaluations; they may be used as bibliographical sources to substantiate therapeutic claims when applying for a registration

of a plant-based medicine, for example in the EU (Anagnostou, 2017, pp. 8-9; Steinhoff, 2017, p. 18).

Table 8 gives an overview of the use-categories covered by indications discussed in these five monographs.

**Table 8. Use-categories of *Arnica montana* addressed in official and authoritative monographs**

Use-categories	Indications in medical literature 400 years	Indications in medical literature > 30 years	Kommission E 1984 official	EMA 2014 official	ESCOP 2003 clinical expertise	WHO 2007 clinical expertise	HagerROM 2012 clinical expertise
card-vasc	0	✓	✓	0	(✓)	✓	✓
gastro-intest	intermittent	0	0	0	0	✓	0
gyn	intermittent	0	0	0	0	✓	(✓)
head	intermittent	0	0	0	0	0	0
infection	intermittent	0	0	0	0	0	(✓)
liver-spleen	pre-modern	0	0	0	0	0	0
musc-skel	✓	✓	✓	✓	✓	✓	✓
nerve	✓	✓	✓	✓	✓	✓	✓
respiratory	intermittent	✓	✓	0	0	✓	✓
skin-mucous	intermittent	✓	✓	0	✓	✓	✓
tonic	✓	✓	0	0	0	0	(✓)
uro	intermittent	0	0	0	0	0	0

*Dark green rows refer to continued use*  
*Light green rows refer to intermittent but present-day use*  
*White rows refer to present-day discontinuation*  
*Brackets (✓) reference historical medicinal uses or folk medicine use*

The *Kommission E Monografie (Commission E Monograph)* is a regulatory monograph by the former German *Bundesgesundheitsamt (BGA)* (German Ministry of Health) that provided approved claims for sale of plant-based medicines based on empirical and scientific evidence.

The *European Union Herbal Monograph* is a regulatory monograph authored by the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) based on consensus of 28 EU Member States. The *Arnica* monograph evaluated was a “traditional use” monograph.

The ESCOP, WHO and HagerROM monographs are expert monographs and provide broader perspectives on clinical use of a medicinal plant.

Appendix 10 tabulates all indications listed for *Arnica montana* in official and authoritative monographs, comparing them with indications listed in medical textbooks over the past 400 years. It is striking that indications listed for the treatment of musculo-skeletal ailments due to injuries and accidents, and pain associated with the musculo-skeletal system and nerves are listed across all independent sources and data points. The *EU Herbal Monograph Arnicae flos 2014* is the only monograph that does not list indications relating to the skin-mucous category. In addition, all sources except the *EU Herbal Monograph Arnicae flos 2014* and *ESCOP Monograph Arnica flos (2003)* also list indications correlating to the cardio-vasc and respiratory use-categories. The five evaluated monographs are now discussed further below.

### **5.2.8 Regulatory monographs**

The following sections evaluate two official monographs, the *Commission E Monograph Arnicae flos (1984)* and the *EU Herbal Monograph Arnicae flos (2014)* as independent qualitative sources to cross-validate therapeutic information recorded in authoritative medical textbooks.

#### **5.2.8.1 The Commission E Monograph Arnicae flos (1984)**

The *Commission E Monograph Arnicae flos* of the former German *Bundesgesundheitsamt* (BAG) (the German Ministry of Health) was published in 1984 (Kommission E, 1984a) and provided the legal basis for the registration of Arnica preparations in the German market as mandated by the Second Medicines Act 1976 (*Arzneimittelgesetz 1976* or AMG 76). It specifies that the composition of the drug consists of the fresh or dry inflorescence of *Arnica montana* L. or *A. chamissonis* Less. subsp. *foliosa* (Nutt.) Maguiere [Fam. Asteraceae]. Its endorsed preparations consist of cut herb or powder, tinctures, creams, and oils. The dosage range is as follows:

Infusion:

- 2 g of herb per 100 ml of water.

Tincture for cataplasm:

- Tincture in 3 - 10 times dilution.

For mouth rinses:

- Tincture in 10 times dilution.

As ointment:

- Not more than 20 - 25 percent tincture.

Arnica oil:

- Extract of 1 part herb and 5 parts fatty oil.
- Ointments with not more than 15 percent of Arnica oil.

The monograph describes the anti-inflammatory, analgesic and antiseptic activities of Arnica and permits claims for the following external indications (translated from German):

- injury and consequences of accidents, e.g., haematoma, dislocations, contusions, and oedema due to fracture
- rheumatic muscle and joint problems
- inflammation of the oral and throat region
- furunculosis (boils)
- inflammation caused by insect bites
- superficial phlebitis.

The approved therapeutic claims of Arnica in the treatment of injuries and effects of accidents (muscle-skeletal and nerve use-categories) are congruent with the therapeutic uses of Arnica listed in the 4<sup>th</sup> edition of Tabernaemontanus' medical textbook published in 1664. The indication of rheumatic muscle and joint problems has been noted in the European medical repertoire of Arnica since the end of the 18<sup>th</sup> century (Löseke 1799), whilst the indications of inflammation of the oral and throat region (respiratory use-category), furunculosis, insect bites (skin-mucous use-category), and surface phlebitis (skin-mucous/cardio-vascular use-categories) are modern nosologies of the 20<sup>th</sup> century (see Appendix 5). Thus, the *Commission E Monograph Arnicae flos* covers indications relating to five of the six use-categories consistently endorsed in clinical medical textbooks (the tonic use-category is missing). It provides a rounded reflection of external clinical uses of Arnica in European healthcare.

Since the *Commission E Monograph Arnicae flos* recommends Arnica for external use only, there are no endorsed indications relating to the internal use of Arnica for supporting the cardio-vascular system and for achieving a tonic effect. This lack of endorsement of internal uses contrasts with medicinal uses of Arnica over the previous 400 years. As already noted, the 1980s were a watershed for risk assessments of medicinal plants, with a new preventative approach to public health and safety resulting in a low tolerance for any risk pertaining to plant drugs. There seems to have been disagreement within the Commission E

committee about the official negative safety assessment of Arnica for internal use. Whilst some members took a cautionary approach and won the argument, others claimed that this monograph incorporates a modern overestimation of Arnica's toxicity relative to the long-standing clinical experiences of its safety when prescribed within the appropriate therapeutic range (Weiss & Fintelmann, 1997, p. 163).

The *Commission E Monograph Arnicae flos* states that interactions with pharmaceutical drugs are unknown. It warns, however, of potential detrimental effects of Arnica preparations in prolonged treatment of damaged skin, such as in injuries or *Ulcus cruris* (indolent leg ulcers), which may cause oedematous dermatitis with the formation of pustules and eczema. Additionally, treatments involving high concentrations of Arnica are noted to cause primary toxic skin reactions with the formation of vesicles or even necrosis (Kommission E, 1984a, para. Nebenwirkungen). Nonetheless, the monograph permits the use of Arnica on small areas of broken skin when applied appropriately. This approval aligns with the traditional use of Arnica as a wound disinfectant on small surfaces.

#### **5.2.8.2 The EU Herbal Monograph *Arnicae flos* (2014)**

The *EU Herbal Monograph Arnicae flos* (Committee on Herbal Medicinal Products (HMPC), 2014b) is a monograph based on traditional clinical usage. Claims in the traditional use category are accepted on the basis of sufficient safety data and plausible effectiveness (Europäisches Parlament, 2004). Its relative brevity compared to the monograph on Arnica authored by the German Commission E derives from a multi-national process mandating that permitted indications, modes of application, proof of effectiveness, and safety (innocuousness) must be agreed upon by majority consensus of all 28 EU Member States (Committee on Herbal Medicinal Products (HMPC), 2013). Accordingly, Member States where Arnica does not have traditional clinical significance could veto long-standing national acceptance by others. Thus, the *EU Herbal Monograph Arnicae flos* reflects a pragmatic political compromise. It had to consider other factors than clinical evaluations. Similar difficulties in harmonising local medical customs across many nations became apparent during the writing of the first German pharmacopoeia in the 1870s (as discussed in the Materials and Methods chapter).

The *EU Herbal Monograph Arnicae flos* (Committee on Herbal Medicinal Products (HMPC), 2014b, p. 3) permits external use of Arnica flower preparations for the following three indications:

- relief of bruises
- sprains
- localised muscular pain.

The pre-approved preparations with Arnica flower are:

- tincture (1:10), extraction solvent ethanol 60% or 70%
- tincture (1:5), extraction solvent: ethanol 60%
- liquid extracts of fresh flowers (1:20), extraction solvent: ethanol 50%.

The dosage regime for semi-solid or liquid preparations for cutaneous (topical) is prescribed as follows:

- semi-solid dosage form: 20-25% tincture in base to apply on the affected area two to three times daily
- liquid dosage form: 2.5 ml of tincture as an impregnated dressing to apply on the affected area three to four times daily
- semi-solid dosage form: 20% tincture in base to apply on the affected area two to three times daily
- semi-solid dosage form: 50% liquid extract in base to apply a thin layer on the affected area two to four times daily.

The pre-approved indications relate to the musculo-skeletal and nervous systems, reflecting the main indications for Arnica as continuously documented over the past 400 years. Thus, these indications accurately capture long-established traditional uses in regular European healthcare. However, the monograph also makes it obvious that the current regulatory approach does not make full use of further available empirical evidence on traditional uses as methodically coded in historical sources. Since the end of the 18<sup>th</sup> century, additional traditional indications have been consistently documented in the German medical literature, and those traditional indications of Arnica could have been considered in this traditional use monograph (see Appendix 5):

- as a circulatory stimulant
- in varicose veins /phlebitis
- in rheumatic muscle and joint problems
- in sore throat

- in wounds
- in boils
- in inflammation of the mouth and throat.

The long-standing clinical indications listed above, despite being consistently recorded in medical textbooks and also legally permitted in one of its Member States, Germany, were not considered by the HMPC for the final monograph on Arnica. The omission of these indications is surprising. The Assessment Report (Committee on Herbal Medicinal Products (HMPC), 2014a) recognises that Arnica's wound-healing effects were already documented in the early modern period by Tabernaemontanus. It further emphasises medieval uses of Arnica for haematoma, injuries, varicose issues, phlebitis, gout, rheumatism, indigestion, and cardiovascular disease. Moreover, the Assessment Report states that Arnica has been used in Germany at least since 1957 as an official remedy for recovery from injury; for the effects of trauma such as haematoma, distortions (dislocation and sprains), contusions (bruises), and oedema due to fracture; for the systemic treatment of rheumatic muscle and joint complaints, furunculosis, inflammations caused by insect bites, and superficial phlebitis; and for the treatment of inflammations of the oral and throat region, such as gingivitis and aphthous ulcers. Notwithstanding this reference to the officially approved uses in the German healthcare system, a systematic appraisal of historical evidence on traditional use could not be found in this Assessment Report on Arnica and the aforementioned additional long-standing indications were not officially listed in the final, approved monograph.

The relative paucity of indications in the *EU Herbal Monograph Arnicae flos* thus exposes some challenges in the execution of the EU Directive 2004/24/EC for traditional use since the Directive stipulates that a medicinal product containing a herbal substance must have proof of tradition for 30 years. The problematic nature of this time frame is noted in the Assessment Report on Arnica itself, stating that only herbal preparations evidenced over the preceding 30 years at a specific posology could be included in the final monograph (Committee on Herbal Medicinal Products (HMPC), 2014a, p. 3). It then excludes traditional water and oil extracts of Arnica despite their consistent listings in the German pharmacopoeia and official compendia (*HAB*), their long-standing documented use in the medical literature, and their official approval by the German Ministry of Health in 1984 (Kommission E, 1984a).

There are different concepts of “tradition” (Dal Cero, 2016, pp. 8-13). A regulator will consider indications depending on the approach to its concept of “tradition”. In the *anthropological* sense, “tradition” is seen as the transfer of knowledge over three generations (Shils, 1981), but Helmstädter and Staiger argue that the life span of a generation may vary widely depending on context (Helmstädter & Staiger, 2012, pp. 94-95). In a *medical* tradition, two steps of transmission are achieved in a period of 21-30 years since it takes between seven and 10 years to train a physician. This timeframe is similar to the guidelines in the EU Directive 2004/24/EG which requests a tradition-of-use proof of a herbal medicinal product for 30 years, of which 15 must be in the EU. The stipulation of 30 years of proof of tradition is, however, a regulatory construct for the purpose of harmonising traditional medicinal products in the European market (Jütte et al., 2017, p. 220). If applied rigidly, this timeframe does not reflect the dynamic nature of medicine and how it evolves in order to stay relevant (Patwardhan, Vaidya, Chorghade, & Joshi, 2008; Shils, 1981; Staub et al., 2016).

Traditional recipes are commonly adapted over time to reflect local conditions, the availability of raw materials, and the therapeutic situation (Schwabl & Vennos, 2015, p. 113). Technical advances, market conditions, customer preferences, and regulatory mandates may all influence the type of preparations sold, while the use of specific plant parts may change due to availability and conservation issues. The World Intellectual Property Organization (WIPO), an international body concerned with the protection of traditional knowledge (TK), also underlines that TK refers to knowledge systems, creations, and innovations which are constantly evolving in response to changing environments. As such, TK is not just continuous reproduction; it is also about innovating and creating within the traditional framework (Intergovernmental Committee on Intellectual Property and Genetic Resources Traditional Knowledge and Folklore, 2010, Appendix, p.14). A rigid requirement of proof of tradition for 30 years may therefore be too short or too long. Such a requirement might also fail to consider that tradition is preserved—even when some modifications in preparations and their applications take place over the years (Helmstädter & Staiger, 2014, p. 5). Accordingly, the use of medicinal plants at a given time is dependent on cognitive features such as perception and assessment, ecological factors, and cultural history; they all contribute to the evolution of a tradition (Leonti, 2011). Thus, the stipulated timeframe of 30 years proof ensured the approval of core indications of Arnica while also

hindering broader representation of Arnica's medical tradition or regional medical diversity in European countries.

Traditional use registrations are accepted in the EU on the basis of sufficient safety data and plausible efficacy. The *EU Herbal Monograph Arnicae flos* cautions against the internal use of Arnica without referencing dose-dependent effects. It lists a raft of cautions, most remarkably ones against topical applications of Arnica in children under 12 years of age or in pregnancy. These are not due to actual safety concerns but a lack of contemporary scientific safety data (Committee on Herbal Medicinal Products (HMPC), 2014b, p. 4). EMA's safety statement on the limitations for topical use significantly departs from that of the preceding German *Commission E Monograph Arnicae flos* which did not limit external use of Arnica to non-pregnant adolescents and adults. It further sits at odds with long-standing traditional uses of Arnica as noted in the medical literature.

### **5.2.9 Authoritative expert monographs**

The following section triangulates three independent authoritative expert monographs on *Arnica montana* and compares them with the two official European monographs as well as the Arnica monographs recorded in the medical literature.

#### **5.2.9.1 The ESCOP Monograph Arnica flos (2003)**

The *ESCOP Monograph Arnica flos* (ESCOP, 2003a, pp. 43-47), is an authoritative monograph published by the professional body representing national phytotherapy organisations across Europe. It specifies the whole or partially broken fresh or dried flowerheads of *Arnica montana* as the official drug which must comply with European pharmacopoeia quality standards (ESCOP, 2003a, p. 43). Endorsed preparations are ointments, creams, gels or compresses made with 5-25% V/V tinctures or fluid extract, or with diluted tinctures (1:3 or 1:10 extraction ratio), or diluted fluid extracts, or a decoction of 2.0g of dried Arnica flower extracted in 100ml of water. There is no guideline on how often they are to be applied, but the monograph states that overdoses are not expected with external use (ESCOP, 2003a, pp. 43-44).

The *ESCOP Monograph Arnica flos* confirms the anti-inflammatory, antimicrobial, and cytotoxic actions of Arnica based on *in vitro* and *in vivo* experiments. It recommends Arnica preparations for six different indications, all as external applications (ESCOP, 2003a, pp. 43-47):

- bruises
- sprains
- inflammation caused by insect bites
- gingivitis
- aphthous ulcers
- symptomatic treatment of rheumatic complaints.

Compared with the approved indications listed in the *Commission E Monograph Arnicae flos*, the *ESCOP Monograph Arnica flos* lists fewer recommendations, since indications of superficial phlebitis, boils (furunculosis) and inflammation of the oral and throat region are absent. Indications noted in the *ESCOP Monograph Arnica flos* therefore exclusively cover the musc-skel, nerve and skin-mucous use-categories. Indications relating to the musculo-skeletal and nervous systems have been consistently recorded in the medical literature over the past 400 years. Indications relating to the skin and mucous membranes have been consistently recorded since the first quarter of the 19<sup>th</sup> century (Richter 1827). This latter use-category is supported by *in vitro* tests demonstrating antimicrobial activity of Arnica constituents on infections localised on skin and mucous membrane surfaces (ESCOP, 2003a, p. 44).

In contrast to the *Commission E Monograph Arnicae flos* (1984) which endorses superficial phlebitis as an approved claim, the *ESCOP Monograph Arnica flos* lists no indications related to the card-vasc use-category. The *ESCOP monograph Arnica flos* discusses, however, two randomised, double-blind, placebo-controlled studies with patients suffering from chronic venous insufficiency (primary varicosis) in the legs, where swelling and pain were significantly more relieved after the *verum* treatment with an Arnica gel or ointment in one study, while comparable improvements but no difference between groups were shown in the other (ESCOP, 2003a, p. 45). Nonetheless, the indication ‘varicose veins’ is not listed in the ‘Therapeutic Indications’ list (ESCOP, 2003a, p. 43); therefore these indications are referenced in Table 8 above and Appendix 10 in brackets and italics only.

The *ESCOP Monograph Arnica flos* highlights the analgesic activity of Arnica in muscle ache which was confirmed in a small clinical trial (ESCOP, 2003a, p. 45). Even so, the indication ‘muscle ache’ is also not listed as a ‘Therapeutic Indication’. This is surprising as a cross-check with the medical literature confirms that the therapeutic action of Arnica to alleviate pain of the musculo-skeletal system has been empirically observed by physicians

at least since the early modern period (see Tabernaemontanus Appendix 5). Rheumatic muscle and joint problems were also official claims in the *Commission E Monograph Arnicae flos* but are not recorded in the ESCOP monograph.

The *ESCOP Monograph Arnica flos* lists the following contra-indications and warnings:

- contra-indicated in allergy to Arnica or other members of the *Compositae* family
- for external use only
- not to be used on open wounds.

The monograph notes that skin irritations have been reported and that dermatitis from Arnica may occur in susceptible individuals. The contra-indication for Arnica on any open wounds is noteworthy as the use of Arnica in boils (furunculosis) and insect bites was permitted in the *Commission E Monograph Arnicae flos*.

#### **5.2.9.2 The WHO Monograph Flos Arnicae (2007)**

The *WHO Monograph Flos Arnicae* (World Health Organization, 2007, pp. 77-87) covers a wide range of detailed expert information on traditional uses and scientific research. As Arnica is harvested, cultivated and used across many countries, the monograph begins with detailed information on the correct identification of this medicinal plant. It provides a botanical and microscopic description for drug identification, including its organoleptic properties which are described as aromatic in odour and bitter and acrid in taste. This aligns with the organoleptic description of Arnica in Tabernaemontanus (see Appendix 4).

The thorough botanical identification methods provided in the *WHO Monograph Flos Arnicae* are essential. Plant substitution, accidental or deliberate adulteration, and the use of non-therapeutic plant fillers are widely recognised as problematic and potentially hazardous (Bennett & Balick, 2014; Heinrich & Verpoorte, 2014, p. 385; Rivera et al., 2014). For example, *Arnica montana* is quite frequently adulterated with Mexican Arnica (*Heterotheca inulides*), *Arnica chamissonis* ssp., and *Calendula officinalis* which are sold as substitutes (Engels & Brinckmann, 2015, p. 6). Additionally, local replacements of one species with another that has similar therapeutic effects is common. A recent investigation of products sold under the name of “Arnica” showed that they did not contain *Arnica montana* but *Trixis inula*, *Heterotheca subaxillaris*, *Grindelia* spp., and *Pseudogynoxys* spp. (Aguilar, 2015, p. iv). While these plants have similar properties to *Arnica montana* and have been used by local populations as legitimate local replacements for *Arnica montana* in relation to

similar complaints, these cases highlight that the vernacular name “Arnica” does not conclusively refer to *Arnica montana* but can refer to other local plant species, much as was the case in pre-Linnean times. Therefore, the *WHO Monograph Flos Arnicae* provides important botanical identification tools to the international community. The unequivocal botanical identification of *Arnica montana* is essential for an accurate vetting of traditional uses for regulatory purposes.

The *WHO Monograph Flos Arnicae* (2007, pp. 77-87) defines the dried flowerheads (*capitula*) of *Arnica montana* as the desired herbal drug part. Other parts of Arnica traditionally used in European countries, namely the herb, root or whole plant, are not listed. Unlike the *Commission E Monograph Arnicae flos*, the *ESCOP Monograph Arnicae flos*, and the evaluated European medical literature, the *WHO Monograph Flos Arnicae* does not reference the fresh flowerhead as starting material for preparations.

The *WHO Monograph Flos Arnicae* recommends the *external* use of Arnica as an undiluted tincture, a compress with either a water infusion or a tincture, a mouth rinse with a 10-fold dilution of a 1:10 tincture, or an ointment with tincture or essential oil of Arnica. There is no posology available for *internal* use, although internal use is referenced under traditional medicine.

The monograph is divided into three sections; “Uses described in pharmacopoeias and well established documents”, “Uses described in traditional medicine” and “Medicinal Uses” (World Health Organization, 2007, pp. 80-81). It cites experimental pharmacology based on *in vitro* and animal studies to support the analgesic, anti-inflammatory, antioxidant, anti-tumour, cardiovascular, choleric and uterine stimulant effects of Arnica.

Under “Uses described in pharmacopoeias and well established documents” the *WHO Monograph Flos Arnicae* (World Health Organization, 2007, pp. 80-81) lists Arnica flower preparations as topical counterirritants for the treatment of pain and inflammation resulting from:

- minor injuries and accidents, including bruises, ecchymosis, haematomas and petechiae
- inflammation of the oral mucous membranes
- insect bites
- superficial phlebitis.

Therefore, this section lists indications belonging to the musc-skel and nerve use-categories, both of which have been consistently referenced over the past 400 years. The inflammation of the oral mucous membranes indication (skin-mucous use-category) was first listed in Strumpf (1855), while the insect bites and superficial phlebitis indications are 20<sup>th</sup> century nosologies. These mirror the indications listed in the *Commission E Monograph Arnicae flos*, except that ‘furunculosis’ and ‘rheumatic muscle and joint problems’ are absent from this section of the *WHO Monograph Flos Arnicae*. Rheumatism is, however, mentioned later in the traditional medicine section.

Under the section “Uses described in traditional medicine” the WHO monograph adds these indications; indigestion (gastro-intest), cardiovascular disease (cardio-vasc), rheumatism (musc-skel; nerve), and to induce menstruation (gyn) (World Health Organization, 2007, p. 81). These indications were collated from a database research on NAPRALERT<sup>4</sup>. A check on this database (accessed 30.6.2017) reveals that most of the listed articles relate to *in vitro* and animal trials. References to medical textbooks by European physicians as well as textbooks on the *materia medica* of other bioregions could not be found. Thus, a large body of empirical evidence from the professional medical literature was missed, meaning that evidence was only partially captured and is larger than shown in this monograph.

While cardio-vascular diseases and rheumatism are listed under traditional use, experimental scientific research since the 1940s confirms the cardio-vascular stimulant and positive inotropic effects of Arnica (Erley, 1965; Gessner, 1949; Schulz, Hänsel, & Tyler, 1998, pp. 260-262). Rheumatism as an indication is listed in the 8<sup>th</sup> commentary to the German pharmacopoeia based on understanding the mechanism of Arnica in the treatment of rheumatism (Böhme & Hartke, 1981). Two clinical trials also confirm the therapeutic efficacy of Arnica in treating osteoarthritis (Knuesel, Weber, & Suter, 2002; Widrig, Suter, Saller, & Melzer, 2007). Consequently, these indications could have been listed in the section ‘Uses described in pharmacopoeias and well established documents’ as well as in the section ‘Medicinal uses’ (see below).

Under the section “Medicinal uses”, the *WHO Monograph Flos Arnicae* states that no clinical data on humans could be found to support specific indications (World Health Organization, 2007, p. 80). This contradicts the results of the database research undertaken

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<sup>4</sup> For further information on NAPRALERT visit <https://www.napralert.org/>.

as part of this thesis which returned for the period up to 2007 several clinical trials, 2007 being the year the WHO monograph was published. The following clinical research studies on phytotherapeutic, non-homoeopathic preparations containing Arnica as the sole active substance and published before 2007 in German, Dutch, French or English showed positive clinical research findings for Arnica for the following indications (see Appendix 11): improvement of coronary circulation (observational study of internal use) (Erley, 1965); improvement of venous insufficiency (RCTs of gel, cream and bath preparation) (Brock, 1991, 2001; Uehleke, 1996a, 1996b); improved recovery of post-training muscular pain with an Arnica gel (RCT) (Moog-Schulze, 1993); and reduced pain and stiffness in people with mild-moderate osteoarthritis of the knee (open multicentre clinical trial) (Knuesel et al., 2002). A further RCT published in the same year as the *WHO Monograph Flos Arnicae*, compares an Arnica gel with a NSAID (ibuprofen 5%) and demonstrated its equivalence in the treatment of pain and function in osteoarthritis (Widrig et al., 2007).

The *WHO monograph Flos Arnicae* deliberates on three safety aspects of Arnica: in pregnancy and lactation, allergy potential, and internal use. Regarding the first, the text states that the safety of Arnica during pregnancy and nursing has not been established based on contemporary toxicity assessments in humans. The *WHO Monograph Flos Arnicae* quotes, however, two rodent studies which report a uterine stimulant effect from Arnica flower tincture (World Health Organization, 2007, p. 82). These studies do not declare the dosage regime applied so do not provide meaningful information in this context. Regarding teratogenicity, the *WHO Monograph Flos Arnicae* states that intraperitoneal administration of 6.0–20.0 mg/kg body weight (bw) of the sesquiterpene lactone helenalin, the key active constituent of Arnica, was not teratogenic in mice. At the upper dose this regime equates to 1,200mg of the single component helenalin alone for a 60kg woman. This is significantly higher than the therapeutically recommended dosage of the whole plant extract that includes in its matrix numerous other constituents besides helenalin. To put these rodent studies into context, empirical data based on long-term regular medical care references the safe and effective dose range as 10 to 30 drops or 0.12ml to 1.2ml of a 1:10 Arnica tincture or a maximum of 2g of dried flowerhead up to 3 times per day. Within the parameter of this dose range, no safety issues for the use of Arnica in pregnancy and breastfeeding have been noted in the medical literature over the past 120 years. Arnica is, however, documented as a gastro-intestinal irritant when taken at high doses and as an abortifacient when taken as an overdose. There are two case reports noted in the literature of deliberate overdoses with

Arnica for inducing an abortion (Bruchhausen, Danner, Baumann, & Achatz-Carmesin, 1990; Lenz & Ardens, 1919, p. 90). In one of them (Lenz & Ardens, 1919, p. 90) a woman took 20g of flowerheads in one single dose. This caused severe bloody vomiting after a few hours combined with severe stomach pains. The abortion took place within a few days. Toxic effects of Arnica are reported to be temporary and transient (Spaich, 1978). Twenty grams is a significant overdose compared with the recommended therapeutic dose.

Regarding the second safety issue, the *WHO Monographs Flos Arnicae* states that Arnica is contraindicated in cases of known allergy to Arnica or other members of the *Asteraceae* family. The text recounts several case reports of dermatitis of toxic or allergic origin following prolonged, external applications with an Arnica flower tincture, highlighting that Arnica is contra-indicated in those suffering from an Arnica allergy. The monograph warns further against *all* applications of Arnica on open or broken skin. This is in line with the *ESCOP Monograph Arnicae flos* but is a departure from the *Commission E Monograph Arnicae flos* and long-standing traditional use of Arnica as an antiseptic for small areas of skin in people with no known allergies to plants in the *Asteraceae* family.

Regarding the third safety issue, the *WHO Monograph Flos Arnicae* recommends against the internal use of Arnica, which concurs with the position of the German Commission E and ESCOP. The quoted rodent studies on the oral median lethal dose (LD50) do not provide useful insights as their relevance for human consumption is unknown (World Health Organization, 2007, p. 82). The WHO bases its recommendation against the internal use of Arnica at any dose range on a historical lethal case of accidental poisoning with a presumed Arnica tincture (World Health Organization, 2007, p. 83). This case, which was originally reported in the French periodical *Journal de Pharmacie et de Chimie* in 1879 (Hager, 1883c, p. 115), became the feature reference case report over the next 130 years, first as a caution against overdosing and then as an argument against *any* internal use of Arnica (Lewin, 1992, p. 764). The original case report recounts that a man accidentally ingested approximately 60-80g of a presumed Arnica tincture of unknown strength. He developed stomach pain and later died. A review of this case questioned whether the lethal dose—now quoted as an average of 70g—was an Arnica preparation, as its very bitter taste and high alcohol content would have made it difficult to swallow (Spaich, 1978, p. 90). At the time of the fatality, the offending preparation was not analysed, and the botanical identification of the starting material not reported. The original report notes that experimental exposure of undiluted Arnica tincture on a hand can cause irritation and

blisters. This was used as the proof that the offending preparation must have been made with Arnica. However, there are other preparations which in high concentrations have a caustic effect on skin. Unequivocal causality was not established. An uncritical reference to this historical case report of presumed Arnica poisoning is problematic from an evidence-based point of view because it does not satisfy basic criteria of scientific reporting such as adequate levels of data to establish clear causality. It is therefore surprising that it continues to be quoted in the *WHO Monograph Flos Arnicae*, and also in contemporary toxicology textbooks and books on clinical herbalism, without apparent awareness of the historic nature of the case or the issues of uncertain causality, dosage and possible misidentification. For example, Bone and Mills (2013) HagerROM (2003), Roth, Daunderer, and Kormann (2006) and Schulz et al. (1998) all quote this case report of ‘Arnica’ tincture poisoning.

The issue of correct botanical identification aside, it is unusual that the *WHO Monograph Flos Arnicae* fails to differentiate between an adverse event and an overdose. It cannot be scientifically justified that misinformed use of a substance implies an inherent toxicity issue when that substance is used within recommended guidelines. Even if Arnica had been correctly identified as the offending plant drug in this case report, the alleged ingested dose was 70 times above the therapeutic dose recommended in long-established traditional European medical prescribing. In addition, internal low dose applications continue to be officially endorsed in the Austrian pharmacopoeia *ÖAB 90* and in *HAB* (Blaschek et al., 2012, pp. 12, 16). Arnica is also permitted in the USA as a food additive at a low dose (U.S. Food and Drug Administration (FDA), 2017). Without causality, dose and strength of the preparation unequivocally established, it is questionable to draw on this case report to prohibit the contemporary internal use of *Arnica montana*. Such reasoning is unfortunate, given that monographs published by the WHO provide a necessary and important resource for international decision makers. For example, the German *Bundesamt für Verbraucherschutz und Lebensmittelsicherheit* (2014, pp. 26-27), a German regulatory agency responsible for the safety of food and food supplements, refers to the *WHO Monograph Flos Arnicae* in its decision to limit Arnica to topical use without cross validating dosage considerations. Similarly, assessments published in WHO monographs find their way via research papers to online sources such as the WebMD<sup>5</sup>, one of the most widely visited databases for consumers, physicians, healthcare professionals and others with

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<sup>5</sup> For further information on WebMD visit <https://www.webmd.com/>.

an interest in healthcare. It is noteworthy that the WebMD's slideshow with the title *Herbal Supplements You Shouldn't try* claims that Arnica can "bring on... death", quoting the *WHO Monograph Flos Arnicae* (WebMD). Because WHO monographs provide valuable expert information on medicinal plants to the international community, this monograph would benefit from an update on safety that reflects important dose considerations for this traditional plant.

In conclusion, the *WHO Monograph Flos Arnicae* provides a comprehensive resource document on Arnica, predominantly reflecting legally permitted traditional uses noted in official and authoritative European monographs, and in experimental research. As tradition is bound to its relating biosphere and culture, not all regional indications may have been captured in this text; they should additionally be considered by a national regulator. Notwithstanding the unresolved issue of internal use of Arnica, this thesis recommends the use of the *WHO Monograph Flos Arnicae* as a regulatory resource for bibliographic evidence.

### **5.2.9.3        The HagerROM. Hagers Enzyklopädie der Arzneistoffe und Drogen (2012)**

The monograph on Arnica in *HagerROM. Hagers Enzyklopädie der Arzneistoffe und Drogen* (also abbreviated in the literature as HagerROM), provides in-depth and up-to-date expertise on *Arnica montana* and related sub-species (Blaschek et al., 2012). The indications, plant parts and preparations that are discussed reflect historical and contemporary uses more comprehensively than any other official and authoritative monograph analysed in this study. This authoritative textbook is updated regularly and so includes the most recently published data on medicinal plants.

As tabulated in Appendix 10, the *HagerROM. Hagers Enzyklopädie der Arzneistoffe und Drogen* covers indications relating to all five use-categories addressed in the *Commission E Monograph Arnicae flos* (card-vasc, musc-skel, nerve, respiratory, skin-mucous), but in a more comprehensive manner. Additionally, the text refers to traditional uses of Arnica in folk medicine in the areas of gynaecology, infection and as a tonic, reflecting long-established applications in traditional European healthcare.

With respect to plant parts, the *HagerROM. Hagers Enzyklopädie der Arzneistoffe und Drogen* discusses Arnica flower, herb and root as the medicinally active drug parts. This

mirrors clinical uses as documented in various editions of the Prussian and German pharmacopoeias, in their related compendiums and supplements as well as in clinical textbooks over the past 400 years (see Historical Database Excel spreadsheet). The various plant parts are to be prepared fresh or dry as tinctures, compresses, teas, gargles, creams or in cosmetic preparations. Most preparations are recommended as external applications, however *ÖAB 90* (the Austrian pharmacopoeia) is referenced as permitting internal use of a water extraction with 0.2g of drug per cup whilst *HAB* permits a dry plant mother tincture of Arnica root at an internal dose of 5 to 10 drops 1-3x daily (Blaschek et al., 2012, pp. 12, 16).

#### **5.2.10 Summary results on medicinal uses of *Arnica montana* listed in regulatory and authoritative monographs**

This section analysed two official monographs (authored by the German Ministry of Health and EMA respectively) and three authoritative monographs (ESCAP, WHO, HagerROM). As displayed in Appendix 10, *all* monographs list the main indications of Arnica already noted in the early modern period textbook authored by Tabernaemontanus, thus confirming the documentary relevance of this historical clinical text. The main indications of Arnica are recorded as the consequences of injuries and accidents such as sprains and strains, torn muscles and ligaments, bruises, oedema, haematoma and musculo-skeletal pain.

The *Commission E Monograph Arnicae flos* published in 1984 is more reflective of clinical practice than the newer *EU Herbal Monograph Arnicae flos* published in 2014. Its indications relate to five use-categories; card-vasc, musc-skel, nerve, respiratory and skin-mucous. Thus the *Commission E Monograph Arnicae flos* approves not only the main indications of Arnica, consequences of injuries and accidents, and musculo-skeletal pain, but further indications relevant in clinical practice: superficial phlebitis, rheumatic muscle and joint problems, inflammation of mucous membranes of mouth and throat, inflammation caused by insect bites, and furunculosis.

The *EU Herbal Monograph Arnicae flos* in contrast narrows approved health claims to complaints of the musculo-skeletal and nervous system only, which are the main indications for which Arnica is most known. These key indications represent a pragmatic political compromise rather than reflecting the totality of consistent traditional uses in various regions of Europe.

Of the three authoritative monographs, *HagerROM. Hagers Enzyklopädie der Arzneistoffe und Drogen* provides the most comprehensive summary of historical, contemporaneous and scientific data on Arnica (clinical: card-vasc, musc-skel, nerve, respiratory, skin-mucous; folk medicine: gyn, infection, and tonic). The clinical indications are congruent with clinical uses discussed by contemporaneous practising physicians. The uses listed under folk medicine are long-established indications previously recorded as mainstream in the historical medical literature. It is a recurring theme throughout this study that indications which are listed as folk medicine from the 1870s onwards were previously listed in the European medical literature as regular medicinal indications.

The *WHO Monograph Flos Arnicae* lists indications across three separate sections; “Uses supported by clinical data” (0), “Uses described in pharmacopoeias and well established documents” (5: card-vasc, musc-skel, nerve, respiratory, skin-mucous) and “Uses described in traditional medicine” (5: card-vasc, gastro-intest, musc-skel, nerve, gyn) (World Health Organization, 2007, pp. 80-81). Database research of clinical trials on *Arnica montana* discovered that there were clinical data available at the time the monographs were published (see Appendix 11). The rheumatism indication listed under traditional use could therefore have been listed under “clinical data”. Therefore, while this monograph documents all main indications of Arnica, their listings in the different sections may benefit from updating. The monograph would also benefit from updates in the safety section that differentiate between the effects of a regular dose and an overdose.

The *ESCOP Monograph Arnicae flos* published in 2003 by ESCOP is the least comprehensive authoritative monograph discussed in this category. It lists the long-established main indications of Arnica relating to the musc-skel, nerve and skin-mucous use-category but does not fully reflect clinical uses of Arnica when compared with its preceding *Commission E Monograph Arnicae flos* or those in the medical literature (see Appendix 10).

The five analysed monographs demonstrate divergence in safety assessment regarding the topical use of Arnica on open wounds. Whilst the *Commission E Monograph Arnicae flos*, the *WHO Monograph Flos Arnicae*, and the Arnica monograph in *HagerROM. Hagers Enzyklopädie der Arzneistoffe und Drogen* permit Arnica as a disinfectant or styptic on small areas of skin, the ESCOP and EMA monographs advise against such use. The EMA safety assessment goes even further by only supporting the use of topical Arnica in non-

pregnant adolescents and adults. EMA justifies this stance by citing a lack of scientific toxicity data rather than factual safety concerns for specific population groups. Concerns regarding the allergy potential of Arnica have been countered by recent studies which indicate low allergy responses in patients, although Arnica allergies have been observed and are troublesome for those affected (Bone & Mills, 2013, p. 378; Jeschke et al., 2009; Merfort, 2010, pp. 189-191).

Four monographs endorse topical use of Arnica only. The Arnica monograph in *HagerROM. Hagers Enzyklopädie der Arzneistoffe und Drogen* references *ÖAB 90* (the Austrian pharmacopoeia) and *HAB*, which both permit low dose internal use of Arnica preparations (Blaschek et al., 2012, pp. 12, 16). This is in line with the evaluated medical literature as well as the commentaries to the Prussian and German pharmacopoeias that documented systemic use of Arnica until the 1980s. Within the parameter of a low dose range, few safety issues for internal use of Arnica have been found in the researched body of literature, and those identified can be mitigated by appropriate use. All serious case reports on Arnica toxicity were noted in the literature related to overdoses (Bertin, 1864; Hager, 1883c, p. 115; Schoenemann, 1938; Topliff & Grande, 2000). Based on this analysis, it would be worth re-evaluating the stance on internal use of Arnica in official and authoritative monographs. The purpose would be to determine a rational differentiation between a safe, therapeutic dosage range and an overdose.

The *HagerROM. Hagers Enzyklopädie der Arzneistoffe und Drogen* is the only monograph that discusses all therapeutically active plant parts of Arnica used in traditional European healthcare, namely flower, herb and root. The other four monographs list Arnica flower as the sole plant part to be used for preparations.

In conclusion, triangulation of qualitative data established that the evaluated modern monographs and the medical literature concur on two clusters of indications relating to therapeutic usage of Arnica which are the treatment of consequences of injuries and accidents, and of pain related to the musculo-skeletal system and nerves. These parallel findings between monographs and medical textbooks validate the empirical evidence recorded in the medical literature. In addition, the triangulation showed that modern monographs cannot be taken as the sole bibliographic sources on traditional uses, as they do not record the totality of long-standing clinical applications or all therapeutically active

plant parts. Consequently, this thesis proposes that regulatory use of modern monographs occurs *alongside* judiciously selected medical textbooks for the validation of health claims.

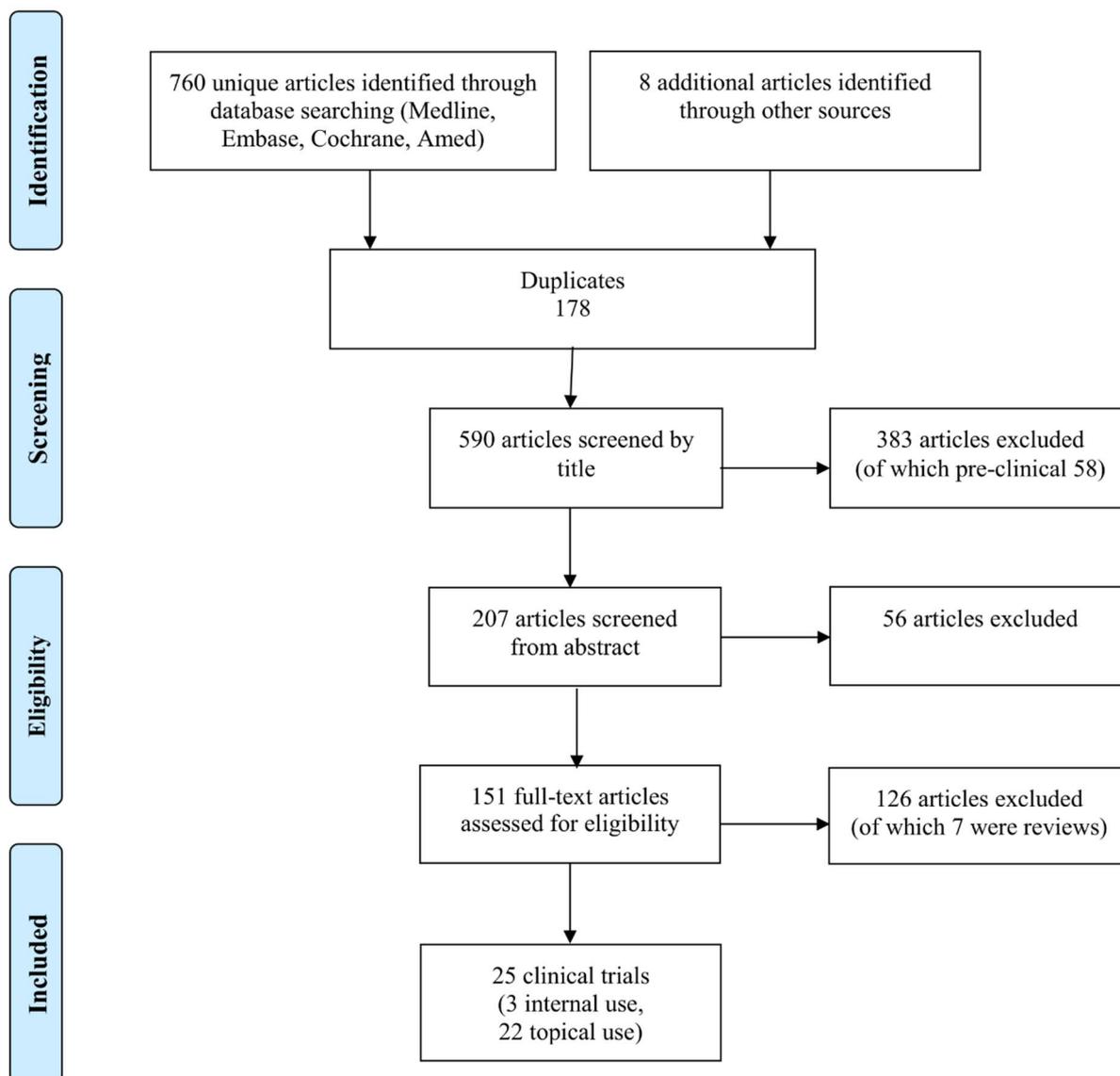
### **5.3 Contemporary scientific research into *Arnica montana***

The following sections analyse contemporary clinical and experimental research into *Arnica montana*. Clinical trials are health interventions in humans conducted to find out whether there is enough evidence to support them as medical treatments. There are various models for clinical trials, the most prevalent being randomised-controlled trials (trial intervention against placebo or established therapy) or non-randomised observational outcome research such as cohort studies, observational studies and surveillance studies (case reports and case series) (Salkind, 2013). Intervention studies can be placed on a continuum, with a progression from efficacy trials to effectiveness trials. Efficacy can be defined as the performance of an intervention under ideal and controlled circumstances, whereas effectiveness refers to its performance under real-world conditions. Newer research methods such as Health Services Research and Program Evaluation are not considered here.

Experimental research uses laboratory and basic science approaches to examine the mechanisms that might underlie a beneficial health intervention. Such research is conducted as a first step for the development of new substances, while for established therapies such as traditional plant medicines it is usually conducted to explain an already confirmed therapeutic effect (Lewith et al., 2011, pp. 9-15).

#### **5.3.1 Clinical research**

To cross-validate the previously established empirical evidence on *Arnica montana* as documented in medical textbooks with results from contemporary clinical research, this study employed a systematic method of literature searching, study selection and data extraction. The literature was searched using the following databases: Medline, Embase, AMED, Cochrane Library, Web of Science and Cinhal. In addition, the bibliographies of selected papers were examined for relevant studies. Searches were limited to English, German, French or Dutch-language material published from the inception of the databases to June 2014. An alert was set up when the search was concluded, and this process identified further literature included in this thesis. The search strategy applied is summarised in Appendix 1 and the results are displayed in the following PRISMA flow diagram:



**Figure 3. Flow diagram of database research to June 2014 of clinical trials on *Arnica montana* flower for cross-validation of clinical research with empirical science**

The study selection criteria were set to exclude articles outside of the scope of this review:

- studies published in languages other than English, German, French or Dutch
- studies on homeopathically potentised *Arnica montana*
- studies on a different *Arnica* species other than *Arnica montana*
- studies on toxicity
- *in vitro* studies
- rodent models
- studies on herb-drug interactions

- studies not declaring dose or concentration of preparation
- papers discussing the same clinical trial
- meta-analyses or systematic reviews (noted separately)
- journal comments
- narratives.

Of the 25 clinical trials retrieved, 11 were conducted with *Arnica montana* as a single substance, three with a combination preparation that measured the additional effect of *Arnica montana*, and 11 which combined *Arnica montana* with other substances without measuring the additional effects of Arnica separately. Trials on combination remedies are included in this study because traditional systems of medicine commonly apply complex multi-component drugs, the use of a single ingredient drug being the exception rather than the rule. Traditional mixtures of active compounds act synergistically on a variety of targets affecting bioavailability, suppressing potential adverse side effects, and altering drug metabolism and excretion of the traditional drug (Verpoorte, 2012, p. 455). However, trials on complex multi-component drugs cannot be used as proof of a specific therapeutic effect of Arnica, rather they point to indications where a synergistic effect of Arnica was sought.

Due to the overall high heterogeneity among the studies and indications under investigation, it was not possible to collate a meta-analysis (Brito, Knipschild, & Doreste-Alonso, 2014, p. 222). This reflects the general challenge of achieving useful or valid results from meta-analyses relating to heterogenic plant medicines (Lewith et al., 2011). Additionally, searching for evidence on plant medicines is not straightforward as various databases have shown to have incomplete listings when it comes to the retrieval of clinical studies conducted with specific medicinal plants (Pilkington, 2007, p. 456).

It is outside of the scope of this study to offer a judgment on the measure of efficacy, the benefits and harms, of the individual studies found. An evaluation of clinical trials conducted until 2014 can be found, for example, in the HMPC Assessment Report on *Arnica montana L. flos* (Committee on Herbal Medicinal Products (HMPC), 2014b) and in the systematic reviews quoted below. The aim of this section is to provide a summary of indications said to be validated by contemporary science compared with indications validated by empirical science.

### 5.3.1.1 Clinical research results

A summary of scientific trials on Arnica retrieved via the systematic database research is displayed in Appendix 11. Clinical research on Arnica began in the mid-1950s. The first preparation under investigation was not a traditional remedy but a novel type of product that contained Arnica and Horsechestnut in combination with synthetic B vitamins for the treatment of elephantitis and changes to prothrombin time (Siebenhaar, 1955; Stöcker, 1953). At that time Arnica was medically prescribed for the internal treatment of cardiovascular diseases for which products were available on the market, for example the test preparation Arnicorin (Chemiewerk Homburg, 1964). Erley (1965) provides the first published observational study on a traditional preparation, Arnica tincture (20 drops 3 times per day) but investigates it for a modern nosology, *Angina pectoris*. RCTs under a more robust scientific framework became prevalent from the 1990s onwards in response to the call by exponents of the EBM movement to provide modern clinical data on all therapeutic interventions in Western medicine (Borck, 2016).

In total, the systematic database research returned 25 clinical trials covering 10 indications across four use-categories (card-vasc, musc-skel, nerve, skin-mucous). Three older clinical studies were conducted on the internal use of Arnica in the treatment of *Angina pectoris*, on prothrombin time, and in elephantitis, all returning positive results. Twenty-two newer clinical trials investigated the efficacy of Arnica in topical applications for varicose veins, bruises, musculo-skeletal pain, arthritis, ulcers, wounds and burns. Clinical trials on musculo-skeletal pain and osteoarthritis are coded to both the musc-skel and nerve use-category as they relate to two indications each.

Table 9 (next page) displays the summary of clinical trials on Arnica as referenced with author IDs established in Appendix 11 compared with similar types (but differently termed) historical indications documented in the medical literature. The results of the studies were positive unless indicated.

Clinical trials on indications relating to the card-vasc, musc-skel, nerve and skin-mucous category substantiate long-standing traditional uses. Clinical research on the effect of Arnica on prothrombine time, elephantitis, and *Angina pectoris* relate to modern nosologies.

**Table 9. Historical indications of *Arnica montana* compared with evidence from clinical trials.**

Use-category	Historical indications	Clinical trials: systemic use	Author ID	Clinical trials: topical use	Author ID
card-vasc	<b>circulatory stimulant</b> (noted since Löseke 1799)  <b>varicose veins</b> (noted since Kroeber 1948)	<b>Angina pectoris</b> (1 observ. study*)  <b>prothrombine time improvement</b> (1 observ. study)  <b>elephantitis</b> (1 case study)	3	<b>varicose veins</b> (6 RCTs*)	4-9
			2		
			1		
musc-skel	<b>bruises</b> (noted since Löseke 1799)  <b>musculo-skeletal pain</b> (noted since Tab. 1664)  <b>rheumatism and stiffness in joints</b> (intermitted since Löseke 1799)			<b>bruises</b> (1 RCT)  <b>musculo-skeletal pain</b> (9 RCTs: 2 not statistically significant)  <b>osteoarthritis</b> (1 RCT; 1 observ. study)	21
					10, 11, 13, 16, 18, 19, 20
					12, 15
nerve	<b>pain related to musculo-skeletal system</b> (noted since Tab. 1664)			<b>musculo-skeletal pain</b> (9 RCTs – already counted)  <b>osteoarthritis</b> (2 RCTs – already counted)	
skin-mucous	<b>ulcers</b> (noted since Richter 1827)  <b>wounds</b> (noted since Hager 1876)			<b>ulcers</b> (1 RCT)  <b>wounds</b> (1 RCT; 1 observ. study)  <b>burns</b> (1 RCT)	23
					22
					25
					24
* “observ. study” relates to observational study; “RCT” relates to randomised-controlled trial.					

The treatment of burns with Arnica is a novel indication. While Arnica is referenced as a potential burn remedy in the lecture notes of the German pharmacologist Schulz (1919), this application is not consistently noted in other textbooks and so does not qualify under traditional use. A closer investigation of the modern RCT on burn treatment reveals that the

preparation under investigation was anthroposophical, containing mainly Nettle with a small proportion of Arnica as a minor adjunct drug, possibly to support circulation and for an antimicrobial effect in wound healing (Huber, Bross, Schempp, & Grundemann, 2010).

Clinical trials conducted within a traditional dosage regime and treatment strategy returned positive results. Trials that applied a dose below traditional dosing, for example Gulick & Kimura's study with a 4% Arnica cream (Gulick & Kimura, 1996), or studies that investigated the effect of Arnica as a one-off application (Rosenzweig et al., 2002) demonstrated no difference between *verum* and placebo. The dose correlation for achieving efficacy is highlighted by a systematic review on topical *Arnica montana* which confirms efficacy in preparations of 10% strength and above for the treatment of pain, swelling and bruises (Brito et al., 2014). Another review also confirmed substantial differences in clinical outcomes depending on the dosage and preparation used (Iannitti et al., 2016, pp. 1, 13). In 2016 Iannitti et al concluded that "cumulative evidence suggests that *Arnica montana* may represent a valid alternative to non-steroidal anti-inflammatory drugs, at least when treating some specific conditions" (Iannitti et al., 2016, p. 1). They established further that topical Arnica preparations demonstrate reproducible clinical benefits, some of which are comparable with anti-inflammatory drugs such as diclofenac, ibuprofen and corticosteroids which are considered the therapeutics of choice for the treatment of osteoarthritis, postoperative oedema, and ecchymosis (Iannitti et al., 2016, p. 13). Their review findings also suggest that Arnica can be used in the context of wound healing for selected clinical needs, which is consistent with the therapeutic use of Arnica in conventional medicine well into the middle of the 20<sup>th</sup> century (Kreitmair, 1952, pp. 441-442).

All RCTs on Arnica from the 1990s are on preparations for external use only due to a change in the regulatory benefit-risk assessments from the 1980s onwards, resulting in regulatory restrictions for the internal use of Arnica in many European countries. No RCTs could be found to alleviate or verify safety concerns of internal use of Arnica at the traditionally recommended therapeutic low dose range.

### **5.3.1.2 Discussion on clinical research into *Arnica montana***

Clinical trials on Arnica support long-standing historical indications for it based on clinical observations in patient care. Accordingly, they provide validation for the reliability of consistently endorsed traditional indications. At the same time, clinical trials do not comprehensively explore the pleiotropic properties and wide-ranging clinical potential of a

medicinal plant (Saller et al., 2014, p. 28). Rather, they investigate a specific indication with a specific proprietary preparation to achieve proof of claim and/or funding for a commercial product. Some regulators may require clinical trials for the registration of a product, as in the EU for the registration of a product under the well-established use category. EMA does, however, not require clinical trials for the simplified registration of a product under traditional use (Verpoorte, 2012, p. 455).

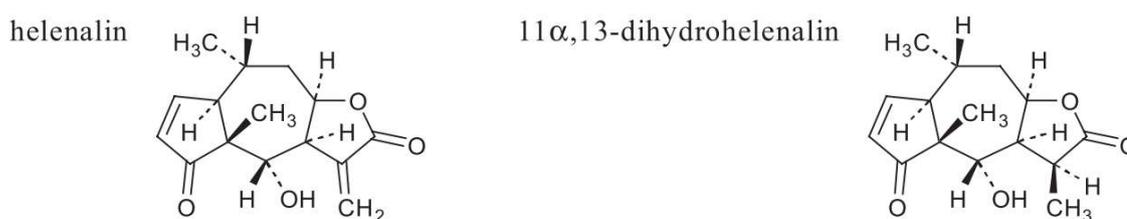
As illustrated in Appendix 5, Arnica has a long history of transmitted clinical uses in numerous pathological conditions: bruises, contusions, concussion, coronary heart diseases, dysmenorrhoea, partum and postpartum care and ailments of the uterus, epilepsy, fractures, dislocations, gout, haematoma, inflammation of the oral and throat region, hair loss, impaired respiration, insect bites, liver, stomach and intestinal complaints, muscle and joint pain from overexertion or injury, neuralgias, oedema, paralysis from accidents and strokes, passive bleeding from various organs, rheumatic muscle and joint pain, spasms, sprains, thrombosis, venous insufficiency (including varicose veins and phlebitis), skin complaints (boils, wounds, ulcers), systemic, respiratory and intestinal infections, and urinary complaints (diuretic). Many of these traditional indications have not been researched with modern methodologies. They could provide plausible leads for clinical research into the therapeutic potential of Arnica.

### **5.3.2 Experimental research**

Apart from the clinical research discussed above, there is a substantial amount of experimental research exploring the composition of constituents in various plant parts of *Arnica montana*. Such research is not required in the EU for the registration of a product that qualifies under a traditional use monograph. However, experimental research provides insights into active constituents and mechanisms that may substantiate therapeutic uses documented in TEM. Arnica is one of the few traditionally used medicinal plants where active constituents, molecular mechanisms, pharmacokinetics, efficacy and toxicity aspects were established early on (Merfort, 2010, p. 188). It is plausible that this was central in assuring Arnica's legal status as an ongoing essential medicine in the Prussian and German pharmacopoeias and thus in regular European healthcare. *In vitro* studies are most relevant to provide scientific data for topical applications. For scientific evidence on internal use, data obtained from bioassays should not be over-interpreted to represent clinical outcomes, since the concentration of the actives, metabolic processes and bioavailability play a central

role for enabling *in vivo* pharmacological effects (Gertsch, 2009).

Experimental research identified over 150 active constituents that may explain the clinical treatment effects of Arnica as recorded in the European medical literature (Kriplani, Guarve, & Baghael, 2017, pp. 927-930; Wijnsma et al., 1995, pp. 51-54). They are alkaloids, amines, antioxidants, carbohydrates, coumarins, flavonoids, terpenoids, volatile oils, phenolic acids, resins, bitters, tannins, and carotenoids, with sesquiterpene lactones (SLs) and volatile oils representing the key active compounds (Blaschek et al., 2012, pp. 8-9; Engels & Brinckmann, 2015, pp. 2-3; ESCOP, 2003a, p. 43; Kos, Lindenmeyer, Tubaro, Sosa, & Merfort, 2005; Kriplani et al., 2017; Wagner & Merfort, 2007; Willuhn, 1972c, 1981; Willuhn & Herrmann, 1979; Willuhn, Rottger, & Wendisch, 1984; World Health Organization, 2007, p. 80). The structures of the representative constituents are presented below (World Health Organization, 2007, p. 80).



**Figure 4. Key active constituents of *Arnica montana***

Arnica is coined a ‘phyto-cortison’ (Becker, 2005, p. 288) based on the anti-inflammatory properties of SLs. Similarly to synthetic cortisone, they inhibit the transcription factors NF- $\kappa$ B and NF-AT responsible for the transcription of genes that encode for inflammatory mediators (Ganzera, Egger, Zidorn, & Stuppner, 2008; Klaas et al., 2002). *In vivo* and *in vitro* studies suggest broad spectrum effects of SLs, mainly of an analgesic, anti-arthritic, antibacterial, anticancer, anti-ecchymotic, anti-inflammatory, antimycotic, antiplatelet, cholagogue, bitter tonic, immune and uterine stimulant nature (Blaschek et al., 2012, pp. 11-12; May, 2013; Willuhn, 1981). SLs are also discussed as playing a role in the cardiotoxic and respiratory analeptic actions of Arnica, the increase of breathing rate and strength (Blaschek et al., 2012, pp. 10-11). These actions are dose dependant and occur at small to medium doses (Gessner, 1949, pp. 825-827; Willuhn, 1981, pp. 5-6). When consumed in large amounts, helenalin has shown to induce skin irritation, gastroenteritis, internal

bleeding in the digestive tract and respiratory paralysis which has been scientifically demonstrated since the 1940s (Gessner, 1949, pp. 825-827; Šutovská et al., 2014; Willuhn, 1981, p. 5). This dose dependant effect is confirmed in case reports as noted elsewhere (Merfort, 2010, p. 189) and concurs with safety observations recorded in the evaluated medical literature.

Flavonoids may relate to antimicrobial, anti-inflammatory, and anti-rheumatic actions whilst volatile oils have shown antiseptic, anti-inflammatory and wound healing activity of Arnica (Roki et al., 2001; Willuhn, 1981). Phenolic and flavonoid components exhibit antioxidant effects (Aguilar, 2015, p. 46). The flavonoids astragalín and isoquercitrín improve ailments that require better systemic or local circulation (Böhme & Hartke, 1981, pp. 161-167). Polyacetylenes have confirmed bacteriostatic and fungicidal actions. In addition, procyanidins are believed to support coronary blood flow and positive inotropic and chronotropic actions, while chlorogenic acid and cynarine may be responsible for the cholagogue, cholaretic and diuretic actions of Arnica (Willuhn, 1981). Its polysaccharide fractions are reported to show immune stimulating properties by increasing phagocytosis through granulocytes (Kriplani et al., 2017, pp. 931-934). Phenolic compounds isolated from Arnica have been related to a hepatoprotective activity (Kriplani et al., 2017, p. 934)

Experimental evidence on Arnica's constituents and their mechanisms of actions point to possible explanations of its therapeutic actions noted over the past 400 years. The scientific literature relates these constituents to the anti-inflammatory, anti-ecchymotic, anti-haemorrhagic, bactericidal, bitter tonic, antineuralgic, antirheumatic, antiseptic, counterirritant, wound and tissue healing effects of Arnica. Additionally, *in vitro* and animal studies point to cardiogenic, circulatory stimulant, central nervous system (CNS) stimulant, diuretic, expectorant, hypotensive, nervine and uterine stimulant effects (Aguilar, 2015; Blaschek et al., 2012; Committee on Herbal Medicinal Products (HMPC), 2014a; Saller et al., 1995; Schulz et al., 1998; Wichtl, 2004; Willuhn, 1981; World Health Organization, 2007, pp. 81-82).

#### **5.4 Summary and conclusions**

The analysis on *Arnica montana* comprehensively triangulated qualitative and quantitative data. The concept that consistent, clinically evaluated observation is a rational methodology which provides data that can be reproduced and validated is supported by parallel findings of empirical evidence recorded in the medical literature, records in pharmacopoeias and

their compendia, endorsements in modern regulatory and authoritative expert monographs, and evidence in the form of clinical trials, and experimental laboratory research. The outcome of the data triangulation suggests that consistent transmissions of repeatedly observed and professionally evaluated treatment outcomes by professionally trained clinicians represent valid clinical observations. This analysis further confirmed that authoritative medical textbooks are the key repositories of medicinal plant knowledge on the European *materia medica*, providing a readily accessible and reliable documentary body of evidence relating to consistent clinical endorsements of *Arnica montana* over a period of 400 years. These results strengthen confidence that empirical evidence from judiciously selected medical textbooks is a suitable bibliographic source of evidence which can be admitted alongside scientific evidence for regulatory purposes. This thesis proposes that such data are admissible as documentary evidence to substantiate traditional claims for the registration of traditional herbal preparations.

The *New vollkommen Kräuter-Buch* by Tabernaemontanus and annotated by the Bauhin editors (4<sup>th</sup> edition, 1664) was confirmed as an appropriate starting point for this longitudinal textual analysis on historical clinical uses of *Arnica montana* in professional European healthcare. The triangulation confirmed that Tabernaemontanus was accurate in determining the pharmacological actions of Arnica, raising the possibility that he was also accurate about the pharmacological actions of other medicinal plants. The later expansion of indications for Arnica from those identified by Tabernaemontanus, to include complaints that benefit from circulation, came about with the discovery of blood circulation in 1628, illustrating that tradition is not static. The current main indications were transmitted in *all* qualitative and quantitative sources over 400 years, and many more were transmitted until the 1980s when the German and EU legislators restricted the internal use of Arnica as well as its use on broken skin, despite clinical validation for some skin infections.

When the regulatory literature is put aside, and data is analysed across the selected professional literature only, then all early modern clusters of complaints were transmitted until at least mid-20<sup>th</sup> century, except complaints relating to the gastro-intestinal system and the liver-spleen. A possible explanation for the dropping of indications belonging to those use-categories is that firstly, Arnica root, the plant part required for the treatment of gastro-intestinal infections, became restricted due to conservation issues—concurring with penicillin becoming the standard of care for infections—, and secondly, the humoral concept of liver-spleen was superseded in the 19<sup>th</sup> century by modern pathophysiology.

However, when the eight clusters of early modern indications are compared with experimental research, the active constituents of *Arnica montana* account for its therapeutic use in all traditional clusters of complaints.

Longitudinal textual comparison of the medicinal uses of *Arnica montana* as recommended in authoritative medical textbooks from the 17<sup>th</sup> century to the 21<sup>st</sup> century concluded that despite changes in explanatory models of health and illness, the main indications for the therapeutic uses of Arnica has remained remarkably consistent. When comparing historic with present-day therapeutic uses of Arnica documented in authoritative medical textbooks, this body of knowledge evidences an uninterrupted medical transmission of two clusters of indications relating to the musculo-skeletal and nervous system:

**Table 10. Consistently endorsed indications for *Arnica montana* in medical textbooks over at least 400 years.**

Use-category	Indications
musc-skel	injuries, sprains and strains, torn muscles and ligaments; bruises, oedema, haematoma
nerve	pain related to musculo-skeletal system and nerves

This is the same cluster of indications that is consistently listed in the commentaries to the Prussian and German pharmacopoeias, and those listed in the main regulatory and authoritative monographs of the 20<sup>th</sup> and 21<sup>st</sup> century, namely the *Commission E Monograph Arnicae flos*, the *EU Herbal Monograph Arnicae flos*, the *ESCOP Monograph Arnica flos*, the *WHO Monograph Flos Arnicae* and the monograph on *Arnica montana* published in *HagerROM. Hagers Enzyklopädie der Arzneistoffe und Drogen*.

In the 18<sup>th</sup> and 19<sup>th</sup> century, insights from physiology and experimental research expanded prior use of Arnica by further indications. The following historical indications meet the criteria of at least 30 years of continued therapeutic applications:

**Table 11. Consistently endorsed indications for *Arnica montana* in medical textbooks > 30 years.**

Use-category	Indications
card-vasc	circulatory insufficiency (since Löseke 1790) varicose veins / phlebitis (topical) (since Kroeber 1948)
respiratory	breathing difficulties / catarrh (until Weiss 1974) sore throat (infection) (since Madaus 1938)
skin-mucous	ulcers, wounds (since Richter 1827) boils (since Schulz 1919) mouth and throat inflammation (since Strumpf 1855)
tonic	heart tonic in exhaustion and debility (since Schulz 1919)

The registration of therapeutic claims for Arnica as a tonic and as a circulatory and coronary stimulant, including to improve breathing, are nevertheless challenging as internal use of Arnica is now restricted. It might be warranted to re-evaluate these regulatory restrictions by the German and EU regulators in the light of consistent and uninterrupted transmission of traditional knowledge on internal applications within the safety parameters of traditional dosing.

The remaining traditional indications which relate to the gastro-intest, gyn, head, infection, liver-spleen and uro use-categories show intermittent listings in the medical literature. Under current EU regulations these would not qualify under the traditional use criteria; some had also been reclassified over time from regular medicinal uses to folk medicine. Nonetheless, they could be analysed on a case by case basis to confirm or discount therapeutic rationale when considering the totality of their evidence. They could also provide important leads for scientific investigation of therapeutic usefulness in contemporary patient care.

The results of this analysis further showed that treatments offering therapeutic benefit in clinical practice were maintained and transmitted by the medical profession whilst those which did not demonstrate practical value were dropped over time. Sometimes indications were discontinued due to regulatory or conservational requirements. There are various reasons as to why an indication may have become obsolete. The following are the most plausible:

- indication was not a core traditional indication, and treatment was replaced by a plant drug that was seen to be more effective (e.g. Cinchona bark instead of Arnica)
- ailment had ceased to be prevalent in the biosphere under discussion (e.g. malaria in Central Europe)
- de-listing of an official plant part as an essential pharmacy item in a national pharmacopeia hindered easy access to that plant part, thus impeding its therapeutic application and related transmission of knowledge of use
- a conservation issue prevented the use of a plant part for the treatment of an ailment (e.g. Arnica root for gastro-intestinal infections)
- advances in biomedicine leading to a preferential treatment based on a biomedical approach (e.g. head injuries)
- a change in the benefit-risk ratio leading to the discontinuation of specific

applications (e.g. regulatory endorsement for external use only since the 1980s), hampering the legal transmission on their traditional uses.

In addition, the current funding model for medicines in Germany and other European countries preferentially reimburses synthetically derived drugs. This affects the official access to traditional plant medicines and thus the ability to maintain tradition as part of conventional healthcare. The Waitangi Tribunal report on New Zealand law and policy affecting Māori culture and identity has come to the same conclusion when noting that funding levels for traditional medicines have been too low to safeguard the practice or ensure the transmission of knowledge about it (Legislation Direct, 2011, p. 211). For this reason, when traditional medicines are investigated for the determination of their regulatory status and related therapeutic claims, the regulatory context with its socio-economic and legal framework needs to be understood alongside pharmacological and toxicological facts.

#### **5.4.1 Evidence from pharmacopoeias and their commentaries**

The Prussian and German pharmacopoeias provide evidence on official plant parts and their preparations officially approved in Germany for regular healthcare from the late 18<sup>th</sup> century to the present day. As such, this body of literature delivers data on the legal status of Arnica in a European country. It is proposed that this evidence is admissible as bibliographic evidence on traditional clinical uses of medicinal plants.

Until the turn of the 20<sup>th</sup> century the official position on Arnica in the German pharmacopoeia and its commentaries was mostly congruent with therapeutic applications discussed in clinically orientated medical textbooks authored by contemporaneously practising physicians. The significant paradigmatic changes in medicine during the 19<sup>th</sup> century to a model chiefly based on natural science prompted ensuing German pharmacopoeia commissions to reduce the of scope of Arnica, and that of other medicinal plants. This is reflected in the reduction of officially endorsed plant parts of Arnica to its flower only, in fewer endorsed preparations and ultimately in fewer sanctioned indications by commentators. The commentaries from the 1<sup>st</sup> to the 10<sup>th</sup> edition of the German pharmacopoeia highlight the following trends:

- reduction of permitted part parts to streamline essential pharmacy stock items (Arnica flower only)
- discontinuation of a plant part due to environmental concerns (Arnica root)

- decreased acceptance of empirical evidence by the academic community in favour of experimental research
  - when the complex mode of action of a plant drug could not be explained (yet) with new experimental science, it resulted in the discontinuation of an indication by some commentators (rheumatism)
  - when the mechanism of action could be explained with new experimental science the indication was re-listed (rheumatism)
- reversal of benefit-risk ratio, as in discontinuation of internal use of Arnica since the 1980s.

While commentaries to the German pharmacopoeia continued to record the main therapeutic applications of Arnica for the musculo-skeletal and nervous system, and thus independently validate the clinical information recorded in the medical literature, they did not reflect its broader traditional and contemporaneous clinical uses. In the second half of the 20<sup>th</sup> century, commentaries re-listed some traditional indications based on insights from experimental research. This was, however, short lived as from the 1980s German regulations limited Arnica's therapeutic applications to external use only (1986; Hartke et al., 1987). In contrast to evidence on harmful impacts from overdoses, overuse or allergic reactions to *Arnica montana*, no experimental or traditional evidence could be found that the traditional low dose regime of internal uses had caused serious harm in those not suffering from allergies to this particular plant species. The limitations of the commentaries are therefore grounded in the reproduction of the controlling regulatory paradigm of a national state which is guided by its legal and socio-economic framework. Since medical textbooks have shown to be a more comprehensive source of verifiable clinical endorsements for plant-based medicines compared with academic commentaries to pharmacopoeias, they are proposed as the *primary* source of evidence to substantiate claims for the registration of traditional herbal preparations. Commentaries are proposed as a *complementary* source of evidence to provide additional tradition-of-use (TOU) data on the main uses of *Arnica montana*.

#### **5.4.2 Evidence from regulatory and authoritative monographs**

Investigation of two official monographs, the *Commission E Monograph Arnicae flos* and the *EU Herbal Monograph Arnicae flos* (traditional use), and of three authoritative monographs, the *ESCOP Monograph Arnica flos*, the *WHO Monograph Flos Arnicae*, and

the *Arnica montana* monograph in *HagerROM. Hagers Enzyklopädie der Arzneistoffe und Drogen* highlighted consistencies as well as divergent views on therapeutic claims, the therapeutically active plant parts, and safety considerations depending on the legal framework and expert consensus at the time of their publication. All five monographs endorse the main indications for *Arnica montana* already noted by Tabernaemontanus; these indications are also congruent with clinical uses documented in the medical literature reviewed. They are consequences of injuries and accidents, and musculo-skeletal pain. Therefore, the triangulation of data from the five monographs and the selected medical literature reviewed at defined datapoints (each a generation apart) confirmed that *all* sources endorse the same indications for Arnica. This is a significant outcome and validates traditional clinical knowledge on *Arnica montana*.

While all these sources concur on Arnica's main therapeutic actions, there are disparities in the five monographs regarding further indications. As already discussed, the most striking change over the past 400 years is Arnica's officially sanctioned systemic use until the mid-1980s, after which regulators in Europe changed their benefit-risk analysis to an approval for external use only. This is reflected in the approved claims in the two official monographs and also in the type of commercial preparations now available in the market place, predominantly creams and gels for topical applications or homoeopathic preparations. The traditional use of Arnica as a tonic and as a circulatory and coronary stimulant has been officially impeded since the implementation of these regulatory restrictions, although off label use occurs (Bäumler, 2007, p. 63).

The *Commission E Monograph Arnicae flos* published in 1984 is more reflective of indications listed in clinical textbooks compared with the newer *EU Herbal Monograph Arnicae flos* published in 2014. The EU monograph is informed by the legal framework of the EU Directive 2004/24/EC. The narrow legal framework and interpretation of the stipulations of the directive led to the exclusion of traditional water and oil extracts despite their long-standing documentation in the German pharmacopoeia, in the *Commission E Monograph Arnicae flos*, and in the medical literature reviewed. No evidence could be located in the HMPC Assessment Report (Committee on Herbal Medicinal Products (HMPC), 2014a) to confirm that traditional indications of Arnica had been systematically tracked for consistent historical uses beyond the stipulated period of 30 years.

Consequently, the *EU Herbal Monograph Arnicae flos* approves three health claims for topical use only: relief of bruises, sprains and localised muscular pain. In addition, the

interpretation of the safety framework stipulated in the EU Directive 2004/24/EC restricted pre-approval of use to adolescents over 12 years of age, adults and elderly only. This is due to absence of contemporary scientific safety data rather than proof of harm. This age restriction is not noted in the *Commission E Monograph Arnicae flos* and the medical literature analysed.

Of the three authoritative monographs examined for this thesis, the Arnica monograph published in *HagerROM. Hagers Enzyklopädie der Arzneistoffe und Drogen* provides the most comprehensive summary of historical, contemporaneous, and scientific information. As tabled in Appendix 10, the indications in the Arnica monograph of *HagerRom* are more congruent with clinical uses endorsed by practising physicians compared to the ESCOP and WHO monographs. Furthermore, the *HagerROM* monograph lists all therapeutically active plant parts of Arnica used in traditional European healthcare, namely flower, herb and root, while the other two authoritative monographs only list Arnica flower as the sole plant part for therapeutic preparations.

The *WHO Monograph Flos Arnicae* lists all the main indications of Arnica plus some additional traditional indications, however their listings allocated to different categories would benefit from updating. As with the *EU Herbal Monograph Arnicae flos* it may be advisable to re-evaluate the WHO's stance on internal use of Arnica so that it makes a rational differentiation between a safe, therapeutic dose range that is underpinned by long-standing clinical use, and an overdose. Establishing a contemporary safe internal dosage for Arnica is a research gap. The *ESCOP Monograph Arnica flos* also lists the main indications of Arnica pertaining to the treatment of the musculo-skeletal and nervous systems and the skin, but it lists the least additional historical indications compared with the other authoritative monographs and the analysed medical literature.

Despite their differences in scope and safety assessments all five monographs provide important clinical and scientific evidence on *Arnica montana* which could be canvassed by the international community as bibliographic evidence. It is important to note though that these monographs reflect the particular legal and socio-economic environments in which they are embedded. Moreover, it is important to note that traditional uses vary in different regions, countries, and continents. Consequently, the scope of approved claims in regulatory monographs should not be replicated by other regulatory authorities without reflection.

### **5.4.3 Comparison of empirical evidence with scientific evidence**

When traditional medical knowledge based on empiricism as documented in the European medical literature is compared with clinical and experimental research on *Arnica montana*, contemporary scientific and historical evidence correspond as listed in Table 12 (next page).

This comparison demonstrates that traditional uses of *Arnica montana* as transmitted by clinicians are scientifically well substantiated. Scientific research confirms benefits in ailments that require a circulatory stimulant, analgesic, anti-rheumatic, anti-inflammatory and skin healing action. It is noteworthy that modern clinical and experimental laboratory research provides few new applications for *Arnica montana* beyond those based on empirical evidence documented in traditional European medicine. Conversely, traditional evidence provides important leads and inspiration for scientific research.

**Table 12. Comparison of historical indications of *Arnica montana* with clinical trials and experimental research.**

Use-categories	Tabernaemontanus 1664	Empirical evidence: consistent medical recommendations 18 <sup>th</sup> to 21 <sup>st</sup> century	Clinical trials	Experimental research
card-vasc	0	<b>circulatory stimulant (topical, systemic)</b> (since Löseke 1790)  <b>varicose veins and phlebitis</b> (since Kroeber 1948)	<i>Angina pectoris</i>  <b>prothrombine time improvement</b> <b>elephantitis</b> <b>varicose veins</b>	(respiratory) analeptic anti-inflammatory antiplatelet anti-sclerotic cardiotonic circulatory stimulant central nervous system stimulant hypotensive
gastro-intest	<b>diarrhoea</b>	<b>diarrhoea</b> (until Kroeber 1948)	0	antibacterial anti-haemorrhagic anti-inflammatory anti-tumour immune stimulant
gyn	<b>to bring on menstruation (amenorrhoea)</b> <b>uterine complaints</b>	<b>to bring on menstruation (amenorrhoea)</b>  <b>uterine complaints</b> (until Madaus 1938)	0	anti-bacterial anti-haemorrhagic anti-inflammatory uterine stimulant
head	0	<b>cerebral concussion</b> (since Richter 1827 until Kroeber 1948)	0	anti-ecchymotic anti-haemorrhagic circulatory stimulant anti-inflammatory
infection	0	<b>infections resulting in fever</b> (until Madaus 1938)	0	antimicrobial anti-inflammatory cytotoxic immune stimulant
liver-spleen	<b>poisoning</b>	<b>poisoning</b> <b>bitter tonic</b> <b>jaundice</b> (until Löseke 1790)	0	anti-inflammatory bitter tonic cholagogue choloretic hepatoprotective lipid and cholesterol lowering

Use-categories	Tabernaemontanus 1664	Empirical evidence: consistent medical recommendations 18 <sup>th</sup> to 21 <sup>st</sup> century	Clinical trials	Experimental research
<b>musc-skel</b>	<b>injuries</b>	<b>injuries, sprains and strains, torn muscles and ligaments</b> <b>bruises, oedema, haematoma</b> <b>rheumatism</b>	<b>musculo-skeletal pain</b>  <b>bruises</b>  <b>osteoarthritis</b>	anti-arthritic anti-ecchymotic anti-rheumatic anti-inflammatory counterirritant
<b>nerve</b>	<b>pain</b>	<b>pain related to musculo-skeletal system, rheumatism, and nerves</b>	<b>musculo-skeletal pain</b> <b>osteoarthritis</b>	analgesic anti-inflammatory antineuralgic
<b>respiratory</b>	0	<b>cough</b> (until Weiss 1974)  <b>sore throat</b> (since Madaus 1938)	0	(respiratory) analeptic antibiotic anti-inflammatory expectorant immune stimulant
<b>skin-mucous</b>	<b>for sneezing (cleansing of mucous membranes)</b>	<b>ulcers or wounds</b> (since Richter 1827) <b>mouth and throat inflammation</b> (since Stumpf 1855)  <b>boils</b> (since Schulz 1919)  <b>varicose veins and phlebitis</b> (since Kroeber 1948)	<b>ulcers</b> <b>wounds</b> <b>burns</b>	antibiotic antifungal anti-inflammatory antiseptic antitumor circulatory stimulant cytotoxic granulopoietic
<b>tonic</b>	<b>for sneezing (tonic)</b>	<b>cardiac stimulant</b> (since Schulz 1919)	0	(respiratory) analeptic anti-inflammatory cardiotonic central nervous system stimulant circulatory stimulant hypotensive
<b>uro</b>	<b>diuresis</b>	<b>diuresis</b> (until Madaus 1938)	0	analgesic anti-inflammatory antibiotic antiseptic diuretic

## **6 THE MEDICINAL USES OF *HYPERICUM PERFORATUM*: THERAPEUTIC INDICATIONS FROM THE EARLY MODERN PERIOD (1588/1664) TO CONTEMPORARY PHYTOTHERAPY (2007)**

Worldwide, *Hypericum perforatum* (St. John's Wort) is one of the most scientifically researched medicinal plants. Its remedial uses have been documented in Europe since classical Hippocratic times and have over 2500 years become deeply embedded in both formal and folk medicine (Czygan, 2003; Dell'Aica, Garbisa, & Caniato, 2007). While St. John's Wort preparations are most readily known today for their efficacy in treating depression and somatoform disorders, there are many additional long-standing clinical indications. In this chapter, a botanical, etymological, and historical introduction to St. John's Wort is followed by a longitudinal textual analysis on empirical knowledge as recorded in medical textbooks over the past 400 years. This analysis uses the same judiciously selected medical literature as that evaluated for Arnica. Commentaries on the Prussian and German pharmacopoeias are not investigated further in this chapter. The results from the previous chapter established that such commentaries detail the same main traditional uses as recorded in the medical literature but do not reflect broader clinical practice. Authoritative expert monographs (by ESCOP, WHO, HagerROM) are also not evaluated further. They were utilised as modern sources in the preceding triangulation of data on Arnica to cross-validate historical indications recorded in medical textbooks. As such they confirmed that the main historical indications of Arnica mirror current indications in contemporary phytotherapy. These modern monographs therefore validated historical textbooks as a suitable bibliographic source of verifiable traditional indications; medical textbooks are therefore tested further as a body of empirical evidence for regulatory purposes.

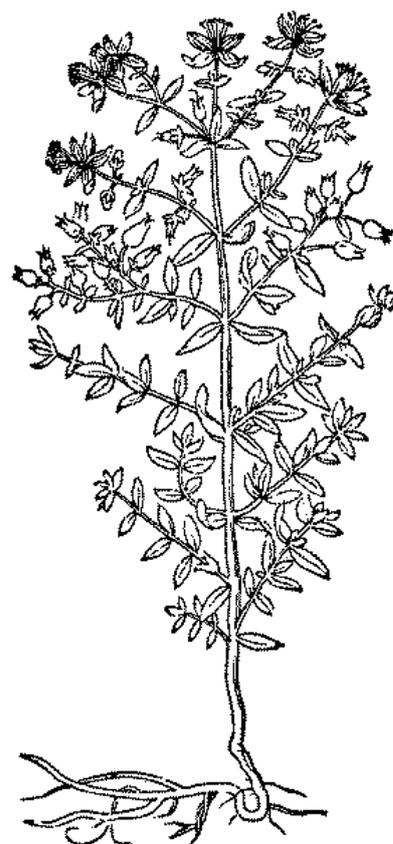
In the following section the Historical Assessment Tool is applied for the systematic collation of traditional indications of St. John's Wort recorded in mainstream textbooks on the European *materia medica*. This is to demonstrate how this method swiftly, summarily, and methodically collates traditional evidence. The analysis proceeds under the assumption that such summaries provide succinct bibliographic evidence for health claims once suitable sources are identified. Traditional evidence on consistent transmission of historical

indications is further compared with approved therapeutic indications in two European regulatory monographs: the *Commission E Monograph Hyperici herba* (Kommission E, 1984b) and the *EU Herbal Monograph Hypericum perforatum L. herba* (Committee on Herbal Medicinal Products (HMPC), 2009b). This is to understand how comprehensively such regulatory monographs reflect traditional medicinal uses of St. John's Wort and what role they could play as evidence on traditional plant medicines regulated in other countries such as New Zealand. In addition, this chapter triangulates the empirical knowledge documented in the medical literature with contemporary clinical and experimental research. The purpose of this step is to cross-validate data derived from qualitative historical sources with data derived from qualitative contemporary sources to strengthen conclusions drawn.

## 6.1 Introduction to *Hypericum perforatum* in European healthcare

### 6.1.1 Botanical profile

*Hypericum perforatum* is a perennial plant belonging to the genus *Hypericum*, a genus which incorporates about 450 species of trees, shrubs, and herbs. It is a member of the Clusiaceae (alternative name Guttiferae) family (Robson, 2003). Though native to Europe, it became naturalised in Asia, Africa, the Americas, Australia, and New Zealand (Blaschek et al., 2012; Dell'Aica et al., 2007, p. 109). St. John's Wort has four subspecies: ssp. *angustifolium* (DC.) GAUDIN; ssp. *latifolium* (KOCH) FRÖHLICH; ssp. *perforatum*; and ssp. *veronense* (SCHRANK) FRÖHLICH (Saller et al., 1995, p. 208). *Hypericum perforatum* is the official species listed in the European pharmacopoeia, the legally-binding pharmacopoeia in all EU countries. It may be accidentally or deliberately adulterated with other *Hypericum* species, such as *H. barbatum*, *H. hirsutum*, *H. maculatum*, *H. montanum*, *H. tetrapterum*, *H. patulum*, and *H.*



**Figure 5. *Hypericum perforatum* in Bock, *Kreutterbuch*, 1577, p. 27.**

*crux-andreae*, or with synthetic red dyes added to its extracts (McCutcheon, 2017, pp. 1-3).

St. John's Wort grows well alongside sunny paths, on the edges of woods, in gravel, in riverbeds, in dry pastures, and on alpine meadows at up to 1,500 meters altitude (Vonarburg, 1993, p. 112). It can reach a height of up to one metre. From June to July in European countries or from December to January in New Zealand, the opposite and paired branches yield intensely yellow flowers containing five petals with many protruding stamens. The oblong leaves are opposite, sessile, and up to two (rarely three) centimetres long, and they display numerous translucent glandular dots which are hypericin-containing oil glands. When St. John's Wort blossoms are rubbed between the fingers, they release a striking blood-red juice. The fruit is a capsule containing fine seeds that are disseminated by the wind when the ripe capsules break open (Buch, 2016; Lauber & Wagner, 2001, p. 280; Pfister et al., 2014, pp. 152-155).

Apart from *Hypericum perforatum* with its typical round stem, there are closely related species which are not official today, but which have traditionally been used for therapeutic purposes. It is possible that at least some of them have similar therapeutic effects to *H. perforatum* (Dall'Agnol et al., 2003; Fenner et al., 2005; Ferraz et al., 2005; Kızıl, Kızıl, Yavuz, Emen, & Hakimoğlu, 2008; Klejdus, Kovacik, & Babula, 2013; Pulokmukherjee, 2001; Robson, 2003, p. 20; Zorzetto et al., 2015). These similar effects of various *Hypericum* species were already identified by ancient Greek physicians as highlighted in the *Hypericum monograph* of Tabernaemontanus (Tabernaemontanus, 1664, p. 1250), and echoed by 19<sup>th</sup> century physicians (Dulk, 1833b, pp. 35-36; Strumpf, 1855). The main contenders are *H. maculatum* with its four-edged stem, *H. tetrapterum* with its four-edged winged stem, *H. montanum* with a round stem and haired leaves, *H. humifusum* with a creeping stem up to 15 cm, *H. hirsutum* with haired leaves growing up to 150cm, and *H. pulchrum* with its heart shaped leaves and growth up to 50 cm. Other *Hypericum* species are grown in gardens as ground covers and are not used medicinally (e.g. *H. olympicum* and *H. polyphyllum*) (Vonarburg, 1993, p. 112).

### **6.1.2 Historical and etymological profile**

The medical tradition and cultural significance of *Hypericum perforatum* in European medicine has been evident since antiquity. The etymology of the genus *Hypericum* is thought to link to the Greek words *hyper* and *eikon*, which translates either as 'above' or 'image', a reference to the ancient Greek custom of placing a sacred plant above the image

of a deity, or as ‘above apparitions’, a reference to its implied apotropaic properties against evil spirits (Czygan, 2003; Dell'Aica et al., 2007). During the early modern period, the implied apotropaic effects of St. John’s Wort were expressed in the Latin name *Fuga daemonum* (banishes demon) (Tabernaemontanus, 1664, p. 1250). The epithet *perforatum* was introduced in the medieval period to describe the translucent glands on the leaves of this species, which, when held against sunshine or light, appear as small black perforations.

The Swedish botanist Carl von Linné confirmed the binominal taxonomy of St. John’s Wort in his seminal work *Species plantarum* (1753) as *Hypericum perforatum* (Czygan, 2003, p. 185). The German name (*Echtes*) *Johanniskraut*, which is mirrored in the English name St. John’s Wort, refers to St. John the Baptist whose name day is 24 June, a time in the Northern Hemisphere when the plant is in full flower. In pre-Christian times, St. John’s Wort was an important plant during the summer solstice (21 June) and was dedicated to the pagan Germanic god of light, Baldur (Fischer, 1991, p. 121). Other German vernacular names are *Herrgottsblut*, *Johannisblut*, *Sonnwendkraut*, *Tüpfelhartheu*, *Christi Wundkraut*, *Christusblut*, *Gottes Gnadenkraut*, *Dunderblume*, *Sonnenwendkraut*, *Hexenkraut*, and *Teufelsflucht* (Vonarburg, 1993, pp. 111-112), many of which point to St. John’s Wort’s significance in Christian traditions that superseded long-standing holy pagan rituals (Dell'Aica et al., 2007, p. 109). The names *Frauenkraut* and *Maria Bettstroh* point to its importance in women’s healthcare.

The medicinal properties of St. John’s Wort have been documented in the Hippocratic Corpus, around 400BC, and praised by subsequent leading Greek physicians, most notably by Theophrastus, Dioscorides, the historiographer Plinius (Pliny the Elder), and Galen (Dell'Aica et al., 2007; Jarić et al., 2017). Over the past 2500 years, it has been used medicinally for the treatment of burns, wounds, sciatica, urinary tract infections, stomach and uterine complaints, bed wetting, diarrhoea, mucosal lesions of the mouth, gout, and respiratory tract ailments. It has also been used as a cholagogue and anti-inflammatory in liver and gallbladder complaints (Mayer, 2014; Saller, Kristof, & Reichling, 1999, p. 118).

Treatment of melancholy with *Hypericum* is referenced in a medical text written in the last decade of the 8<sup>th</sup> century, the *Lorscher Arzneibuch*, the oldest surviving German medieval monastic medical text (Mayer, 2014, p. 290). Melancholy was understood as a depressive state that arose from the stagnation of black bile (*melas* is black and *kholē* is bile in Greek), a humoral concept relating to disturbed digestion and altered moods (Francia & Stobart,

2014, p. 301). In humoralism, fear, sadness, gloom, and fright were typical symptoms of melancholic illnesses (Zimmermann, 1975, pp. 91-96). Such mental and emotional afflictions are today commonly understood and referenced as depression (Tschupp, 1998, pp. 44-47). In the 16<sup>th</sup> century, Paracelsus praised St. John's Wort as a *groß arcanum* (a remedy of great mystical strength) that chases away evil influences and the mad fantasies that drive people to despair (Czygan, 2003, pp. 187-188), a property that was aptly captured in the aforementioned name *Fuga daemonum*.

St. John's Wort preparations are best known today as natural treatments for mild-to-moderate depression because of both their equivalent efficacy to synthetic antidepressants and their high safety profile (Ng, Venkatanarayanan, & Ho, 2017). They are used as a cost-effective alternative to generic antidepressants (Solomon et al., 2013).

### 6.1.3 Official status

Despite its long-standing clinical uses in alpine regions of Central Europe, including Germany, St. John's Wort was not selected as an essential medicine in the first edition of the German pharmacopoeia (Hager, 1872). As shown in Table 13 (next page), it remained absent until 1986 when the *Deutsches Arzneibuch DAB 9* harmonised with the *Europäisches Arzneibuch (Ph. Europea)*. This pan-European pharmaceutical reference work provides legally binding pharmaceutical manufacturing standards for all essential medicines in countries of the EU and other signatory states (DAB 9, 1986, p. 3).

While the Prussian pharmacopoeia had listed St. John's Wort from 1799 onwards, this historically significant medicinal plant, its plant parts (*flores, herba, sumitates*), and *oleum* preparation became de-listed from its 6<sup>th</sup> edition (Gurlt, 1847). During this period, the committee of the Prussian pharmacopoeia was compelled to publish a pharmacopoeia that projected a modern image of the pharmaceutical profession by aligning themselves with what they perceived as the peak of natural science (Tschupp, 1998, pp. 121-122). Many traditional medicinal plants that could not be explained by a defining active constituent or a mechanism of action became de-listed, despite long-standing medicinal use (Jütte, 1996, pp. 165-166; Schulz, 1919, pp. 2-3). The de-listing of St. John's Wort in the Prussian pharmacopoeia was in line with the Swiss pharmacopoeia, where it was also absent until 1991 (Pharmacopoeia Helvetica, 1995), but it contrasted with pharmacopoeias of other European countries such as France, Spain, Portugal, and the former Yugoslavia, where St. John's Wort remained an official drug (Kroeber, 1948, p. 193).

**Table 13. Listings of *Hypericum perforatum* in the Prussian and German pharmacopoeia.**

Editions	1799 1 <sup>st</sup> edition	1804 2 <sup>nd</sup> edition	1813 3 <sup>rd</sup> edition	1827 4 <sup>th</sup> edition	1829 5 <sup>th</sup> edition	1846 6 <sup>th</sup> edition	1862 7 <sup>th</sup> edition
Listings in the Prussian pharmacopoeia	✓ flores, herba (summita- tes), oleum	edition could not be located	✓ flores, herba (summita- tes), oleum	✓ flores, herba (summita- tes), oleum	✓ flores, herba (summita- tes), oleum	0	0

Editions	1872 1 <sup>st</sup> ed.	1882 2 <sup>nd</sup> ed.	1890 3 <sup>rd</sup> ed.	1900 4 <sup>th</sup> ed.	1910 5 <sup>th</sup> ed.	1926 6 <sup>th</sup> ed.	1968 7 <sup>th</sup> ed.	1978 8 <sup>th</sup> ed.	1986 9 <sup>th</sup> ed.	1993 10 <sup>th</sup> ed.	2002 (1999- 2002)	2012 DAB 2012
Listings in the German pharmacopoeia	0	0	0	0	0	0	0	0	0	0	0	0
								not listed in DAB but listed in DAB compendium HAB 1 (1978-1985) for mother tincture	not listed in DAB 9 but harmonised with Ph. Europea where it is listed	not listed in DAB 9 but harmonised with Ph. Europea where it is listed	not listed in DAB 9 but harmonised with Ph. Europea where it is listed	not listed in DAB 9 but harmonised with Ph. Europea where it is listed

The de-listing of St. John's Wort as an essential drug in Germany from mid-19<sup>th</sup> century onwards, despite its ongoing use in medical care, exemplifies the regulatory privileging of newly developed synthetic drugs over historical plant medicines during this time. Prefaces to commentaries for the German pharmacopoeia illustrate a new era of academic enthusiasm for chemistry-based medicines and a critical position towards historical plant medicines (Anselmino & Gilg, 1911a, p. V). Consequently, traditional medicines were removed in great numbers. Between its 1<sup>st</sup> and 5<sup>th</sup> editions, the German pharmacopoeia eliminated 258 traditional plant medicine entries, which from 896 to 638 entries was a reduction of 29% (Jütte, 1996, p. 166). In contrast, the 5<sup>th</sup> edition of the German pharmacopoeia listed 65 synthetic medicines, up from 15 in the 2<sup>nd</sup> edition (Deutsches Arzneibuch, 1910; Pharmacopoea Germanica, 1882). This trend accelerated in the 20<sup>th</sup> century.

In the 1970s the second, revised German drug law attempted to minimise regulatory inequalities of plant-based medicines; it did so by granting phytotherapy a position as a *Besondere Therapierichtung* (special therapy) (Deutscher Bundestag, 1976)). Consequently, the former *Bundesgesundheitsamt* (BGA) (German Ministry of Health) established the *Kommission E* (Commission E), a scientific advisory board providing scientific and clinical expertise for the evaluation of the safety and effectiveness of phytotherapy and herbal substances. The Commission E granted a positive monograph for St. John's Wort (Kommission E, 1984b), approving a number of traditional uses. This reinstatement was aided by results from clinical research from the 1970s onwards which demonstrated the efficacy of St. John's Wort in depressive states (Hoffmann & Köhl, 1979). Although St. John's Wort was never listed in the German pharmacopoeia itself, it became represented after more than 100 years absence through the European pharmacopoeia with which the *DAB* harmonised in 1986.

## **6.2 *Hypericum perforatum* in medical textbooks**

Over the past 400 years, clinical medical textbooks have consistently recorded therapeutic uses of *Hypericum perforatum* for patient care. Key indications have remained remarkably consistent, even though paradigmatic explanatory models of health and illness have changed. Table 14 (next page) provides an overview of use-categories of *Hypericum perforatum* addressed in mainstream medicine since the early modern period.

The clinical endorsements of St. John's Wort from the 1600s to the present can be summarised as follows:

- indications relating to digestion, to the musculo-skeletal and nervous systems, to the skin and mucous membranes, and to somatoform disorders were consistently endorsed by physicians at least over 400 years
- indications relating to complaints of the uro-genital systems and respiratory tract also show long-standing endorsements over 400 years, yet with some intermittent absences in medical textbooks
- systemic infection fighting applications are noted by Tabernaemontanus in the 17<sup>th</sup> century, but are mostly absent in the literature from the end of the 18<sup>th</sup> century onward when the treatment of malaria became obsolete in many parts of Europe
- the apotropaic use of St. John's Wort was an important application in Europe of the

early modern period, mainly in folk medicine. The medical literature beyond the 17<sup>th</sup> century does not list this application; instead it endorses the use of St. John's Wort for disorders that are referenced today as somatoform disorders.

**Table 14. Use-categories of *Hypericum perforatum* addressed in medical textbooks.**

Use-categories	Tabernaemontanus 1664	Löseke 1790 / Plenck 1794	Richter 1827	Strumpf 1855	Hager 1878	Schulz 1919	Madaus 1938	Kroeber 1948	Weiss 1974	Saller et al 1995	Bäumler 2007
apotrop	✓	0	0	(✓)	(✓)	0	0	0	0	0	(✓)
card-vasc	0	0	0	0	0	✓	✓	✓	✓	✓	✓
gastro-intest	✓	✓	(✓)	✓	(✓)	(✓)	✓	✓	✓	✓	✓
gyn	✓	0	0	✓	0	(✓)	✓	✓	0	✓	✓
head	✓	0	0	0	0	0	✓	✓	0	✓	✓
hormonal	0	0	0	0	0	0	0	✓	0	0	0
infection	✓	0	0	✓	0	0	0	(✓)	0	0	✓
liver-spleen	✓	0	0	✓	0	0	✓	✓	0	(✓)	(✓)
musc-skel	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
nerve	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
respiratory	✓	✓	(✓)	✓	(✓)	(✓)	✓	✓	0	✓	(✓)
skin-mucous	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
somatoform	✓	0	✓	✓	(✓)	(✓)	✓	✓	✓	✓	✓
tonic	0	0	0	✓	0	0	✓	0	✓	✓	✓
uro	✓	0	0	✓	0	✓	✓	✓	✓	(✓)	✓

*Dark green rows refer to continued use*  
*Light green rows refer to intermittent but present-day-use*  
*White rows refer to present-day discontinuation*  
*Indications in italics and brackets (✓) reference historical uses or folk medicine uses*

The 19<sup>th</sup> century brought an expansion of historical uses for St. John's Wort as well as a discontinuation of some indications:

- indications relating to the tonic use-category are first mentioned in mid-19<sup>th</sup> century and are endorsed intermittently from WW2 onwards

- the use of St. John's Wort for congestive states of the cardio-vascular system was introduced at the beginning of the 20<sup>th</sup> century and remains recommended for venous congestion (topical use)
- St. John's Wort was briefly used during war times for the treatment of head injuries, such as cerebral concussion and epilepsy from trauma (head use-category). Whilst such injuries are now treated with biomedical approaches as a first line treatment, the application of St. John's Wort in the management of migraines, headaches, and meteoropathy remains
- the use of St. John's Wort for liver detoxification and poisoning became obsolete from mid-19<sup>th</sup> century onwards.

Beneficial outcomes in patient care have been documented when St. John's Wort was used in the following modes of administration: fresh or dry comminuted herb or herb powder extracted in water (tea), alcohol (tincture / extract), and oil (see Historical Data spreadsheet). These preparations were applied for both external and internal use. The traditional dosage range is documented from 15 drops of fresh-plant tincture (1:10 extraction ratio) to 1g to 6.9g of drug (or fresh plant equivalent). A traditional way of observing this dose is by taking 1-2 cups of freshly prepared medicinal tea mornings and evenings (1 teaspoon of plant material per cup equates to about 1.8g of dried St. John's Wort) (Saller et al., 1995, pp. 208-216). The recommended dose for small children up to three years of age is noted as 1 cup of medicinal tea per day and 2-3 cups per day from 3 years onwards.

Following this overview, the analysis now turns to the detailed medicinal uses that were transmitted in TEM over the past 400 years. This progression will help to ascertain which specific indications have documentary proof of consistent therapeutic use.

### **6.2.1 *Hypericum perforatum* in Tabernaemontanus (edition 1664)**

The 4<sup>th</sup> edition of the early modern period monograph on St. John's Wort by Tabernaemontanus (1664, pp. 1249B-1252A) and which was annotated by the Bauhin editors provides the starting point for this longitudinal textual analysis. This clinical text summarises the medicinal uses of St. John's Wort over two millennia as noted in the bibliographic reference list in the preface of the book. The monograph was used *pars pro toto* to represent its medicinal applications by physicians during the early modern period

until the mid-18<sup>th</sup> century when it was last printed. The codified data were transcribed and translated into modern German (see Appendix 12) before being translated into English and allocated to pre-defined use-categories to enable further analysis on its indications (see Appendix 13).

### 6.2.2 *Hypericum perforatum* in medical textbooks from 1790-2007

Analysis of the indications listed in Tabernaemontanus with the data extracted from the medical literature over the ensuing centuries provides consistent evidence for numerous historical uses that continue to be endorsed in contemporary phytotherapeutic practice. Appendix 14 summarises the consistently documented therapeutic uses of *Hypericum perforatum* in the medical literature over the past 400 years. When historic and present-day therapeutic uses of St. John’s Wort are compared, the clinical observations by practising physicians provide tradition-of-use (TOU) data on five clusters of complaints, as detailed in Table 15. These indications meet the criteria for consistent medicinal use well beyond the typically required three generations or three transmission steps.

**Table 15. Consistently endorsed indications for *Hypericum perforatum* in medical textbooks over at least 400 years.**

Use-category	Indications
<b>gastro-intest</b>	inflammation and catarrh of the gastro-intestinal system, gastro-enteritis, and dyspeptic disorders
<b>musc-skel</b>	musculo-skeletal injuries resulting in sprains, strains, bruises, and inflammation; rheumatic disorders
<b>nerve</b>	pain from inflammation and injuries to the nerves and musculo-skeletal system; rheumatic disorders
<b>skin-mucous</b>	burns (topical) and wounds (systemic and topical)
<b>somatoform</b>	psychovegetative disturbances such as depressive moods, anxiety, nervous unrest, and hormonally driven dysphoria in relation to the female menstrual cycle

Historical uses were expanded on at the beginning of the 20<sup>th</sup> century when an effect of St. John’s Wort in congestive states was observed (Schulz, 1919, p. 229). This description led to its continued endorsement in the topical treatment of venous congestions, namely haemorrhoids and varicose veins. In this research, these two indications have been allocated to the card-vasc use-category. One could argue that they could also be allocated to the skin-mucous use-category since the recommended treatment is topical. However, because the

rationale for their use was noted as a decongestant, the card-vasc use-category is more fitting. Decisions on allocations must be kept in perspective: use-categories are a construct to help researchers group data; they have no relevance from a regulatory point of view. It is the *indication* itself that requires evidence of consistent use in the context of evidence-based policy.

In addition to the cardio-vascular indications, a further indication becomes prevalent in the 20<sup>th</sup> century, that of mental exhaustion. The tonifying effect of St. John’s Wort was first mentioned by Strumpf (1855). These additional indications listed in Table 16 relate to the card-vasc and tonic use-categories and would qualify under a traditional use criterion that requests at least three continuous generations of therapeutic use.

**Table 16. Consistently endorsed indications for *Hypericum perforatum* in medical textbooks throughout the 20<sup>th</sup> century.**

Use-category	Indications
card-vasc	congestive states of the venous system; varicose veins and haemorrhoids (topical applications)
tonic	tonification in exhaustion and dysphoria

Indications relating to the uterus and the menstrual cycle have been intermittently recommended since the 17<sup>th</sup> century. Additionally, there are various indications relating to spasms, inflammation, and catarrh of the mucous membranes of the respiratory and urinary tract. The following indications listed in Table 17 are the most consistently repeated:

**Table 17. Intermittent-but-persistent indications for *Hypericum perforatum* in medical textbooks over at least 400 years.**

Use-category	Indications
gyn	uterine and menstrual complaints
respiratory	catarrh of the mucous membranes of the respiratory tract
uro	irritability in the urinary tract; diuresis

These intermittent-but-persistent indications could be considered under a traditional use criterion that acknowledges the dynamic nature of tradition. The plausibility of these indications would be strengthened if they were backed by experimental research or clinical trials. Sections 6.4 and 6.5 will deal with this evidence.

### **6.3 *Hypericum perforatum* in regulatory monographs**

Traditional indications listed in the European medical literature are now compared with two recent official European monographs that reflect the regulatory guidelines on therapeutic uses of St. John's Wort: the *Commission E Monograph Hyperici herba* by the German Ministry of Health and the *EU Herbal Monograph Hypericum perforatum L. herba* by the European Medicine Agency (EMA). These official monographs are used as exemplars to compare legally permitted claims with indications consistently endorsed in the medical literature.

The overview in Tables 18-20 demonstrates that the *Commission E Monograph Hyperici herba* provides an approved claim in each of the use-categories addressed by historical medical documentation where traditional indications persisted over 400 years. In contrast, the *EU Herbal Monograph Hypericum perforatum L. herba* provides approved claims in only three of these. Where indications in medical textbooks were listed intermittently or more recently over the past 30 years, they were not listed in either of the official monographs. Only indications relating to the gastro-intest, skin-mucous, and somatoform use-categories are consistently listed in all three sources as illustrated in Table 18. These results will be further explored in the sections that follow.

**Table 18. Comparison of empirically endorsed medicinal uses of *Hypericum perforatum* > 400 years with two official monographs.**

Use-category	Indications – medical literature over 400 years	Commission E Monograph 1984	EU Herbal Monograph 2014 traditional use
<b>gastro-intest</b>	inflammation and catarrh of the gastro-intestinal system, gastro-enteritis, and dyspeptic disorders	dyspeptic complaints	mild gastrointestinal discomfort
<b>musc-skel</b>	musculo-skeletal injuries resulting in sprains, strains, bruises, and inflammation; rheumatic disorders	acute and contused injuries, myalgia (topical)	0
<b>nerve</b>	pain from inflammation and injuries to the nerves and musculo-skeletal system; rheumatic disorders	acute and contused injuries, myalgia (topical)	0
<b>skin-mucous</b>	burns (topical) and wounds (systemic and topical)	first-degree burns (topical)	minor inflammation of skin (such as in sunburn) and minor wounds
<b>somatoform</b>	psychovegetative disturbances such as depressive moods, anxiety, nervous unrest, and hormonally driven dysphoria in relation to the female menstrual cycle	psychovegetative disturbances, depressive moods, anxiety and/or nervous unrest	temporary mental exhaustion

**Table 19. Comparison of additional empirically endorsed medicinal uses of *Hypericum perforatum* > 30 years with two official monographs.**

Use-category	Indications – medical literature >30 years	Commission E Monograph 1984	EU Herbal Monograph 2014 traditional use
<b>card-vasc</b>	congestion and inflammation in the venous system, e.g. varicose veins, haemorrhoids (topical)	0	0
<b>tonic</b>	tonification in exhaustion	0	temporary mental exhaustion (also listed under somatoform category)

**Table 20. Comparison of intermitted-but persistent medicinal uses of *Hypericum perforatum* with two official monographs.**

Use-category	Indications – medical literature: intermittent-but-persistent therapeutic indication	Commission E Monograph 1984	EU Herbal Monograph 2014 traditional use
<b>gyn</b>	uterine and menstrual complaints	0	0
<b>respiratory</b>	catarrh of the mucous membranes of the respiratory tract	0	0
<b>uro</b>	irritability in the urinary tract; diuresis	0	0

### 6.3.1 The *Commission E Monograph Hypericum perforatum L. herba*

Before St. John’s Wort became one of the most scientifically studied medicinal plants in the world, empirical evidence was accepted by the German regulatory authority as demonstrating the plant’s plausible effectiveness. As already noted, scientific pluralism in medicine beyond natural science was explicitly mandated by the Second Medicines Act (Arzneimittelgesetz 1976 (AMG 76)), which went into effect in Germany on January 1, 1978 (Deutscher Bundestag, 1976). This legal remit guided the writing of the *Commission E Monograph Hyperici herba* (Kommission E, 1984b). It is noteworthy that the monograph explicitly states that it approves the mild antidepressant action of the herb and its preparations based on its evaluation of numerous reports from physicians (Kommission E, 1984b, para. Anwendungsgebiete).

The approved indications relate to the following modes of administration: comminuted herb; herb powder; liquid and solid preparations for internal use and liquid; semi-solid preparations for external use; and preparations made with fatty oils for both external and internal use. No preparations or standardisations based on more recently developed pharmaceutical extraction methods are listed, apart from the option to standardise crude drugs to their hypericin content. The average daily dosage for internal use is recorded as 2-4 g of herbal substance or 0.2-1 mg of total hypericin in other preparations. The monograph lists no contraindications for these preparations at this dosage and notes that herb-drug interactions are not known for the traditional preparations listed.

The approved claims are consistent with empirical medicinal uses noted in the medical literature of the past 400 years. The monograph differs, however, from this body of literature in that it approves only *external* preparations for the treatment of complaints of the musculo-skeletal and nerve systems whereas such complaints were traditionally treated

systemically as well. Additionally, more recent 20<sup>th</sup> century indications, namely varicose veins, haemorrhoids, and tonification in exhaustion, did not pass the Commission E evaluation—although the latter could be a subset of ‘psychovegetative disorders.

### **6.3.2 The European Community Herbal Monograph *Hypericum perforatum L., herba***

The Committee on Herbal Medicinal Products (HMPC) of EMA released two monographs on St. John’s Wort, one on well-established use and one on traditional use. In this study, only the traditional use monograph is evaluated. Claims in the traditional use monograph are accepted on the basis of sufficient safety data and plausible efficacy (Europäisches Parlament, 2004). The *EU Herbal Monograph Hypericum perforatum L. herba* (traditional use) officially endorses therapeutic indications relating to three different areas of health concerns: 1) for the relief of temporary mental exhaustion; 2) for the symptomatic topical treatment of minor inflammations of the skin (such as sunburn) and as an aid for healing of minor wounds; and 3) for symptomatic relief of mild gastrointestinal discomfort. These indications cover the use-categories gastro-intestinal tract and skin-mucous membranes, whereas “temporary mental exhaustion” (Committee on Herbal Medicinal Products (HMPC), 2009c, p. 3) can be assigned to both the somatoform and the tonic use-categories depending on the cause. All approved therapeutic indications relate to the same use-categories also addressed by long-standing empirical uses of St. John’s Wort in medical textbooks over 400 years. Complaints of the musculo-skeletal and nervous systems are absent in this monograph.

When the health claims approved by HMPC and the Commission E are additionally compared to indications recorded in Tabernaemontanus 1664, it becomes evident that contemporary regulatory monographs have considerably narrowed clinical applications to fewer areas of treatment. While regular medicine in early modern Europe recommended St. John’s Wort in the treatment of complaints relating to 12 use-categories, the *Commission E Monograph Hyperici herba* approves indications relating to five of those and the *EU Herbal Monograph Hypericum perforatum L. herba* relating to three—with the additional use-category of tonic first documented in the reviewed literature mid-19<sup>th</sup> century. As already noted in the overview in Table 18, this disparity means that only indications relating to the gastro-intest, skin-mucous, and somatoform use-categories are consistently listed in all three sources. Table 21 compares the indications in these three sources.

**Table 21. Indications for *Hypericum perforatum* listed in the early modern period compared with approved claims in regulatory European monographs.**

Use-categories	Tabernaemontanus edition 1664 (starting point)	Commission E Monograph 1984	EU Herbal Monograph traditional use 2014
<b>apotrop</b>	✓	0	0
	talisman against ghosts and demons		
<b>gastro-intest</b>	✓	✓	✓
	abdominal pain, colic, diarrhoea, worms	dyspeptic complaints ( <i>dyspeptische Beschwerden</i> )	gastrointestinal discomfort
<b>gyn</b>	✓	0	0
	birth complications, menstruation, unease before and during menstruation, puerperium		
<b>head</b>	✓	0	0
	epilepsy, stroke		
<b>infection</b>	✓	0	0
	Malaria tertiana		
<b>liver-spleen</b>	✓	0	
	liver detoxification, poison		
<b>musc-skel</b>	✓	✓	0
	musculo-skeletal injuries (ligaments, tendons, fascia, nerves, muscles)	acute and contused injuries ( <i>scharfe und stumpfe Verletzungen</i> )	
	rheumatism	myalgia ( <i>Myalgien</i> )	
	stiff limbs and joints; relaxing lame joints		
	spasms in wounds		
<b>nerve</b>	✓	✓	0
	pain (abdomen, limbs, musculo-skeletal, rheumatism, womb, wounds)	myalgia ( <i>Myalgien</i> )	
	hip pain / sciatica		
	nerve injuries		
	nerve pain		
	trembling, tremor		
<b>respiratory</b>	✓	0	0
	pleurisy, spitting of blood		
<b>skin-mucous</b>	✓	✓	✓
	burns	1 <sup>st</sup> degree burns ( <i>Verbrennungen 1. Grades</i> )	minor inflammation of skin (such as in sunburn)
	wounds (deep, large, infected, inner, outer)		minor wounds
	bleeding (wounds)		
	ulcers		

Use-categories	Tabernaemontanus edition 1664 (starting point)	Commission E Monograph 1984	EU Herbal Monograph traditional use 2014
<b>somatoform</b>	✓	✓	✓
	demons (banish)	psychovegetative disturbances ( <i>psychovegetative Störungen</i> )	temporary mental exhaustion
	melancholy	depressive moods ( <i>depressive Verstimmungszustände</i> )	
		anxiety ( <i>Angst</i> )	
	unease before and during menstruation	nervous unrest ( <i>nervöse Unruhe</i> )	
<b>tonic</b>	0	0	✓
			temporary mental exhaustion (also noted under somatoform use-category)
<b>uro</b>	✓	0	0
	bladder stone, gravel, kidney detoxification, poison, urine voiding		

HMPC is currently revising the *EU Herbal Monograph Hypericum perforatum L. herba* (traditional use) after a consultation period with Member States in 2018. The draft monograph proposes including two additional indications, namely for the supportive treatment of nervous restlessness (as also noted in the Commission E monograph) and sleep disorders (Committee on Herbal Medicinal Products (HMPC), 2018). If accepted, these indications would broaden indications in the somatoform use-category.

### 6.3.2.1 Areas recommended for re-assessment for approved claims

When 17<sup>th</sup> century indications are examined from a contemporary viewpoint, it becomes apparent that the empirical observations recorded by Tabernaemontanus, and repeated in the subsequent medical literature, relate to key actions of St. John's Wort on specific human body tissues present in several body systems. The pleiotropic effects of the now-confirmed anti-inflammatory, antimicrobial, astringent, and wound healing actions of St. John's Wort (Bone & Mills, 2013, pp. 827-828) are especially beneficial on lesions of the mucous membranes and the skin. These effects have been historically recorded in complaints of the gastro-intestinal tract, the respiratory and urinary tract, the uterus, in inflammatory conditions of the skin, and in congestive and inflamed conditions of veins. The *EU Herbal*

*Monograph Hypericum perforatum L. herba* acknowledges these pleiotropic effects for the mucous membranes of the gastro-intestinal system and for afflictions of the skin (wounds, burns), but not for mucosal lesions in the respiratory and uro-genital tracts. The results of this thesis suggest that historical indications relating to gynaecology, particularly uterine and menstrual complaints, and irritations in the respiratory and urinary tract should be re-evaluated for regulatory approval based on St. John's Wort's pleiotropic actions on *all* mucous membranes throughout the body.

Moreover, St. John's Wort has relaxant, neuroprotective, spasmolytic, antidepressant, and euphoric effects (Bone & Mills, 2013, pp. 827-828), all of which may be beneficial for a variety of neurovegetative disturbances. These multiple pharmacological actions may explain St. John's Wort's broad historical uses for depressive moods, anxiety, nervous unrest, and hormonally driven dysphoria in relation to the female menstrual cycle. Since the 20<sup>th</sup> century these pharmacological effects have additionally been applied in the treatment of headaches and exhaustion (see Appendix 14). Temporary mental exhaustion is currently the only pre-approved somatoform application in the *EU Herbal Monograph Hypericum perforatum L. herba*. This analysis suggests that the broader historical treatments of neurovegetative disturbances merit a re-evaluation for approval in the EU traditional use monograph.

Anti-inflammatory effects are also relevant in the treatment of musculo-skeletal injuries and in nerve pain as recognised in the *Commission E Monograph Hyperici herba*. Based on consistent documentary evidence of clinical uses of St. John's Wort in the treatment of trauma, pain, sprains, strains, bruises, and inflammation or myalgia of various origins, including rheumatic disorders, these could also be re-considered under Directive 2004/24/EC. In addition, congestion and inflammation in the venous system (such as varicose veins and haemorrhoids) may also meet the criterion of 30 years of consistent medical use.

#### **6.3.2.2 Endorsed preparations in the *EU Herbal Monograph Hypericum perforatum L. herba***

The EU herbal monograph on St. John's Wort (traditional use) lists the comminuted or powdered herbal substance as the official drug. Approved preparations are a tea preparation, a 1:10, 1:5-7, or a 1:2 ethanol-water extract, and a 1:4-20 or a 1:13 vegetable oil extract. The monograph also authorises expressed juice from the fresh herb. Additionally, it lists a

4-7:1 pharmaceutical extract in solid pharmaceutical form as a traditional preparation, a composition that was developed in the latter part of the 20<sup>th</sup> century. The text refers to the European pharmacopoeia for quality standards. The recommended daily dose, usually taken as three separate dosages, is between 600mg and 6000mg (fresh juice up to 7500mg).

### 6.3.2.3 Special warnings and precautions for use

While the *Commission E Monograph Hyperici herba* did not raise safety concerns with traditional applications and dosages, the *EU Herbal Monograph Hypericum perforatum L. herba* (traditional use) stipulates several “special warnings and precautions for use” (Committee on Herbal Medicinal Products (HMPC), 2009b, p. 6). As already noted in the analysis on Arnica, such warnings reflect an increasingly cautionary approach to risk in public health since the mid-1980s, a trend which became heightened in the context of the EU regulatory framework that is informed by not only scientific but also political considerations. The warnings and precautions recommend:

- limiting UV exposure during treatment
- not using St. John’s Wort in children and adolescents under 18 years of age because of the absence of sufficient scientific safety data
- not using St. John’s Wort during pregnancy and lactation because of the absence of sufficient scientific safety data
- paying attention to gastrointestinal disorders, allergic skin reactions, fatigue, and restlessness that may occur.

Although these warnings and precautions in the *EU Herbal Monograph Hypericum perforatum L. herba* are not noted as contra-indications but relate to the withholding of a pre-approval under the simplified registration pathway, they demonstrate the challenge of integrating empirical safety data into a modern evidence-based healthcare model that is primarily set up to provide safety guidelines for novel and potentially toxic synthetic drugs. The precautions of not using St. John’s Wort for children under 18 years of age and for pregnant or lactating women is not based on evidence of harm, but on absence of toxicological data. This precaution is absent in the historical and contemporary medical literature and not raised via modern epidemiology or pharmacovigilance. For instance, evaluation of an open label pilot study and a multi-centre post-marketing surveillance study with a total of 85 patients completing the studies showed that the *Hypericum perforatum* preparations under investigation were well tolerated in children under 12 years of age

(Hübner & Kirste, 2001), and in adolescents from 12-17 years of age (Simeon, Nixon, Milin, Jovanovic, & Walker, 2005).

St. John's Wort was historically prescribed during the *puerperium* (see Appendix 14) and continued to have relevance as a *peri-* and *post-partum* treatment during the 20<sup>th</sup> century (Clair & Saller, 2015; Käppeli, 2001; Stadelmann, 2005). Smeriglio, Tomaino, and Trombetta (2014, pp. 1113-1114) note in their overview of the literature of the most frequently consumed herbal remedies during pregnancy that St. John's Wort is applied by some women in the treatment of mild to moderate depression instead of synthetic antidepressants. A prospective study comparing pregnant women taking St. John's Wort preparations, pregnant women taking anti-depressive drugs, and healthy pregnant women not exposed to any known teratogens concluded that there are no differences in rates of live births, prematurity and major malformations between the three groups (Moretti, Maxson, Hanna, & Koren, 2009). The data were similar to the risk expected in the general population. Though further large-scale studies are still needed, this first published study on the effects of St. John's Wort in human pregnancy provides some evidence of foetal safety.

The current, limited clinical and experimental data on St. John's Wort suggest no increase in foetal harm when exposed during pregnancy (Avila, Whitten, & Evans, 2018; Kolding, Pedersen, Henriksen, Olsen, & Grzeskowiak, 2015; Mills & Bone, 2005, pp. 585-593; Moretti et al., 2009). Overall, St. John's Wort preparations have shown to be better tolerated than synthetic antidepressants, with adverse events (AEs) being mild, transient, and significantly lower than events recorded for synthetic antidepressants (Schulz, 2006). The difference in severity of AEs is clinically relevant for patients' quality of life (QOL) and therefore relevant in the regulatory safety assessment of St. John's Wort in a patient-centred healthcare setting.

#### **6.3.2.4 Herb-drug interactions**

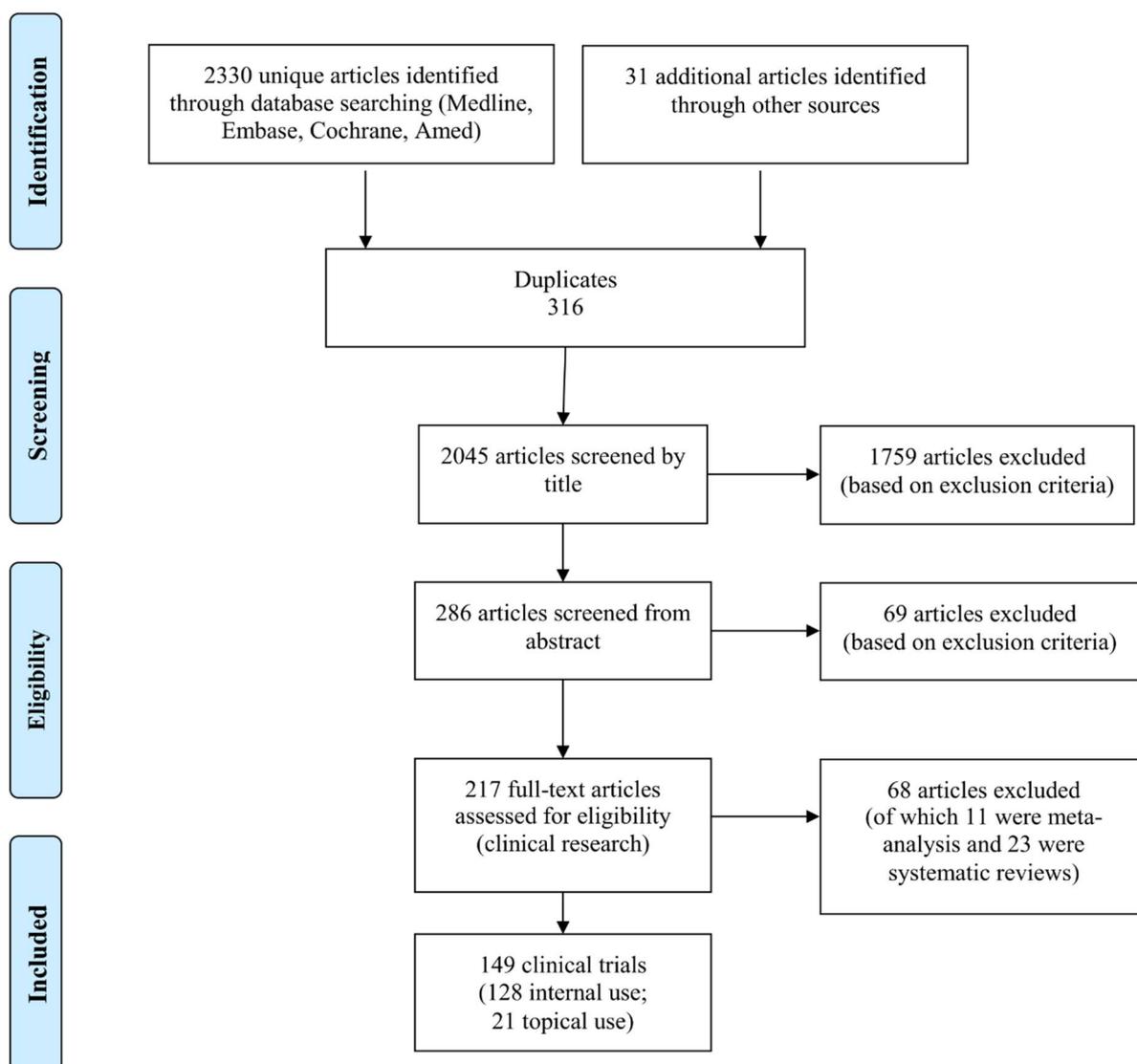
The *EU Herbal Monograph Hypericum perforatum L. herba* (Committee on Herbal Medicinal Products (HMPC), 2009b) includes a section on herb-drug interactions. This traditional use monograph is mainly concerned with traditional preparations that are not known to induce herb-drug interactions at normal therapeutic doses (Mueller et al., 2009; Mueller et al., 2006; Mueller et al., 2004). However, it also includes one newer pharmaceutical-type dry extract (DER 4-7:1), which makes a discussion on potential herb-drug interactions necessary. To minimise this potential effect, the *EU Herbal Monograph*

*Hypericum perforatum* L. herba states that the daily intake of St. John's Wort preparation is to be less than 1mg of hyperforin (Committee on Herbal Medicinal Products (HMPC), 2009b, p. 9).

Herb-drug interactions are not examined in historical medical textbooks, such interactions being a modern phenomenon. Until the 1990s, when some German manufacturers started to standardise their St. John's Wort preparations to a higher-than-naturally occurring content of hyperforin, herb-drug interactions were not a topic of concern in the literature or noted by pharmacovigilance centres (Meier, 2001; Nahrstedt & Butterweck, 2010). However, research has shown that modern preparations high in hyperforin may cause interactions with some specific synthetic drugs (Mai et al., 2004; Mueller et al., 2009; Mueller et al., 2006). Clinical studies define a high-hyperforin extract as one that contains  $\geq 10$  mg of hyperforin per daily dose and a low-hyperforin extract as one that contains  $\leq 4$  mg hyperforin per daily dose (Arold et al., 2005; Whitten, Myers, Hawrelak, & Wohlmuth, 2006). Hyperforin is naturally unstable and traditional medicinal teas and tinctures have been shown to be low in or free of hyperforin, meaning that these preparations are unlikely to be relevant CAP3A inductors (Meier, 2001). For this reason, the Swiss Agency for Therapeutic Goods, Swissmedic, have exempted traditional tea preparations from safety warnings (Swissmedic, 2002, p. 7). Medsafe (2014) in New Zealand have also highlighted the low risk of herb-drug preparation with low hyperforin content.

#### **6.4 Clinical research on *Hypericum perforatum***

To cross-validate empirical evidence on *Hypericum perforatum* with results from contemporary clinical research, this study employed a systematic method of literature searching, study selection, and data extraction. As noted in the Material and Methods chapter, the literature was searched using the following databases: Medline, Embase, AMED, Cochrane Library, Web of Science, and CINAHL. In addition, the bibliographies of included papers were examined for relevant studies. Searches were limited to English, German, French, or Dutch language material published from the inception of the databases to June 2014. The search strategy applied is summarised in Appendix 1, and the results are displayed in the following PRISMA flow diagram. An alert was set up when the initial search was concluded, and this process identified further literature included in this thesis.



**Figure 6. Flow diagram of database research to June 2014 of clinical trials on *Hypericum perforatum* flowering areal parts for cross-validation of clinical research with empirical evidence**

The study selection criteria were set to exclude articles outside the scope of this review:

- studies published in languages other than English, German, French or Dutch
- studies on homeopathically potentised *Hypericum perforatum*
- studies on a different *Hypericum* species other than *Hypericum perforatum*
- studies on toxicity
- *in vitro* studies
- rodent models
- studies on herb-drug interactions

- studies not declaring dose or concentration of preparation
- papers discussing the same clinical trial (as an already-selected paper)
- meta-analyses or systematic reviews (noted separately)
- journal comments
- narratives.

The search strategy identified a total of 2320 unique articles. After consideration of title and abstracts using the study selection criteria, 149 full papers on unique clinical trials of St. John's Wort preparations were retrieved and scrutinised. Of these, 128 clinical trials related to internal use and 21 to topical use. Furthermore, the search strategy identified 11 meta-analyses and 23 systematic reviews, most of them relating to the medicinal use of St. John's Wort in depressive disorders.

Of the 149 clinical trials selected and examined, three clinical trials have been attributed to two use-categories. Of the total of 152 attributions, 131 are on clinical trials that were conducted with St. John's Wort solely and 21 on clinical trials with a combination of St. John's Wort and other substances, but without measuring the additional effects of St. John's Wort separately. The clinical trials on combination remedies are included in this study because complex formulations are common in traditional European medicine. These trials cannot be used, though, as scientific proof of a specific therapeutic effect of *Hypericum perforatum*; rather, they point to indications where a synergistic effect with *Hypericum perforatum* was sought. The main substances combined with St. John's Wort were Black Cohosh (*Cimicifuga racemosa*) for menopausal complaints, Chaste Tree berry (*Vitex agnus-castus*) for PMS and menopausal complaints, and various combinations with Valerian (*Valeriana officinalis*), Lemon balm (*Melissa officinalis*), and Passionflower (*Passiflora incarnata*) for nervous system support. In clinical trials for topical use, St. John's Wort was combined with Neem oil, Onion (*Allium cepa*), Calendula (*Calendula officinalis* or *Calendula arvensis*), and copper sulphate.

It is outside the scope of this thesis to judge the recorded effects (benefits and harms) in these clinical studies. An evaluation of clinical trials conducted until 2009 can be found, for example, in the HMPC Assessment Report on *Hypericum perforatum* L., herba (Committee on Herbal Medicinal Products (HMPC), 2009a), and in the systematic reviews and meta-analyses quoted below. This thesis summarises indications said to be validated by

contemporary science and compares them with historical indications that were validated by empirical science as in repeated clinical observations in patient care.

#### **6.4.1 Clinical research results**

The summary of the retrieved scientific trials on St. John's Wort is displayed in Appendix 15. The 149 clinical trials identified cover indications relating to nine use-categories. Unless marked, all studies confirmed positive results. One trial (Li, Li, Wang, & Yu, 2005) was allocated to both the card-vasc and the somatoform use-categories as it investigated two separate indications (myocardial function and depression). Another trial (Kundakovic et al., 2012) was allocated to both the skin-mucous and card-vasc use-categories as it investigated venous ulcers, a condition that originates in a lack of venous flow. A third trial (Pereira, Pradella-Hallinan, & Alves, 2013) was allocated to both the musc-skel and nerve use-categories, as Restless Legs Syndrome (or Willis-Ekbom's disease) is thought in current aetiology to be related to nerve dysfunction. Nineteen studies (from 1979 to 2015) were conducted with traditional preparations, while 135 studies (from 1991 to 2014) were conducted with modern pharmaceutical preparations (mostly standardised tablets) (see Appendix 15).

Most clinical trials (75) were set up to validate St. John's Wort's efficacy in treating depression. This significant level of research interest was in part stimulated when the German Commission E released a positive monograph on St. John's Wort that officially approved the indications 'psychovegetative disturbances, depressive moods, anxiety and/or nervous unrest' (Kommission E, 1984b, para. Anwendungsgebiete). These indications became accepted claims for marketing authorisation and eligible for funding in the official German healthcare system. Most of the clinical trials yielded positive results, results which were also confirmed in 23 systematic reviews and 11 meta-analyses. Eight meta-analyses of RCTs established that St. John's Wort was significantly superior to placebos in cases of mild to moderate depression while being equivalent to synthetic antidepressants, but with fewer adverse effects (Jou et al., 2005; Kim, Streltzer, & Goebert, 1999; Laakmann, Jahn, & Schule, 2002; Linde, Berner, Egger, & Mulrow, 2005; Linde et al., 1996; Rahimi, Nikfar, & Abdollahi, 2009; Röder, Schaefer, & Leucht, 2004; Whiskey, Werneke, & Taylor, 2001). Two meta-analyses of RCTs established that St. John's Wort was superior to placebos for depressive symptoms (Kasper & Dienel, 2002; Werneke, Horn, & Taylor, 2004). Additionally, one meta-analysis established the following: St. John's Wort (as a

monotherapy) was superior when compared to a placebo for the improvement of menopausal complaints such as hot flushes and sleep problems; Black Cohosh in combination with St. John's Wort was more effective when compared to a placebo for controlling menopausal symptoms such as hot flushes and neurovegetative symptoms, and that this combination was more effective than Black Cohosh on its own; and, when compared with placebo, St. John's Wort in combination with Chaste Tree berries significantly improved the recovery in overall PMS-like symptoms (Liu et al., 2014). The first updated meta-analysis published since the database research cut-off has reconfirmed that St. John's Wort has comparable efficacy and better safety for patients with mild-to-moderate depression as standard selective serotonin reuptake inhibitors (SSRIs) (Ng et al., 2017).

The comparison below links indications examined in the retrieved clinical trials with similar types of (but differently termed) historical indications documented in the medical literature, where applicable. The author ID is established in Appendix 15. The results of the studies were positive unless indicated.

**Table 22. Historical indications compared with evidence from clinical trials.**

Use-category	Historical indications	Clinical trials: systemic use	Author ID	Clinical trials: topical use	Author ID
card- vasc	circulatory insufficiency / congestive states (since Schulz 1919)	Raynaud's phenomenon (1 RCT* - negative)	2	venous skin ulcer (1 observ. study*)	3
		improved platelet response (1 observ. study)	4		
		ventricular function recovery (1 RCT)	1		
gastro- intest	abdominal pain and colic (since Tab. 1664)	colic, IBS (1 RCTs- decrease of symptoms but inferior to placebo)	5		
	diarrhoea (since Tab. 1664)	IBS, GIT symptoms (1 observ. study)	6		
	inflammation and catarrh of the gastro-intestinal system; gastro-enteritis and dyspeptic complaints (since Schulz 1919)				
gyn	pre-menstrual unease (since Tab 1664)	pre-menstrual tension (1 observ. study; 5 RCTs)	7, 8, 17, 18,19,21	bacterial vaginosis (1 observ. study; 1 RCT)	20, 22
	dysmenorrhea (since Strumpf 1855)				
	puerperium (Tab 1664)				
	white discharge (Strumpf 1855)				
	excessive bleeding (since Strumpf 1855)				
menopausal complaints (since Madaus 1938)	menopause symptoms - hot flushes, night sweats, pre-menstural tension (7 RCTs; 1 observ. study)	9-11, 13-16, 12			
head	epilepsy and stroke (since Tab. 1664)	shielding or improving cognitive function (12 RCTs)	23-34		
		spatial memory improvement in smokers (1 RCT – negative)	35		

Use-category	Historical indications	Clinical trials: systemic use	Author ID	Clinical trials: topical use	Author ID
<b>mus-skel</b>	<b>spasms and trembling</b> (since Tab. 1664)	<b>Restless Legs Syndrome / Willis-Ekbom's disease</b> (1 RCT)	36		
<b>nerve</b>	<b>nerve pain and musculo-skeletal injuries</b> (since Tab. 1664)  <b>neuralgias</b> (since Schulz 1919)	<b>pain / neuropathy</b> (1 RCT)	37		
		<b>Restless Legs Syndrome / Willis-Ekbom's disease</b> (1 RCT)	36		
		<b>Burning Mouth Syndrome</b> (1 RCT)	38		
<b>skin-mucous</b>	<b>burns</b> (since Tab 1664)			<b>burns</b> (3 observ. studies)	39, 52, 53
	<b>wounds</b> (since Tab 1664)			<b>wounds</b> (3 RTCs; 2 observ. studies)	40, 46, 56 49, 55
	<b>ulcers</b> (since Tab 1664)			<b>ulcers</b> (1 RCT; 1 case report)	43 54
				<b>venous skin ulcer</b> (1 observ. study)	48
				<b>dermatitis</b> (2 RCTs)	45, 41
				<b>dry, damaged, inflamed skin</b> (2 RCTs; 1 observ. study)	44, 51 42
				<b>herpes infection</b> (1 RCT)	47
				<b>psoriasis</b> (1 observ. study)	50

<b>Use-category</b>	<b>Historical indications</b>	<b>Clinical trials: systemic use</b>	<b>Author ID</b>
<b>somato-form</b>	<b>banish demons</b> (since Tab 1664)  <b>melancholy</b> (since Tab 1664)  <b>depression, nervous breakdown, and traumatic neurosis</b> (since Kroeber 1948)  <b>nervous tension and somatoform dysfunction</b> (since Madaus 1938)  <b>insomnia</b> (since Madaus 1938)  <b>exhaustion</b> (since Madaus 1938)  <b>mania</b> (since Richter 1827)  <b>hysteria</b> (since Madaus 1938)	<b>anxiety</b> (2 RCTs; 3 observ. studies)  <b>depression</b> (54 RCTs – 6 were non superior to placebo;  18 observ. studies)  <b>somatoform disorders with autonomic dysfunction</b> (3 RCTs)  <b>SAD</b> (1 RCT)  <b>sleep</b> (3 RCTs)  <b>OCD</b> (2 observ. studies – 1 negative)  <b>social phobia</b> (1 observ. study; 1 RCT – negative)  <b>ADHD</b> (1 RCT – negative; 1 observ. study)  <b>addiction</b> (4 RCTs – 2 negative; 2 observ. studies – 1 negative)  <b>autism</b> (1 observ. study)	58, 72**, 111**, 143**, 150**  57, 59, 60-65, 67, 69-74, 77-81, 83, 86, 88, 90, 91, 93-98, 100, 104-107, 112, 115-117, 120, 121, 123, 124, 126, 127, 129, 130, 132, 133, 135, 136, 142, 147, 149, 151  76, 84, 85, 87, 89, 99, 101-103, 110, 111, 114, 122, 131, 134, 146, 148, 152  108, 143, 113  75  66, 82, 138  92, 118  150 119  137, 144  109, 140, 141, 145  125, 128  139
	<b>tonic</b>	<b>tonification</b> (since Strumpf 1855)  <b>mental exhaustion and neurasthenia</b> (since Madaus 1938)	<b>fatigue</b> (1 observ. study)
*“observ. study” relates to observational study; “RCT” relates to randomised-controlled trial; ** relates to studies that have two indications and that are already counted in another category			

#### 6.4.2 Discussion of clinical research on St. John's Wort

Clinical trials on St. John's Wort conducted with EBM methods support several long-standing traditional indications. All belong to the same use-categories as indications noted in the medical literature (cardio-vasc, gastro-intest, gyn, head, musc-skel, nerve, skin-mucous, somatoform, tonic). Most trials (75) were set up to validate St. John's Wort's efficacy in the treatment of depression. Parallel findings between historical empirical evidence and evidence in the form of clinical trials support the concept that consistent, clinically evaluated observation is a rational methodology that provides data that can be reproduced and validated. These findings challenge the proposition that traditional indications are random or placebo.

Another important finding is that humoralism and contemporary medicine are expressions of two separate and distinct medical paradigms, applying distinctly different descriptions and explanatory models of illness. Despite these differences, historical and modern treatments with St. John's Wort appear to be for similar disorders. For instance, physicians in the early modern period targeted the elimination of 'black bile' (= melan-choly) and the banishment of a 'demon' (*Fuga daemonum*). In the ensuing period, traditional indications described signs and symptoms of psychovegetative disturbances such as melancholy, depressive moods, anxiety, nervous unrest, and hormonally-driven dysphoria in relation to the female menstrual cycle (see Appendix 14). Today, St. John's Wort is used in the treatment of depression as defined in the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM).

While traditional descriptions and modern nosological paradigms may point to similar disorders, there is a need to exercise caution with retrospective diagnosis (Karenberg, 2009; Leven, 1998). This is one of the challenges of research into historical indications where some subjective interpretation of historical indications is unavoidable in the codification process. However, not only historical but also modern classifications of diseases pose challenges, as they are a changing construct (Karjalainen, 1999). For example, the mechanisms underlying the complex illness of depression are still not well understood. The monoamine theory of neurotransmitter dysfunction—one of the theories—is inconsistent with the pharmacodynamic effects of some antidepressants that do not target this pathway (Davis, 2002, pp. 1139–1163). Depression has been linked to a number of other drives, including low-grade chronic inflammation and chronic physiological or psychological stress. Neuroinflammation has also been linked to psychiatric illnesses (Najjar, Pearlman,

Alper, Najjar, & Devinsky, 2013). It is conceivable that these drivers can be linked to the historical nosology ‘neurasthenia’ or exhaustion where the beneficial toning effect of St. John’s Wort has been documented since the mid-19<sup>th</sup> century. There is a hypothesis that St. John’s Wort’s mechanism of action is mediated by the interrelationship between the immune, oxidative defence, and neuroendocrine systems (Nahrstedt & Butterweck, 2010, p. 1017). It is a distinct feature of plant-based medicines that they exert complex effects which regulate multiple human receptors and over-arching processes concurrently (pleiotropic effect) (Chen et al., 2016; Johnson & Fahey, 2012). With their multitarget properties affecting molecular, genetic and cellular levels they address regulatory mechanisms that have a wide-reaching systemic effect (Saller et al., 2014). Such pleiotropic effects of St. John’s Wort in the treatment of somatoform disorders have been traditionally observed and documented. They are now increasingly corroborated by clinical trials (see Appendix 15) and by experimental research (see section below).

There are further parallel findings between the empirically observed effectiveness of St. John’s Wort, and its efficacy confirmed by clinical trials. Treatment with St. John’s Wort for abdominal pain, colic, diarrhoea, and inflammation of the gastro-intestinal system was noted at least since Tabernaemontanus (1664). Some clinical research now points to the treatment potential of St. John’s Wort for gastro-intestinal disorders. One observational study found St. John’s Wort to be beneficial in treating Irritable Bowel Syndrome (IBS) (Wan & Chen, 2010) and one RCT found it decreased IBS symptoms; however, in the latter study it was inferior to placebo (Saito et al., 2010).

Some correlations between historical indications and clinical research are also apparent in gynaecology (pre-menstrual tension and uterine or vaginal complaints) (see Appendix 15, lines 8-23) and afflictions of the nerves and muscles (trembling and pain) (Pereira et al., 2013; Sardella et al., 2008; Sindrup, Madsen, Bach, Gram, & Jensen, 2001). In addition, clinical trials yielded positive results with St. John’s Wort in treating wounds, ulcers, and burns—either as a mono-substance or when combined with other herbal substances (Reichling, Weseler, & Saller, 2001; Schempp, Pelz, Wittmer, Schopf, & Simon, 1999; Süntar et al., 2011; Süntar, Oyardi, Akkol, & Ozcelik, 2016; Weseler, 2004). Treatment of wounds and ulcers with St. John’s Wort was first described in the Hippocratic Corpus (Jarić et al., 2017) and was extensively discussed by Tabernaemontanus (1664), and successive authors. Historical empirical observations agree with contemporary findings from experimental research that demonstrate antimicrobial properties of hydrous solutions (tea)

of St. John's Wort against gram-positive bacteria, with special activity towards methicillin-resistant strains of *Staphylococcus aureus* (Reichling et al., 2001; Weseler, 2004).

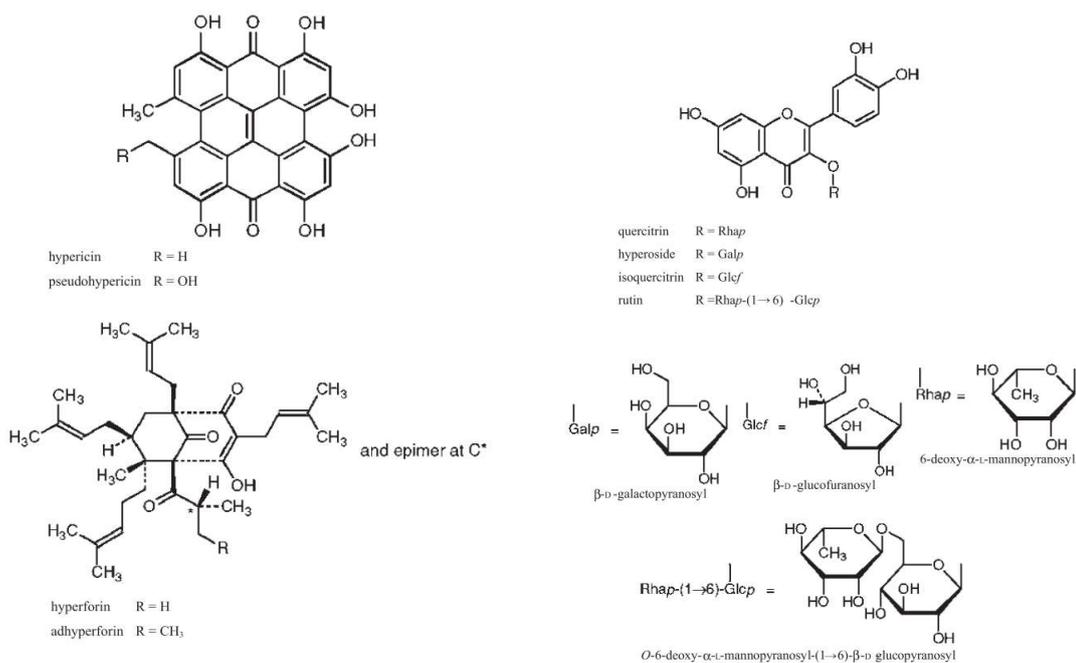
The use of St. John's Wort for improving cognition is a novel application not noted under traditional use (Ellis, Stough, Vitetta, Heinrich, & Nathan, 2001; Johnson, Ksciuk, Woelk, Sauerwein-Giese, & Frauendorf, 1994; Lehl & Woelk, 1993; Siepmann, Krause, Joraschky, Muck-Weymann, & Kirch, 2002; Timoshanko, Stough, Vitetta, & Nathan, 2001). Although not all clinical studies have been able to demonstrate an improvement in cognition, St. John's Wort was observed to not impair it, a known side-effect of synthetic anti-depressive medication.

## **6.5 Experimental research**

Comprehensive experimental research on the active constituents of traditionally used plant medicines gives insights into their chemistry, biological activity (pharmacology and toxicology), and synergistic properties (Medina, Martinez-Poveda, Amores-Sanchez, & Quesada, 2006; Nahrstedt & Butterweck, 2010; Saller et al., 1999; Saller, Melzer, & Reichling, 2003). A substantial amount of experimental research has investigated the composition of the active constituents in St. John's Wort which accumulate in the buds, blossoms, and flowerheads before or during the flowering period (Saller et al., 1999). Various models of experimental research have identified the following key constituents of St. John's Wort (Dell'Aica et al., 2007, pp. 110-112):

- naphthodianthrones (including hypericin and pseudohypericin)
- flavonoids (including biapigenin, quercetin, and rutin), phenolics (including hyperforin, adhyperforin, xanthones, bioflavonoids, and procyanidins)
- condensed tannins
- essential oils
- other constituents: various acids (including traces of amino acids), carotenoids, colin, nicotinamide, pectin, saturated linear hydrocarbon chains, and alcohols.

The structures of the representative constituents are presented below (World Health Organization, 2010, pp. 205-206):



**Figure 7. Key active constituents of *Hypericum perforatum***

The scientific literature relates these active constituents of St. John's Wort to the following therapeutic actions (Bone & Mills, 2013, pp. 827-838; Dell'Aica et al., 2007; Medina et al., 2006; Saller et al., 2003; Saller et al., 1995):

- |  |                          |
|--|--------------------------|
| antibacterial                            | cognitive-enhancing      |
| anticancer / antiangiogenic / antitumour | diuretic                 |
| antidepressant                           | immune modulating        |
| antifungal                               | neuroprotective          |
| anti-inflammatory                        | photodynamic             |
| antioxidant                              | spasmolytic              |
| antiretroviral / anti-viral              | styptic (tannins)        |
| anxiolytic                               | sedative / hypnotic      |
| bitter tonic                             | sexual function enhancer |
| capillary tightening                     | wound healing.           |

Not all constituents have yet been identified, and it has been suggested that numerous undetected active constituents and co-effectors contribute to the overall clinical efficacy of this medicinal plant (Nahrstedt & Butterweck, 2010, p. 1020). Isolated active constituents

exert lower or different effects than those observed with whole plant preparations, so the entire plant extract must be considered as actively contributing to St. John's Wort's therapeutic effects.

Experimental research points to possible mechanisms that may explain long-standing clinical uses of St. John's Wort. Experimental research into traditional extracts such as hot water infusions (tea) and hydro-ethanolic tinctures is particularly relevant for validating traditional indications of St. John's Wort. Such extracts represent the two key historical solvents (menstrua) while modern solvents may extract different constituents with modified effects. In line with St. John's Wort's consistent traditional usage in treating wounds, ulcers, and burns (see the skin-mucous use-category in Appendix 14), experimental research has shown an antimicrobial action of traditional water and water-ethanol extracts of St. John's Wort against gram-positive bacteria, with special activity towards methicillin-resistant strains of *Staphylococcus aureus* (Reichling et al., 2001). Experimental human research has additionally shown anti-inflammatory effects (Weseler, 2004, p. 304), with NF-kB and IL-12 being the specific targets (Calixto, Campos, Otuki, & Santos, 2004; Kang, Chung, & Kim, 2001).

When St. John's Wort extracts are to be applied internally, experimental lab bench studies on isolated cells and animal models can only be taken as providing preliminary data because human biological systems typically work differently and complexities concerning absorbability and pharmacokinetics need to be additionally considered (Agrosí, Mischiatti, Harrasser, & Savio, 2000; Teuscher, Melzig, & Lindequist, 2004; Williamson & Clifford, 2017). Appropriate test models are essential to avoid false positive or false negative results (Winterhoff, 2007, p. 3). The necessity of such cautions has also been demonstrated with *in vitro* investigations of herb-drug interactions, investigations which showed a poor *in vitro*-*in vivo* correlation (Unger, 2014, p. 17).

When experimental and clinical research is compared with historical empirical knowledge documented in the European medical literature, contemporary scientific and empirical evidence correspond as follows (shown in Table 23 below.):

**Table 23. Comparison of historical indications of *Hypericum perforatum* with clinical trials and experimental research.**

Use-categories	Tabernaemontanus 1664	Consistent empirical uses 18 <sup>th</sup> – 21 <sup>st</sup> century	Clinical evidence	Experimental research
<b>apotop</b>	talisman against ghosts and demons	0	0	anxiolytic
<b>card-vasc</b>	0	congestion and inflammation in the venous system, e.g. varicose veins (topical use)  <i>(sine 20<sup>th</sup> century)</i>	venous skin ulcer Raynaud's phenomenon improved platelet response ventricular function recovery	anti-inflammatory capillary tightening wound healing
<b>gastro-intest</b>	abdominal pain colic diarrhoea worms (horses)	inflammation and catarrh of the gastro-intestinal system gastro-enteritis dyspeptic complaints	colic IBS	antibacterial antifungal antiviral anti-inflammatory antioxidant capillary tightening spasmolytic styptic wound healing
<b>gyn</b>	birth complications menstruation: unease before and during menstruation menstruation puerperium (post-birth confinement)	menstrual complaints (variously breast complaints, PMT, dysmenorrhoea, menorrhagia, uterine spasms, endometriosis, and white discharge)  hormonally driven dysphoria in relation to the female menstrual cycle	pre-menstrual tension bacterial vaginosis	antibacterial antidepressant anti-inflammatory capillary tightening spasmolytic styptic wound healing
<b>head</b>	epilepsy stroke	headaches migraines	shielding or improving cognitive function	anti-inflammatory antioxidant cognitive-enhancing neuroprotective spasmolytic

Use-categories	Tabernaemontanus 1664	Consistent empirical uses 18 <sup>th</sup> – 21 <sup>st</sup> century	Clinical evidence	Experimental research
<b>infection (systemic)</b>	Malaria tertiana	intermittent: malaria, chronic infections, fever, and viral infections	0	antibacterial antifungal antioxidant antiviral anti-inflammatory immune modulating wound healing
<b>liver-spleen</b>	liver detoxification poison	intermittent: liver and gallbladder disorders	0	bitter tonic
<b>musc-skel</b>	hip pain / sciatica musculo-skeletal injuries (ligaments, tendons, fascia, nerves, and muscles) rheumatism stiff limbs and joints relaxing lame joints spasms in wounds	musculo-skeletal injuries resulting in sprains, strains, bruises and inflammation  rheumatic disorders	restless legs syndrome / Willis-Ekbom's disease	anti-inflammatory antioxidant immune modulating spasmolytic wound healing
<b>nerve</b>	hip pain / sciatica nerve injuries pain (abdomen, limbs, musculo-skeletal, rheumatism, womb, and wounds) trembling lame joints	pain from inflammation and injuries to the nerves and musculo-skeletal system  rheumatic disorders	pain / neuropathy Burning Mouth Syndrome restless legs syndrome / Willis-Ekbom's disease	anti-inflammatory antioxidant immune modulating neuroprotective sedative / hypnotic spasmolytic
<b>respiratory</b>	pleurisy spitting of blood	catarrh of the mucous membranes of the respiratory tract	0	antibacterial antifungal anti-inflammatory antioxidant antiviral capillary tightening immune modulating wound healing

Use-categories	Tabernaemontanus 1664	Consistent empirical uses 18 <sup>th</sup> – 21 <sup>st</sup> century	Clinical evidence	Experimental research
<b>skin-mucous</b>	bleeding in wounds burns ulcers wounds (deep, large, infected, inner, and outer)	burns (topical) wounds (systemic and topical)	burns dermatitis dry, damaged, or inflamed skin herpes infection psoriasis ulcer venous skin ulcer wounds	antibacterial anticancer antifungal anti-inflammatory antioxidant antiviral capillary tightening immune modulating wound healing
<b>somatoform</b>	demons (banish) melancholy  menstruation: unease before and during menstruation	psychovegetative disturbances such as depressive moods, anxiety, and nervous unrest  hormonally driven dysphoria in relation to the female menstrual cycle	ADHD addiction anxiety autism depression and related symptoms of anxiety, restlessness, insomnia, and exhaustion OCD SAD sleep social phobia somatoform disorders with autonomic dysfunction	antidepressant anti-inflammatory antioxidant anti-retroviral / antiviral anxiolytic cognitive enhancing immune modulating neuroprotective photodynamic sedative / hypnotic spasmolytic
<b>sex</b>	0	0	0	sexual function
<b>tonic</b>	0	tonification in exhaustion		antidepressant anti-inflammatory antioxidant anxiolytic cognitive enhancing immune modulating neuroprotective photodynamic

Use-categories	Tabernaemontanus 1664	Consistent empirical uses 18 <sup>th</sup> – 21 <sup>st</sup> century	Clinical evidence	Experimental research
uro	bladder stone and gravel, kidney detoxification poison urine voiding (diuretic agent)	intermittent: kidney stones, bladder spasms, enuresis, bed wetting, and bladder catarrh	0	anti-inflammatory anxiolytic diuretic spasmolytic wound healing

Parallel findings between traditional indications and results from experimental research and clinical trials are encouraging. They give further assurance that empirical science, when it is underpinned by repeated and clinically evaluated observational data, leads to valid and verifiable therapeutic indications.

## 6.6 Summary and conclusions

This chapter discussed the historical and therapeutic significance of *Hypericum perforatum* in Traditional European Medicine. The Historical Assessment Tool was applied to the medical literature to demonstrate a scientific method that systematically collates traditional-use-evidence on traditional plant medicines. The triangulation of empirical knowledge as recorded in European medical textbooks that were authored by formally trained physicians and transmitted over the past 400 years established the following:

- There are several consistently transmitted indications in the medical literature that have persisted for over 400 years. They belong to five use-categories: gastro-intest, musc-skel, nerve, skin-mucous, somatoform.
- There are further indications in the medical literature which fulfil the criteria of at least three transmission steps (75 years of consistent medical use). They belong to two use-categories: card-vasc, tonic.
- Further comparison of empirical evidence from the medical literature with approved health claims in European regulatory monographs showed the following:
  - the *Commission E Monograph Hyperici herba* approves indications belonging to all of the five use-categories that had empirical evidence on indications consistently transmitted over 400 years (gastro-intest, musc-skel, nerve, skin-mucous, somatoform)

- the *EU Herbal Monograph Hypericum perforatum L. herba* provides approved claims belonging to three of these use-categories (gastro-intest, skin-mucous, somatoform)
- indications relating to the gastro-intest, skin-mucous, and somatoform use-categories are listed across all three sources
- intermittent-but-persistent traditional indications listed over 400 years, nor those that were newly listed over the past 150 years, were approved in either of the regulatory monographs, except for the indication ‘temporary mental exhaustion’ which is approved in the EU monograph.

Table 24 summarises these findings:

**Table 24. Comparison of historical indications of *Hypericum perforatum* with European regulatory monographs.**

Use-categories	Tabernaemontanus 1664	Consistent empirical uses 18 <sup>th</sup> – 21 <sup>st</sup> century	Commission E Monograph 1984	EU Herbal Monograph 2014 traditional use
<b>apotop</b>	talisman against ghosts and demons	0	0	0
<b>card-vasc</b>	0	congestion and inflammation in the venous system, e.g. varicose veins (topical use) (since 20 <sup>th</sup> century)	0	0
<b>gastro-intest</b>	abdominal pain colic diarrhoea worms (horses)	inflammation and catarrh of the gastro-intestinal system gastro-enteritis dyspeptic complaints	dyspeptic complaints	mild gastrointestinal discomfort
<b>gyn</b>	birth complications menstruation: unease before and during menstruation menstruation puerperium (post-birth confinement)	menstrual complaints (variously breast complaints, PMT, dysmenorrhoea, menorrhagia, uterine spasms, endometriosis, and white discharge)  hormonally driven dysphoria in relation to the female menstrual cycle	0	0
<b>head</b>	epilepsy stroke	headaches migraines	0	0

Use-categories	Tabernaemontanus 1664	Consistent empirical uses 18 <sup>th</sup> – 21 <sup>st</sup> century	Commission E Monograph 1984	EU Herbal Monograph 2014 traditional use
<b>infection (systemic)</b>	Malaria tertiana	intermittent: malaria, chronic infections, fever, and viral infections	0	0
<b>liver-spleen</b>	liver detoxification poison	intermittent: liver and gallbladder disorders	0	0
<b>musc-skel</b>	hip pain / sciatica musculo-skeletal injuries (ligaments, tendons, fascia, nerves, and muscles) rheumatism stiff limbs and joints relaxing lame joints spasms in wounds	musculo-skeletal injuries resulting in sprains, strains, bruises and inflammation  rheumatic disorders	acute and contused injuries, myalgia (topical)	0
<b>nerve</b>	hip pain / sciatica nerve injuries pain (abdomen, limbs, musculo-skeletal, rheumatism, womb, and wounds) trembling lame joints	pain from inflammation and injuries to the nerves and musculo-skeletal system  rheumatic disorders	acute and contused injuries, myalgia (topical)	0
<b>respiratory</b>	pleurisy spitting of blood	catarrh of the mucous membranes of the respiratory tract	0	0
<b>skin-mucous</b>	bleeding in wounds burns ulcers wounds (deep, large, infected, inner, and outer)	burns (topical) wounds (systemic and topical)	first-degree burns (topical)	minor inflammation of skin (such as in sunburn) and minor wounds
<b>somatoform</b>	demons (banish) menstruation: unease before and during menstruation melancholy	psychovegetative disturbances such as depressive moods, anxiety, and nervous unrest  hormonally driven dysphoria in relation to the female menstrual cycle	psychovegetative disturbances, depressive moods, anxiety and/or nervous unrest	temporary mental exhaustion
<b>tonic</b>	0	tonification in exhaustion	0	temporary mental exhaustion (also listed under somatoform category)

Use-categories	Tabernaemontanus 1664	Consistent empirical uses 18 <sup>th</sup> – 21 <sup>st</sup> century	Commission E Monograph 1984	EU Herbal Monograph 2014 traditional use
uro	bladder stone and gravel, kidney detoxification poison urine voiding (diuretic agent)	intermittent: kidney stones, bladder spasms, enuresis, bed wetting, and bladder catarrh	0	0

Analysis relating to St. John's Wort mirrors the results of the analysis relating to Arnica. The regulatory monographs authored by the Commission E and EMA (HMPC) independently validate and officially approve the main traditional uses of St. John's Wort as recorded in authoritative medical textbooks. However, neither monograph reflects all consistently transmitted traditional uses and the broader clinical scope of this medicinal plant. Of the two monographs, the *Commission E Monograph Hyperici herba* approves more traditional uses compared to the *EU Herbal Monograph Hypericum perforatum L. herba*. Both regulatory monographs will provide important bibliographic evidence for the approval process for NHPs in New Zealand if the proposed list of pre-approved texts by the former Natural Health and Supplementary Products Bill is accepted. Yet they are unable to replace the broader empirical evidence of traditional uses that were consistently transmitted in authoritative medical textbooks. Multiple pharmacological actions (pleiotropic properties) may explain St. John's Wort's wide-ranging historical uses.

Alongside the analysis of indications listed in medical textbooks, this chapter undertook a systematic appraisal of clinical and experimental research. This scientific evaluation demonstrated the general rationality and validity of empirical therapeutic uses of St. John's Wort (Dell'Aica et al., 2007; Reichling et al., 2001). Triangulation of data derived from both qualitative and quantitative sources thus suggests that consistently endorsed traditional indications are not random but instead based on empirically observed pharmacological effects (see Table 23).

A surprising discovery arising from this systematic analysis relating to St. John's Wort is the significant gap that can exist between the official assessment of the therapeutic importance of a medicinal plant by a regulator and its assessment by practising clinicians authoring clinically-oriented textbooks. Despite its ongoing clinical significance, St. John's Wort became de-listed as an essential drug in the 6<sup>th</sup> edition of the Prussian Pharmacopoeia

(Gurlt, 1847). It was never selected for the German pharmacopoeia and only became a pharmacopoeia listed medicine in Germany when *DAB* harmonised with the European pharmacopoeia in 1986 (DAB 9, 1986), two years after the publication of the *Commission E Monograph Hyperici herba* (Kommission E, 1984a). In contrast, St. John's Wort's medicinal uses have been documented since classical Hippocratic times and so became deeply embedded in both formal and folk medicine. In the analysed medical literature St. John's Wort was consistently used by physicians in patient care (see Table 15). In response to the publication of the 1<sup>st</sup> edition of the German pharmacopoeia, the German *Apotheker-Verein* (Association of Apothecaries) released in 1889 a non-official but normative supplementary text for those medicinal plants that were de-listed from the German pharmacopoeia (Deutscher Apotheker-Verein, 1897, p. III). This supplementary text included a monograph for St. John's Wort, thereby confirming that while it was no longer deemed an essential medicine by the German regulator, it was still deemed essential in clinical practice. Today, St. John's Wort is one of the most researched medicinal plants in the world (Saller et al., 2003) and is said to be the most important and most frequently used traditional medicine in alpine regions of Central Europe (Committee on Herbal Medicinal Products (HMPC), 2009a, p. 75). Its efficacy has been established by almost 150 clinical trials (see Appendix 15).

Different regulatory frameworks are shown to have impact on permitted health claims and safety requirements. The *Commission E Monograph Hyperici herba* echoes clinical considerations as deemed central to clinical practice during the 1980s and 1990s (American Botanical Council, n.d.). The approved indications reflect more comprehensively the body of therapeutic indications as validated by 400 years of consistent medical use in a professional setting. This monograph did not restrict therapeutic uses for children, pregnant or lactating women. In comparison, the *EU Herbal Monograph Hypericum perforatum L., herba* reflects the more recent regulatory situation in Europe. Alongside clinical assessments it was additionally influenced by a scientific and political consensus process involving delegates of all EU 28 Member States, resulting in the approval of a reduced body of traditional indications. Under the simplified registration pathway it did not pre-approve St. John's Wort in any form, even as medicinal tea, for a large segment of the population (children under 18 years of age; pregnant and lactating women). Mainly this was due to a lack of availability of genotoxicity studies (Committee on Herbal Medicinal Products (HMPC), 2009a). Notwithstanding a desired harmonisation under one regulatory

framework, there remain differences in how the regulatory EU stipulations are implemented. In some Member States where traditional medicines are historically used for the paediatric population, some traditional products were able to register for paediatric use under EU Directive 2004/24/EC (Austria and Germany). In countries where traditional medicines are less prevalent for the paediatric population they were not, such as in Scandinavian countries (Knöss & Chinou, 2012, p. 1315). This indicates that divergent views remain on the level of evidence that national authorities deem appropriate for substantiating the safety and effectiveness of their traditional medicines.

Such uncertainties do not exist only geographically across the EU Member States but also across various EU laws. If a traditionally-used substance is regulated under drug law (EU Directive 2004/24/EC), proof of safety must be provided (i.e. genotoxicity studies). If the same traditionally-used substance is regulated as a dietary supplement under food law, no pre-market approval is necessary (Quintus & Schweim, 2012, p. 380). For pre-existing natural substances, absence of documented harm is taken as an adequate demonstration of probable safety. Consequently St. John's Wort preparations in the form of dietary supplements continue to be readily accessible to all population segments without restriction, whereas they may be unavailable as a traditional medicine regulated under drug law unless preclinical research has been undertaken.

Divergent views on the safety requirements for medicinal plants remain one of the biggest hurdles for traditional medicine to overcome in order to integrate into mainstream healthcare. Historical clinical safety assessments differ from safety assessments derived under a scientific framework where a higher level of proof is requested. This situation may in part stem from historical developments in European medicine. Before the advancement of biomedicine, plant-based medicines were the key therapeutics in clinical practice across all demographics and age groups, notwithstanding specific cautions noted in clinically oriented textbooks, such as against the use of certain medicinal plants in pregnancy or against strongly acting substances in children. Regarding paediatric use, not all historical medical textbooks provided a specific paediatric posology, but an agreed dosage range for children was commonly accessible to clinicians (Kahnt, 1900, pp. 67, 138). Medicinal teas, for example, are considered a particularly benign preparation for paediatric care and are endorsed by representatives of phytomedicine organisations in Europe (Reuter, 1994). Phytotherapeutic textbooks by clinicians also note the tolerance of St. John's Wort in common childhood issues such as bed wetting, ear infections, nappy rash, sunburn, and

more recently in mood disorders such as anxiety and depression (McIntyre, 2005, pp. 265, 227, 213, 138, 276; Mills & Bone, 2005, p. 590; Santich & Bone, 2008, p. 16). A lack of pharmacovigilance data on harm seems to support St. John's Wort's tolerance in paediatric care. In countries where St. John's Wort is readily taken by all population segments, its use has not raised serious safety concerns. In New Zealand, for example, where the OTC sale of St. John's Wort is not restricted for the paediatric population or for pregnant and breastfeeding women, its therapeutic use has not come to the attention of the New Zealand pharmacovigilance centre. In the latest report published in 2016, CARM received a total of 3,944 reports of suspected adverse reactions to medicines. 2,522 were associated with synthetic drugs, 1385 were associated with vaccines, and 37 (or 1.5%) were associated with CAM. Twelve CAM reports (0.003%) were considered serious (Medsafe, 2017). The Suspected Medicine Adverse Reaction Search function on the Medsafe website does not disclose which CAM substances were involved in the ARD reports, nor if causality was established. However, a search under the term 'Hypericum' established that none of the case reports related to St. John's Wort preparations.

Outside New Zealand, St. John's Wort is noted as a medicinal plant used in pregnancy (Smeriglio et al., 2014). Its historical names, *Frauenkraut* (woman's herb) and *Maria Bettstroh* (Maria's bedstraw) point to its historical importance in women's healthcare. St. John's Wort was prescribed during birth and the *puerperium*, as noted in Tabernaemontanus (see Appendix 13, p.11-12). It continued to be relevant as a *peri-* and *post-partum* treatment in midwifery during the 20<sup>th</sup> century (Clair & Saller, 2015; Käppeli, 2001; Stadelmann, 2005). Clinical and experimental data on St. John's Wort did not suggest increased frequency of malformation or of other harmful effects on the foetus when used during pregnancy (Kolding et al., 2015; Mills & Bone, 2005, pp. 585-593; Moretti et al., 2009). These findings suggest that a combination of historical safety observations and pharmacovigilance data could provide a way forward for regulatory safety assessments on pre-existing traditional therapies.

Regarding the safety of St. John's Wort in children and adolescents, observational data from long-term clinical uses have not raised concerns with traditional preparations. There is a small body of scientific evidence that suggests that *Hypericum perforatum* preparations are well tolerated in children under 12 years of age (Hübner & Kirste, 2001) and in adolescents from 12-17 years of age (Simeon et al., 2005). In contrast, a systematic re-evaluation of synthetic anti-depressants in children found that data from unpublished trials changed the

benefit-risk balance from favourable to unfavourable for several pharmaceutical drugs, mainly due to an increased risk of suicide (Whittington et al., 2004). Warning against the use of synthetic anti-depressants in treating depression in children may leave a treatment gap unless safer alternatives are approved and integrated into clinical care. This thesis argues that St. John's Wort could play a role in filling treatment gaps due to its apparent safety and established efficacy.

In conclusion, the comprehensive data analysis relating to St. John's Wort has confirmed that bibliographic evidence from judiciously selected textbooks on the botanical *materia medica*, where pharmacological evaluations are consistently transmitted by clinical experts, generally provides reliable data on therapeutic uses. Triangulation of qualitative historical data with modern regulatory monographs has highlighted the congruency between the key historical indications of St. John's Wort with modern approvals. A further triangulation of historical data with quantitative data has demonstrated efficacy of several traditional indications when they were investigated with clinical trials. The results of this thesis therefore support a conclusion that authoritative textbooks provide reliable and verifiable empirical evidence suitable for the regulatory registration of traditional medicines as part of an evidence-based healthcare system. The development of an appropriate regulatory framework for safety requirements remains a great challenge for the integration of traditional medicines.

## **7 EU REGULATIONS ON TRADITIONAL HERBAL MEDICINAL PRODUCTS (THMPS)**

One aspect that this thesis sought to document is how international regulators approached the challenges of regulating traditional medicines in the era of contemporary evidence-based health policy. The most comprehensive attempt in the West to harmonise policy around the regulation of traditional medicines has occurred in Europe within the integrative processes of the European Union (EU). Harmonising policy across the EU has presented multiple challenges. Many of the 28 Member States had different approaches to the regulation of their traditional medicines. Other countries may therefore benefit from examining how the EU has dealt with the dilemma of integrating traditional medicines from various regions into a contemporary evidence-based health system.

The Directive 2001/83/EC of the European legislative framework and its amendment Directive 2004/24/EC has three objectives (Knöss, 2014a, p. 30; Knöss & Chinou, 2012; Peschel, 2014):

- 1) To ensure a future for traditional plant medicines where European citizens can access medicines of their choice, even if traditional uses of plant medicines have not yet been substantiated by clinical efficacy data according to modern requirements. The Directive mandates that the characteristics of plant medicines are considered when assessing their quality, effectiveness, and safety.
- 2) To protect public health by providing a legislative framework for safe and high-quality medicinal products containing herbal active ingredients.
- 3) To harmonise legislation across the 28 EU Member States to enable the free movement of medicinal herbal products within Europe.

This chapter will summarise key features of the legislative framework of the EU before discussing considerations for the development of a health policy framework on traditional medicines in New Zealand.

### **7.1 Access to medicines of choice**

In the context of the European legislative framework, Directive 2004/24/EC was the result of significant effort to protect pluralism in medicine. By creating a new status for traditional

herbal medicines based on plausible levels of effectiveness, the ‘traditional use’ category, this legislation legally supports and protects treatment choices for consumers. Traditional Herbal Medicinal Products (THMPs) are regulated *as medicines rather than as dietary food supplements*, falling under the scope of pharmaceutical good manufacturing practice and pharmacovigilance legislation (Claeson, 2014, p. 465). Thus, they have a higher status than plant-based therapeutics in many other countries, including New Zealand. The separation of traditional plant medicines from dietary supplements is significant. It recognises that they transcend nutritional purpose by having a pharmacologic effect to prevent and treat illnesses. As such they are distinct from nutrients—whether foods, natural or synthetic dietary supplements—and pharmaceutical drugs. This separate regulatory framework enables the acknowledgment of *both their specific pharmacological effects and their long-standing role in traditional medicine of European countries*. This EU approach to traditional medicines is noteworthy for other countries dealing with their regulations of traditional medicines.

One of the key conditions for gaining simplified registration in the EU Member States is that a THMP has been used medicinally for at least 30 years, 15 of which must have been within the EU. As such the traditional use category requires bibliographic evidence of traditional use, but no clinical trials. Health claims are accepted on the basis of plausible effectiveness and sufficient safety data (European Parliament, 2004). EU herbal monographs provide information necessary for the registration of a traditional product for sale, namely approved indications, suitability of use, and safety information such as information regarding undesirable effects and interactions with other medicines. Analyses of the *EU Herbal Monograph Arnica flos* (Committee on Herbal Medicinal Products (HMPC), 2014b) and *EU Herbal Monograph Hypericum perforatum L., herba* (traditional use) (Committee on Herbal Medicinal Products (HMPC), 2009b) confirmed that the main therapeutic indications consistently recorded in the assessed medical literature are also approved by the monographs authored by HMPC (see Appendix 10 and Table 7). This ensures continued access to these traditional medicines.

### **7.1.1 Impact of definition of tradition on access to THMPs**

Notwithstanding consumer access to THMPs, issues have emerged since the enactment of the Directive 2004/24/EC that appear to hamper the full potential of this legislative framework. Assessment Reports on the two analysed monographs show that traditional

indications were mainly based on recent bibliographic materials even when reference to some historical applications was provided (Committee on Herbal Medicinal Products (HMPC), 2009a, 2014a). Consequently, the EU monographs did not make full use of the availability of consistent empirical evidence as coded in historical sources. This may have been one of the reasons why there are relatively few approved traditional claims in the evaluated EU monographs. Legally, ‘proof of tradition’ in the context of Directive 2004/24/EC does not necessarily mean long-standing traditional use of medicinal plants. It means that a THMP must have been medicinally used for at least 30 years. Under this legal approach, medicinal plants, indications, or preparations that may have been discontinued for a short while, for example due to conservation issues or questions over a plant’s mechanism of therapeutic actions, do not qualify for the simplified ‘traditional use’ registration pathway. This is even when they were consistently used in TEM over long periods of time, sometimes for centuries. As Peschel (2014, p. 482) explains (*italics by the author*), “it is not sufficient to document that a *plant has been used for several 100 years in a certain tradition*. It is still insufficient showing that a *specific preparation from a specific plant part has been used in certain indications*, but it is required to demonstrate that a *specific preparation from a specific plant in a specific strength and dosage had been used for more than 30 years in a specific indication*. This stipulation is often the reason why HMPC was unable to include a certain indication or extract into a monograph. Therefore, this regulatory framework does not reference tradition in the anthropological sense of three generations or 75 years, as applied by the World Health Organization (2013), or in the sociological sense of at least two transmission steps (Shils, 1981) as applied by the Canadian regulatory framework (Hirschhorn, 2005, p. 28).

The 30 year stipulation means that there is no requirement to incorporate systematically the long-standing historical evidence of traditional medicines into the drafting of the EU monographs. One possible explanation for this might be that current health policies largely draw on the EBM model. This model does not generally consider long-standing historical evidence as significant or valid for an overall benefit-risk analysis (Helmstädter & Staiger, 2014; Rawlins, 2008), although the EU Directive 2004/24/EC moderates this position by acknowledging 30 years of traditional evidence. The Assessment Reports for both *Arnica montana* and *Hypericum perforatum* exemplify the consequences of this approach. In both instances, a systematic historical analysis of their traditional uses as suggested with the Historical Assessment Tool could not be located (Committee on Herbal Medicinal Products

(HMPC), 2009a, 2014a). As a result, several indications for Arnica (see Table 11) and for St. John's Wort (see Tables 18 and 19) that may have met the criterion of consistent medicinal use are not listed in the final EU monographs.

By framing regulations of THMPs from an EBM viewpoint, this approach may underestimate the need for traditional evidence to be systematically evaluated as part of the scientific enquiry. Such a thorough enquiry would fulfil a key recommendation advocated by the *WHO Traditional Medicine Strategy 2014-2023*, a strategy that seeks to “identify sources of evidence, whether historical, traditional or scientific, which support or invalidate a particular therapy (World Health Organization, 2013, p. 47). Early proponents of EBM also made clear that “evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients” (Sackett et al., 1996, p. 71). Extending the meaning of tradition beyond 30 years might help to expand the scope of traditional medicines, although the ultimate decision on accepting an indication lies with the assessment of the THMPC.

### **7.1.2 Impact of stipulations for traditional multi-component formulations**

The regulatory concept behind EU Directive 2004/24/EC facilitates a pre-approval of THMPs mainly for those that contain one active ingredient. This is because EU monographs are monographs on individual medicinal plants and can only be referenced under this Directive by products containing the same or a comparable active substance as described in the monograph. Guideline EMEA/HMPC/104613/2005 stipulates that evidence about traditional use for each of the single active substances in a combination will *not* be sufficient to establish the traditional use of a multi-component formulation. Evidence for a multi-component combination is required in its entirety from a comparable combination product rather than just the parts of that product (Peschel, 2014, p. 484). In practice, most remedies from traditional systems of medicine are multi-component formulations rather than single-plant formulations. The simplified registration pathway presents difficulty for such multi-component remedies unless a historic formulation has been fixed for 30 years, which is not common. Multi-component formulations are in principle possible with the provision of additional scientific evidence. This does, however, appear to be challenging for traditional remedies, as most products registered to date under the ‘traditional use’ criteria are mono-component products (Peschel, 2014, p. 479). In addition, by April 2018, only two binding List Entries related to a multi-component formulation (Knöss & Wiesner, 2017, p.

13). This contrasts with 72 approved multi-component formulations listed under the preceding German Commission E monographs<sup>6</sup>.

### **7.1.3 Restrictions for THMPs from non-EU traditions**

Under the current EU legislation, the requirement to demonstrate a minimum of 15 years of medicinal use in the EU has shown to be an obstacle to the registration of non-EU European traditional herbal products for example from Switzerland, and those from traditions outside of Europe, such as traditional products from Ayurvedic, Chinese, Kambo Korean, Mongolian, Thai, Tibetan, Unani, or Vietnamese medicine. This includes products that had been approved in European countries previously (Qu et al., 2014; Schwabl & Vennos, 2015). A Commission Report states that the Commission does not envisage extending the scope of the simplified registration procedure to traditional medicines from outside the EU, specifically because such medicines are based on a holistic approach to healthcare (Commission of the European Communities, 2008, p. 10). The Commission concludes that for such products a separate legal framework should be assessed. Paradoxically, the traditional use of European plant medicines is also underpinned by a holistic approach to healthcare incommensurable with the pharmaceutical model of ‘one drug, one indication’. Thus, an updated legislative framework may be helpful, not only for regulations of traditional medicines from *outside* the EU, but also for traditional medicines from *inside* the EU, in order to overcome “the difficulties encountered by Member States in applying the pharmaceutical legislation to herbal medicinal products” (Commission of the European Communities, 2008, p. 10).

## **7.2 Protection of the public**

A key feature of regulations in Western healthcare systems is their intent to safeguard public health by ensuring that therapeutic interventions are high in quality, safe, and effective (Kelber et al., 2014, p. 448). Directive 2004/24/EC seeks to achieve this by integrating traditional medicines into pre-existing pharmaceutical legislation that governs the quality, safety and efficacy of pharmaceutical drugs. In addition, under EU Directive 2004/24/EC traditional herbal medicinal products may be accepted under the traditional use criteria only if sufficient data proof demonstrates that such products are not harmful (Knöss,

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<sup>6</sup> For a freely accessible English translation of all German Commission E monographs visit: <https://buecher.heilpflanzen-welt.de/BGA-Commission-E-Monographs/>

2018, p. 371). There are discussions by the Commission of the European Communities on the meaning of “proof” and what form the demonstration of “not harmful” should take (Commission of the European Communities, 2008, pp. 4-5). The EU Directive 2004/24/EC, 16c (c) accepts the safety of a medicinal preparation as plausible if no risk has been demonstrated for a substance used commercially for 10 years (well-established use) or 30 years (traditional use) (European Parliament, 2004, p. 87). The Directive explains:

The long tradition of the medicinal product makes it possible to reduce the need for clinical trials, in so far as the efficacy of the medicinal product is plausible on the basis of long-standing use and experience. Pre-clinical tests do not seem necessary, where the medicinal product on the basis of the information on its traditional use proves not to be harmful in specified conditions of use. However, even a long tradition does not exclude the possibility that there may be concerns with regard to the product's safety, and therefore the competent authorities should be entitled to ask for all data necessary for assessing the safety. (European Parliament, 2004, p. 85, point 5)

In theory, this framework could permit assessments based on the documented absence of harm for a proposed preparation and posology rather than proof of its safety through toxicological tests. The HMPC's subsequently published guideline EMEA/HMPC/32116/2005 acknowledges that bibliographic safety clearance could be granted after a systematic and comprehensive scientific literature search of post-marketing safety studies and an assessment of epidemiological data of adequate power (Committee on Herbal Medicinal Products (HMPC), 2006, p. 5). However, in practice, all THMPs were seen to require assessment of their genotoxic potential as a test of proof of no harm (Wiesner, 2014, p. 468). Thus, pre-approval of THMPs is currently granted based on demonstrated long-term safe traditional use *together* with negative results from genotoxicity, reproductive, and developmental toxicity tests. The implementation of this approach was seen in the Assessment Report *Hypericum perforatum* L., *herba* (Committee on Herbal Medicinal Products (HMPC), 2009a, p. 31) that was unable to pre-approve St. John's Wort for pregnancy and lactation due to the absence of specific toxicity data.

The absence of modern toxicology tests for most medicinal plants, the significant financial outlay required to generate the required scientific data, and the reluctance of phytotherapy companies to make use of the new Directive together resulted in the elimination of long-

standing traditional medicines that were previously considered safe and available in the market place (Abdel-Tawab, 2018, pp. 373, 384; Gallagher, 2013, p. 19). The absence of modern toxicology data is also the reason given why there are few legally binding EU List Entries (12 entries by April 2018) and why most EU herbal monographs do not support the traditional use of medicinal plants for pregnant or lactating women, or for young children and adolescents despite an absence of adverse drug reactions from clinical use (Knöss, 2018, p. 386; Knöss & Wiesner, 2017, p. 13). The requirement to provide toxicology testing before granting marketing authorisation for children (Wiesner, 2014) resulted in the pre-approval of only 14 medicinal plants for internal use and six for topical use for this demographic. Just one plant, Oats, has no age restrictions (Committee on Herbal Medicinal Products (HMPC), 2018).

If a traditional medicinal product is not registered as a THMP, this same product may still be available in the market place as a food supplement (*Nahrungsergänzungsmittel*, NEM), as a medical device, or as a cosmetic. European food law is less strict than European drug law and does not request toxicity data for pre-existing and commonly used food substances (Quintus & Schweim, 2012, p. 380). However, few health claims can be made for nutritional products, requiring them to be aimed at a ‘physiological effect’ rather than a ‘pharmacological effect’ (Steinhoff, 2013, p. 239). In practice, consumers commonly use herbal products for their traditionally stated pharmacological effects regardless of their classification by the regulator. This unsatisfactory situation was addressed in a Commission Report by the European Parliament:

The introduction of the simplified registration procedure was based on the assumption that safety and efficacy could be adequately substantiated by long-standing use *without* requiring additional testing and systematic documentation on all point of Annex 1 of Directive 2001/83/EC regarding safety.... In its guideline on non-clinical documentation for herbal medicinal products in applications for a marketing authorisation (bibliographic and mixed applications) and in applications for simplified registrations, the HMPC is of the view that the genotoxicity potential of herbal preparations should *always* be assessed.... In order to ensure the successful application of the Directive, the issues relating to genotoxicity demand careful scientific and legal consideration. As stated in the HMPC report, the systematic request for genotoxicity data had made the proposal of list entries difficult since

these data are generally not available. It has probably also contributed to the small number of applications reviewed so far. Consequently, a request for genotoxicity data to assess traditional herbal products should be made on a case-by case basis when there is a *specific* concern for safety, as required by the relevant provisions in the legislation. This ensures the protection of public health while allowing the registration of traditional herbal medicinal products. A more restrictive approach would create the risk that the products concerned will end up being marketed under another classification (and not as medicinal products) without the necessary quality, safety and efficacy controls applicable under pharmaceutical legislation.

(Commission of the European Communities, 2008, pp. 4,5)

Despite the concerns raised in the Commission Report, few adjustments have been made to date to the interpretation of the legislation, and the legislation itself has not yet been amended. The permission of a simplified “bracketing and matrixing” concept for the assessment of genotoxicity (Kelber et al., 2012, p. 1124) seems to have had only a minimal impact on the number of applications for THMPs or the authorisation of new List Entries.

### **7.2.1 Approved levels of claims**

Restrictions on claims permitted for TMHPs are a way of safeguarding public health. The Directive 2004/24/EC restricts indications eligible for a simplified registration of a THMP to minor, self-limiting health complaints that can be treated without supervision (Gallagher, 2013). To increase public safety further, this Directive selectively covers only traditional plants with undisputed innocuousness. In addition to this focused selection of medicinal plants eligible for a simplified registration process, monographs, as already noted, usually restrict usages in women during pregnancy and lactation, as well as in children and adolescents. Most monographs further limit the duration of usage to a defined short period, typically two weeks. This stipulation is to minimise the potential health risk for consumers who may otherwise delay seeing a physician when seriously ill by attempting to self-medicate (Claeson, 2014, p. 465). Treating the symptoms of non-serious diseases which could also be symptoms of serious diseases, for example benign prostatic hyperplasia, may be acceptable with the disclaimer that a physician must exclude serious conditions before such treatment begins (Committee on Herbal Medicinal Products (HMPC), 2011).

While many of these precautions are sensible for safeguarding public health, the high

requirements set for a qualification under the simplified registration scheme compared to the limited scope of permitted health claims for THMPs may have been a contributing factor to the limited uptake of this regulatory pathway. Health surveys confirm that traditional plant medicines are an attractive option for patients and treatment providers in the management of chronic illnesses to improve health-related quality of life and reduce reliance on synthetic medications associated with risks of harmful adverse events (Cameron et al., 2009; Euromonitor, 2011; Institut für Demoskopie Allensbach, 2010). Phytotherapy is also a preferential choice for adults with multiple diseases and somatoform disorders, as well as for children (Kopp, 2015, p. 215; Saller et al., 2014, p. 26). Studies from Western countries suggest that pregnant women often resort to using traditional plant medicines that are familiar to them and they consider to be safe (Holst, Wright, Haavik, & Nordeng, 2009; Holst, Wright, Nordeng, & Haavik, 2009). The frequent use of traditional therapeutics in these consumer groups supports the idea that they have an urgent need for access to high-quality, safe products. If THMPs are not officially available for these demographics, they might purchase the same remedies as food supplements instead, which are regulated under lower quality requirements. Regulators therefore have the difficult task of balancing public safety as well as ensuring that medicines of choice are available.

The two-week maximum treatment period commonly mandated as a disclaimer on THMP labels appears to be a short timeframe for the management of many health complaints, particularly chronic ones, or for the use of THMPs in prophylaxis. It could be advantageous if mandatory labelling advice did not discourage consumers from self-care practices or from the management of symptoms of chronic, non-life-threatening conditions with traditional remedies. Patients may choose to include both herbal and pharmaceutical OTC medicines to deal with their needs. Clear indications on labels, including the establishment of disease-relationship, would support patients in their choice.

### **7.3 Harmonisation**

To facilitate the simplified registration of traditional plant medicines in all EU Member States, the HMPC at EMA was mandated to publish herbal monographs. By April 2018, HMPC published 154 monographs of which 13 were for well-established use (Knöss & Wiesner, 2017, p. 13). These monographs provide an important pathway for enabling the free movement of medicinal herbal products within Europe. The establishment of such monographs is a significant investment by the EU to support harmonised access to THMPs

across all 28 EU Member States. The shortness of many monographs may reflect the scientific and political process as laid down in the 2004 EU Directive, which mandates that permitted indications, modes of application, proof of effectiveness, and safety (innocuousness) should be reached by consensus. If consensus cannot be reached, the monographs must be agreed upon by the absolute majority of the members of the HMPC Committee (Committee on Herbal Medicinal Products (HMPC), 2013, p. 6). In the voting procedure, it appears that consensus was rarely reached, highlighting the divergence of views on clinical and scientific assessments, as well as the influence of pre-existing regulatory regimes, legal statuses, and practical uses of THMPs in the various Member States (Claeson, 2014, p. 466; Silano, De Vincenzi, De Vincenzi, & Silano, 2004).

List Entries published by the European Commission provide, in principle, another legal avenue for a harmonised registration of traditional products across the EU. In contrast to the monographs authored by HMPC, List Entries *are* legally binding across all Member States and products that adhere to their guidelines *must* be registered. By April 2018, only 12 List Entries had been published to support the registration process. This low number has been linked to the absence of genotoxicity data for many medicinal plants used in traditional medicines (Knöss, 2018, p. 374).

There are national differences on the status of traditional plant medicines across the EU Member States; regulations, classifications, definitions, and the use of traditional plant medicines have evolved at national levels. The implementation of Directive 2004/24/EC has shown that it is challenging to assimilate them under one EU-wide regulatory framework. To add to this challenge, the policy framework employed was initially set up for regulating a distinctly different class of medicines, that of pharmaceutical drugs (Commission of the European Communities, 2008). The implementation of the Directive has shown that on the one hand it legally protects the availability of traditional medicine but on the other hand it has been associated with an overall decrease in traditional products (Knöss, 2014b, p. 448). The analysis by Kazemekaitis (2010, pp. 14-15) showed that when an EU Member State had customary products with different indications and/or applications from those of the majority of the other EU Member States, those products tended to disappear from the market because they could not comply with the particulars of the new Directive. This suggests that harmonisation of local traditions across various regions of Europe requires further work for the unimpeded availability of these regional traditional plant medicines.

## 7.4 Concluding observations on EU regulations

In summary, the EU Directive 2004/24/EC is a legal commitment to pluralism in medicine that secured the future of traditional European therapeutics as regular medicines. Overall, the Directive succeeded in its objective of providing legal access to medicinal products originating from plants, protecting the public by implementing a legislative framework for safe and high-quality THMPs, and creating a framework that facilitates the harmonisation of free movement of medicinal herbal products within Europe. For the first time in the EU, a Member State can license a THMP based on pre-approved health claims and implement a harmonised, simplified registration process for traditional medicines. Moreover, List Entries by the European Commission provide an additional legal pathway for licensing THMPs. Unlike the EU monographs which rely on voluntary implementation, List Entries are legally binding for all Member States. The EU legislator has therefore legally advanced the status of medicinal products originating from plants.

However, analysis of the EU health policy on traditional medicines has revealed several key impediments that became apparent during implementation. A relatively low uptake of the simplified registration pathway for THMPs by manufacturers occurred possibly because of low levels of permitted health claims, high and costly requirements for toxicology testing, and a narrow definition of the meaning of the term ‘tradition’. Consequently, for European citizens the potential of traditional medicines in primary healthcare and self-care remains untapped. A specific issue that has emerged is that EU monographs list relatively few traditional uses that can be referenced for health claims. While these monographs are regularly reviewed and updated in consultation with all 28 Member States, those currently approved omit a number of long-standing traditional uses and preparations which are customary in several Member States (Kazemekaitis, 2010). When the Historical Assessment Tool was applied as a systematic research tool to locate consistently transmitted indications of Arnica and St. John’s Wort, several long-standing indications emerged that could have been considered in the EU monographs. These additional indications are listed in Appendix 10 and Tables 18-20.

The variance between the results of the Historical Assessment Tool and the indications listed in the EU monographs may be explained by the narrow legal-political regulatory framework under which the authoring of EU monographs had to operate. For each monograph the HMPC needed to find a political and scientific compromise and majority

consensus across 28 Member States, each with their different traditions, independently operating national competent authorities, and divergent stances on the legitimacy of plant medicines as a treatment option. In contrast, the tool applied in this thesis was unimpeded by such political and legal restraints and could solely focus on the triangulation and systematic collation of traditional indications consistently recorded across various data sources, datapoints and research methods. The Historical Assessment Tool may therefore provide a factual instrument to tabulate proof of long-standing traditional indications which are based on empirical observations and evaluated and transmitted by clinical experts. Once suitable evidence sources are established, the succinct tabulation of tradition-of-proof evidence may provide an accelerated pathway and practical basis for evaluating traditional indications in a regulatory context. This could reduce both time and cost. In addition, this tool could be used for translational use of traditional health claims. This is where the safety of a preparation has been established and such preparation is recorded as pre-approved in a monograph. Approval may then be extended when this preparation is associated with another long-standing traditional indication not yet listed in a monograph. Such an approach could help to update the current monographs and make them more inclusive for regional customs in Member States.

#### **7.4.1 Challenges to a comprehensive assessment of safety**

The views of HMPC at EMA on genotoxicity testing as a prerequisite for pre-marketing approval of *all* THMPs, have been seen as too restrictive by the European Commission (Commission of the European Communities, 2008, pp. 4,5) and as unworkable by phytotherapy companies (Cranz, 2010, p. 86). Thus, divergent views on sensible levels of proof of absence of harm have emerged as one of the biggest hurdles for registering traditional medicines, despite their long track record of relatively low risk and the general absence of severe adverse effects. Curiously, herbal formulations that encountered regulatory hurdles under Directive 2004/24/EC are permitted in the EU market in the food category without pre-market approval (Quintus & Schweim, 2012). Regarding implementation of the vision of the EU Directive 2004/24/EC to provide ease of access to traditional medicines, it remains to be seen if the European Commission clarifies its expectations further.

The safety of traditional medicines is a complex topic that merits a more detailed investigation beyond the scope of this thesis. There is currently no international,

standardised safety assessment framework for traditional medicines. Regulatory benefit-risk assessment may also change over time due to shifting views on acceptable levels of risk, as seen in the European regulatory history of Arnica. Safety assessments employ a qualitative and not a quantitative approach and therefore involve some element of subjectivity. As such, the safety of a therapeutic substance cannot be considered in isolation from its presumed benefits. Some regulators therefore acknowledge that value judgements form an integral part of decision making on therapeutic interventions (Culyer & Rawlins, 2004; US Congress Office of Technology Assessment, 1978, p. 101). Typically, the higher an attributed or clinically proven benefit is, the higher the tolerance for risk. Conversely, if no benefit is attributed then tolerance for risk tends to be low. When empirical evidence is not duly considered and RCT evidence is not available, these relationships affect traditional medicines disproportionately; the regulatory consequence might be a stipulation for proof of ‘no risk’. Under the EU Directive 2004/24/EC, the high safety threshold set for THMPs has resulted in a drop in the number of traditional medicines across the EU, even for those that previously held market access approvals.

To evaluate the clinical effects of traditional medicines, long-standing traditional knowledge is the strongest source of real-world data currently available. The WHO supports the inclusion of traditional observational data for the evaluation of safety and efficacy of traditional plant medicines (World Health Organization, 2012, p. 17; 2013). This thesis argues that the systematic collation of historical safety data in a large population relating to the traditional use of a plant part or a plant preparation should be given due consideration. Whereas absolute safety does not exist, it is warranted that tradition-of-use data are incorporated into the totality of evidence for the safe and effective use of medicinal plants (Anton et al., 2012a, 2012b; Cordell, 2014; Helmstädter & Staiger, 2012; Neely et al., 2011). Such evidence was noted for acceptance in New Zealand under the formerly proposed Natural Health and Supplementary Products Bill<sup>7</sup>.

Long-term beneficial use and consumer satisfaction point to plausible effectiveness and acceptable tolerance of plant-based drugs as commonly prescribed in European medicine (Benedum et al., 2000). Despite the potential for under-reporting, repeated serious events and side-effects occurring in a large population are unlikely to have gone unnoticed. Today,

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<sup>7</sup> See Draft Permitted Substances List: <https://medsafe.govt.nz/regulatory/PILSearch.asp>

the most common risks associated with using herbal drugs arise from a lack of stringent quality control measures rather from the pharmacological activity of the traditionally known and used herbal ingredients themselves (Bowen et al., 2012).

Quality risks affect all medicines. For traditional plant medicines, such risks relate to misidentification or mislabelling of herbal ingredients with an incorrect species, adulterations (e.g. addition of undeclared pharmaceuticals), substitutions (e.g. the fatal substitution of *Stephania tetrandra* with nephrotoxic *Aristolochia fangchi*), and contamination with heavy metals, pesticides, herbicides, and microbes (Ekar & Kreft, 2019; He, Ung, Hu, & Wang, 2015; Keane, Munn, Vivier, Higgins, & Taylor, 1999). In turn, lack of efficacy may be linked to incorrect harvesting times of the medicinal plant such as when active constituents are not at their prime, the collection of the wrong plant part or species, and incorrect processing. These risks can be minimised with proper quality control measures during harvesting and manufacturing. The WHO has recognised these quality risks with traditional plant medicines and has provided resources on good harvesting and good manufacturing practices (GMP) (Akerlele, 1992; World Health Organization, 1994, 2003). For those conditions which have better treatment outcomes with biomedical intervention than with traditional medicines, a very different risk arises from delay in seeking medical help. These various risks support the urgency around regulation of traditional plant medicines for New Zealand.

In conclusion, it can be stated that the EU approach to the regulation of traditional plant medicines succeeded in guaranteeing legal access to these therapeutics. At the same time fulfilment of the objective of the Directive was hampered by its high level of requirements that resulted in an overall reduction of available traditional remedies compared to the period before the implementation of the Directive. This outcome is noteworthy for other regulators who wish to implement regulation of traditional plant medicines based on the EU approach.

## 8 DISCUSSION

### 8.1 Relevance and significance of results

This thesis sought to examine how the empirical knowledge base underpinning traditional plant medicines can be incorporated into a contemporary regulatory framework that is evidence-based and appropriately accommodates long-standing traditional therapeutics. While many factors influence health policy decisions, evidence from health interventions is the central starting point (Dobrow, Goel, & Upshur, 2004). It is often implied that traditional therapeutics lack the modern scientific evidence to substantiate their effectiveness and safety and so are prevented from being formally integrated into a modern evidence-based healthcare system. Consequently, there is a vital need for robust information that can guide regulation for traditional plant medicines.

Governments are challenged to implement health policies that are efficient, safe, efficacious, and cost-effective, thus meeting the healthcare needs of their citizens. These policies should also reflect values-based healthcare focused on patients and consumers and their rights to self-determination of treatment options (Code of Health and Disability Services Consumers' Rights Regulations 1996; Greenhalgh et al., 2015; McCarthy & Rose, 2010). The WHO Regional Office for Europe recommends that patients play a distinct role in protecting their health, choosing appropriate treatments for episodes of ill health and for managing chronic diseases (Coulter, Parsons, & Askham, 2008, p. 2). Policy interventions aimed at increased patient engagement by improving health literacy, treatment decision-making, and self-management of chronic conditions could be of benefit for the public. To support patients as 'primary health care workers', health policies should support ease of access and affordability to safe and efficacious interventions, but also to interventions of their choice. In its regional guidelines for the Western Pacific, the WHO (2012, p. v) highlights the important contribution of traditional systems of medicine to national and individual healthcare, and to the promotion of health equity. In addition, it stresses to governments that all people have a right to quality health services which are accessible, affordable, and acceptable. In its global *Traditional Medicine Strategy 2014-2023* (World Health Organization, 2013), the WHO calls for governments to integrate traditional medicines into contemporary healthcare, asking that they promote, regulate and research them more extensively. However, despite policy gaps, many countries, including New Zealand, do not recognise traditional medicine and its therapeutics as an integral part of

their healthcare services and they do not provide regulations and formal access to them, including insurance coverage (Cordell, 2014, p. xxix; International Bioethics Committee (IBC), 2013). If traditional medicines were to become recognised under an appropriate regulatory framework, their potential in primary healthcare could be fully realised by enabling of patient access. Long-standing empirical evidence is particularly important where scientific evidence is wanting or completely absent, a situation common within traditional healing practices.

Historical documentary sources have been permitted overseas as bibliographic evidence (e.g. in the EU, Canada, and Australia) (Europäisches Parlament, 2004, p. L 136/187); Health Canada, 2012, pp. 5-8; Therapeutic Goods Agency, 2019, pp. 15-18). Switzerland, similarly to the EU, accepts bibliographic evidence on traditional indications and safety for those plant medicines (*Phytoarzneimittel*) that are well-established (10 years) or traditionally used (30 years) (Swissmedic, 2018). However, as noted in sections 3.3 and 3.4 of this thesis, few previous studies have investigated systematic ways to record and evaluate traditional indications as documented in historical sources, and compared this empirical evidence with contemporary evidence. As illustrated in section 3.7, even fewer have investigated how historical research into traditional plant applications could support modern scientific methodologies to inform evidence-based health policies. In the Western regulatory context, traditional clinical knowledge is an underutilised source of data on health interventions. Consequently, the aim of this research was to explore a method by which long-standing traditional evidence on therapeutic uses of medicinal plants can be systematically coded and collected.

The Historical Assessment Tool, explained in sections 4.4.1 and 4.9, was developed and tested as a systematic and reproducible method of organising the large amount of pharmacological data recorded in bibliographic sources. Longitudinal textual analysis of medicinal uses over 400 years triangulated data from qualitative and quantitative sources helped meet the objective of this thesis: to establish if clinically orientated historical sources within the European *materia medica* could provide a pathway for substantiating therapeutic claims for traditional plant indications in an evidence-based policy framework. This question is pertinent for existing traditional therapies because RCTs are seen as an insufficient and impractical method of validating the large volume of medicinal plants, their synergies, and their numerous indications as applied in clinically complex settings (Mills, 2011).

Authoritative medical textbooks were methodically surveyed as key repositories of clinical knowledge on the European *materia medica*. The results provided a reliable body of documentary evidence relating to the consistent clinical endorsements of traditional indications of *Arnica montana* and *Hypericum perforatum* over 400 years. The *New vollkommen Kräuter-Buch* by the German physician, apothecary, and botanist Tabernaemontanus (first published in 1588) and annotated by the Bauhin editors (4<sup>th</sup> edition, 1664) was confirmed as a suitable starting point for such a longitudinal textual analysis on historical clinical uses. Triangulation of data confirmed that the 16<sup>th</sup> century physician was accurate in determining therapeutic uses of Arnica and St. John's Wort, raising the possibility that he was also accurate in determining therapeutic uses of other medicinal plants. The results from the evaluation of these two exemplars suggest that the clinical conclusions from repeated empirical observations have withstood the test of time due to the frequency, consistency, and extent of the treatment effects reported.

By way of illustration, evaluation of Arnica in the selected qualitative and quantitative sources demonstrates uninterrupted medical transmission of two clusters of indications over a 400-year period; its therapeutic use in the treatment of consequences of injuries and accidents, and its use for pain related to the musculo-skeletal system and nerves (see Table 10). These two clusters of indications are consistently listed in the historical medical literature and contemporary textbooks reviewed at the defined datapoints (each a generation apart), in the commentaries of the Prussian and German pharmacopoeias, in the main European regulatory monographs of the 20<sup>th</sup> and 21<sup>st</sup> century authored by the German Commission E and the European Medicine Agency, and in the authoritative monographs authored by ESCOP, the WHO, and the publishers of HagerROM. Where clinical trials have been conducted on traditional indications, they have also returned positive results confirming benefits for ailments listed in traditional sources, namely for those that require circulatory stimulant, analgesic, antirheumatic, anti-inflammatory, and skin healing actions (see Appendix 11). In addition, experimental research points to Arnica's mechanisms of therapeutic actions (Kriplani et al., 2017; Merfort, 2010; Wijnsma et al., 1995).

Similarly, the analysis of data on St. John's Wort also showed congruency between indications already noted by Tabernaemontanus, albeit in different terminology, and the subsequent qualitative and quantitative data sources that were evaluated. Consistent indications are recorded in all medical textbooks as well as the two evaluated regulatory monographs covering three clusters of complaints. They relate to inflammation and catarrh

of the gastro-intestinal system (gastro-enteritis, dyspeptic disorders); to burns (topical) and wounds (systemic and topical); and to psychovegetative disorders (depressive moods, anxiety, nervous unrest, and hormonally driven dysphoria in relation to the female menstrual cycle). The validity of these traditional indications was further supported when cross-checked with outcomes from clinical trials. Data from experimental research provided insights into active constituents and possible mechanisms related to the empirically observed effects of St John's Wort, most importantly (in modern terminology) its antidepressant, anxiolytic, antiviral, antimicrobial, anti-inflammatory, nervine tonic, spasmolytic, and vulnerary actions (Dell'Aica et al., 2007; Reichling et al., 2001).

These results of the systematic analysis of Arnica and St. John's Wort confirm the WHO's assessment (2012, p. 17) that traditional medicines administered over long periods lead to the empirical evolution of dosages and formulations that maximise therapeutic effectiveness and minimise risk. The undertaken analysis infers that clinical knowledge transmitted over several generations of clinicians provides a reliable form of empirical evidence which aligns with modern assessments for the ailments investigated. This conclusion is further strengthened by clinical trials consistent with traditional dosage and treatment strategies, returning positive results on efficacy as seen with Arnica (see Appendix 11). However, trials applying a dose below traditional dosing as recorded in medical textbooks, or trials that investigated the effect of Arnica as a one-off application, demonstrated no difference between *verum* and placebo. Continuous clinical recommendations by clinicians do not appear to be random but based on therapeutic effects as empirically observed in patient care over long periods.

The analysed data also suggest that traditional knowledge is comprehensive. Recent clinical research has provided only one new application (burns) for *Arnica montana* beyond those based on traditional use already noted over at least 150 years (see Table 9). This lack of innovation is also true for *Hypericum perforatum* where contemporary investigations for traditional indications already noted in the early modern era by Tabernaemontanus returned positive results. These include gastro-intestinal inflammation, menstrual complaints, pain and injuries of the musculo-skeletal system, wound care, and psychovegetative disturbances such as melancholy (today attributed to depression), and discomfort around menstruation (today attributed to hormonally driven dysphoria in relation to the female menstrual cycle). In contrast, new indications for addiction, social phobia, Obsessive-Compulsive Disorder (OCD), and Attention Deficit Hyperactivity Disorder (ADHD) have returned mixed results

(see Appendix 15). Based on the results of these analyses, this thesis argues that the method of empiricism used in traditional medicine delivers a comprehensive and reliable body of evidence on traditional plant medicines that can be canvassed for evidence-based policy.

## **8.2 Traditional knowledge as empirical evidence in the context of evidence-based policy**

The findings of this thesis suggest that a reliable pathway exists for addressing gaps of evidence for traditional medicines. Contemporary professional use of medicinal plants relies on long-standing clinical expertise because it represents reliable observations of treatment outcomes (Mills, 2011; Wiese, 2016). It is suggested that these empirical data could also be an important source of evidence for regulators. Consequently, and once suitable sources are identified, summaries of traditional-use-evidence could provide succinct bibliographic data for regulatory purposes. It is the distinct advantage of literary sources that they can be critiqued, challenged, and corrected if they contain inconsistencies. This minimises erroneous information. Traditional clinical knowledge was recorded according to the medical theory under which it operated. This may now seem quaint or antiquated. For example, St. John's Wort was variably thought to eliminate evil spirits, black bile, or melancholy before it was attributed as a treatment for depression. Despite such disparities in medical theories and their explanatory models, applications grounded in observational clinical outcomes continued. In other words, the observed treatment effects persist even if what is believed it to be curing has changed.

British anthropologist Gregory Bateson (1979) provides a useful metaphor when describing various representations of knowledge. He compares knowledge of the material world to a map which describes a terrain. The map itself is not the terrain, only a representation of it. Many different maps can describe the same terrain. Data recorded in the medical literature can extend the typologies of evidence, metaphorically the map, by integrating long-standing clinical uses as validated and empirically informed sources. Currently, such evidence is neglected in EBM, as proponents of this movement have created a hierarchy of knowledge where evidence from RCTs, as conducted on highly selected groups of patients, is elevated above clinical expertise, as drawn from observations on average patients treated in real life clinical practice. Traditional knowledge, the transmitted clinical expertise *over several generations* of clinicians, is entirely absent in the various EBM pyramids of evidence. The findings from this investigation question this absence.

Numerous issues arise from privileging statistical analysis from RCTs as evidence for decisions on health policies (Bensing, 2000; Kahlert, 2012; Rawlins, 2008; Speller et al., 1997). In the context of this thesis, the most problematic is the limiting of the evidence base (Holmes et al., 2006; Lewith et al., 2009; Traynor, 2002, p. 165). Moreover, those clinical trials that are undertaken are often not representative of how a medicinal plant is used in clinical practice or by consumers (Mills, 2011; Veal, 2004). As Khan et al. (2018, p. 247) note, an assessment of efficacy in a clinical trial is not principally designed to inform the real-life efficacy of an intervention, but to clear regulatory hurdles. For health policies on traditional plant medicines, RCTs are useful but limiting sources of data on the overall scope of such medicines (Witt, 2013). Hence health policy makers should exercise great caution when using RCTs as the sole policy evaluation tool, and instead should extend the overall methodological repertoire (Grice et al., 2017; Kahlert, 2012, p. 7).

Scientific evidence is not a substitute for traditional knowledge (Evans, 2006, p. 95). As the International Council for Science (2002) explains, each makes different contributions. Critically evaluated observational data are now established as a central tenet of medical science and regulatory practice in German speaking countries as demonstrated by the legislative mandate of the German Commission E, the EU Directive 2004/24/EC, and Swiss regulations (Deutscher Bundestag, 1976; European Parliament, 2004; Swissmedic, 2018). The results of triangulating clinical data on Arnica and St. John's Wort confirm that long-standing empirical observations as recorded in clinically oriented medical textbooks are reliable upon testing. This thesis suggests that both traditional and scientific evidence be recognised in a regulatory framework, especially because delineating biomedicine as the only medical system underpinned by 'true science' does not reflect clinical reality. When the evidence base of biomedicine has been assessed, questions have arisen about how much of medical practice can be based on "best evidence" (RCTs) because empirical evidence remains vital to biomedical practice (Coulter, 1998; Hufford, 2003; Imrie & Ramey, 2000; Smith, 1991; US Congress Office of Technology Assessment, 1978, 1983). The majority of clinical decisions require some other form of evidence (Djulgovic et al., 2000, p. 103). Most notably, modalities such as surgery are almost exclusively based on empirical expertise and expert opinions. There appears to be a growing understanding of the inherent complexity of real-world healthcare interventions and of the need to find new ways to evaluate these interventions as they are actually practiced (Boon et al., 2007). This thesis argues that for health policies on traditional medicines to be appropriate and relevant,

traditional clinical knowledge should be incorporated as an integral part of the evidence base.

### 8.2.1 Traditional management of risks of medicinal plants

Historical medical textbooks are also repositories of observational data on side-effects and serious adverse events. Traditional systems of medicines managed risks of therapeutics well before the development of modern analytical methods (Etkin, 1993, p. 97). As medicinal plants have been widely used throughout human history, including by those frequently deemed vulnerable such as children, the elderly, pregnant, and breastfeeding women, these risks needed to be managed broadly. They continue to be managed in traditional systems of medicine because the majority of the world population still treats some or all aspects of its health with traditional medicines (International Bioethics Committee (IBC), 2013).

Pre-modern systems of medicine (i.e. TEM, TCM, and Ayurveda) have been formally codified through repeated trial and error, clinical judgement, pattern recognition, tacit knowledge, and inspiration. In European medicine, experimentation on human physiology also played a role, influencing compounding rules of medicines and safety considerations (Saad & Said, 2011, pp. 107-109). As early as the 1<sup>st</sup> century AD, risks with medicinal plants such as adulteration, substitution, and toxic effects were extensively discussed by Dioscorides (Heinrich et al., 2017; Riddle, 1985, p. 1111). Analysis of medical textbooks evaluated for this thesis showed that historical sources either warn against the use of certain toxic plants, offering advice on risk mitigation by suggesting the synergistic use of plants that moderate irritating or toxic herbs (for example combining Arnica with mucilage drugs to mitigate stomach irritation), or else they recommend a specific extraction method that guards against extracting potentially toxic substances such as alkaloids. Textbooks on the European *materia medica* demonstrate that different therapeutic effects with different extraction methods were known, as exemplified in the Arnica and St. John's Wort monographs by Tabernaemontanus (Appendices 3, 4, 12, and 13). This clinical expertise mirrors records in other textbooks of the early modern era (Schanz, 2009, p. 143).

Typical historically noted risks are: primary toxic effects such as *Teucrium* spp. being unsafe unless extracted as a traditional water infusion; undesirable side-effects as in bitter herbs possibly causing nausea; allergic reactions such as contact allergy to *Arnica montana*; reproductive toxicity (e.g. abortifacients, toxicity of berberine containing herbs to the foetus), and physical dependence as with *Papaver somniferum*. In traditional medicine,

infants and children are administered mostly the same herbs as adults, albeit at lower doses. Powerful laxatives and strongly tasting bitters and spices, as well as those with potentially toxic compounds, are not recommended in traditional paediatric care (Santich & Bone, 2008).

In addition, each system of medicine uses theory to formulate effective and safe therapeutic strategies. The early modern textbook by Tabernaemontanus illustrated that humoralism categorised all pharmakons into the four qualities of hot, cold, moist, and dry, each with their respective degrees of one to four, their organoleptic properties of sweet, sour, bitter, and salty, and their specific actions such as anodyne, laxative, or anti-diarrhoeal (Tobyn, 1997, 2013, pp. 224-243). The degrees refer to intensity of action (Madaus, 1938b, pp. 3-4; Salmon, 1710, pp. x-xv). Traditional plants classified at an intensity level of one or two are unlikely to cause harm when used appropriately, those classified at an intensity level of three are likely to require some risk mitigation strategy, and those classified at an intensity level of four are not suitable for use without supervision and can cause injury if used incorrectly or for too long. This suggests that historical clinical judgement is noteworthy.

### **8.2.2 Limitations to safety information recorded in historical medical textbooks**

There are limitations to the safety information that can be gained from historical medical literature. They relate to herb-drug interactions and safety issues with accumulative poisons. Interaction data are not available from historical sources because many synthetic drugs are a recent discovery. Modern herb-drug interaction research is an emerging field that is challenged to distinguish between *theoretically deduced* interaction and *real* interaction in order that assessments are relevant for real-life applications. This is necessary because plants are made up of complex substances; thus the conflation of risk of an isolated or purified compound with that of a whole plant, where such a compound occurs in the presence of a complex matrix, is problematic (Huang et al., 2016; Jacob, Khan, & Lee, 2017; Shirakami & Shimizu, 2018). For this reason, some regulators, for instance Health Canada (2012, p. 9), do not consider theoretical safety concerns in the absence of clinical data.

The type of preparation also determines the likelihood of herb-drug interactions. This can be illustrated with traditional plant preparations of St. John's Wort, which contain low levels of hyperforin and are unlikely to cause herb-drug interactions; in contrast modern standardised St. John's Wort preparations that contain high levels of hyperforin have been

shown to induce herb-drug interactions (Mai et al., 2004; Medsafe, 2014; Mueller et al., 2009; Nahrstedt & Butterweck, 2010; Soleymani, Bahramsoltani, Rahimi, & Abdollahi, 2017; Swissmedic, 2002, pp. 7-8; Whitten et al., 2006).

Herb-drug interactions are most likely to take place when synthetic medicines with a narrow therapeutic range are co-administered with plant-based medicines (Shi & Klotz, 2012). Other potential herb-drug issues relate to parallel interactions where a herb and a drug with similar effects are combined without modification of the drug dose, opposing interactions where the action of a herb counters the desired effect of a drug, or adverse interactions where a herb reinforces the adverse reaction of a pharmaceutical drug or vice-versa.

The assessed historical medical literature records safety concerns for immediate toxic effects on the skin as well as systemic irritations but is uncertain regarding accumulative poisons. For Arnica, potential toxic effects have been noted at least since the 19<sup>th</sup> century. They relate to overdose, overuse, and allergic reactions. These risks were historically mitigated by recommendations on dosage (a low average daily dose of 1g per day), restrictions on usage to small areas when applied to open surfaces, and contra-indication of use in allergies. In contrast, the detection of hepatotoxicity, carcinogenicity, and reproductive and developmental toxicity (teratogenic potential) due to long-term use or accumulative poisons relies on newer methods of detection. This limitation means that accumulative poisons were traditionally less well understood than those immediately acting, and their side-effects less recognised and recorded (Moreira, Teixeira, Monteiro, De-Oliveira, & Paumgarten, 2014, p. 254; Reuter, 1994, p. 152). Today, medicinal plants with potential high-risk profiles are usually excluded as OTC medicines and more appropriately classified in a practitioner-only category. They are not permitted as OTC medicines under the EU Directive 2004/24/EC. For those traditional plant medicines which are currently accessible over the counter, adverse reaction reporting data suggest that when correctly selected, compounded and administered, traditional plant medicines are unlikely to cause toxic effects such as liver injury, notwithstanding idiosyncratic reactions (Frenzel & Teschke, 2016). Even when considering potential underreporting and compared with their prevalence of use, plant-based medicines appear to have a very low probability worldwide of an ADR, including those investigated as exemplars in this thesis (Abdel-Tawab, 2018, pp. 377-381; Wegener, Deitelhoff, & Silber-Mankowsky, 2015, pp. 247-248).

The issue of accumulative poisons is not unique to traditional plant medicine; rather, it

affects all medicines. EBM relies on clinical trials to ascertain safety risks. RCTs have, however, been shown to be an inadequate tool for measuring safety, in particular in relation to infrequent and uncommon adverse effects of drugs (Rawlins, 2008; Stephens, Talbot, & Waller, 2004). RCTs are usually designed to evaluate efficacy of a therapeutic intervention rather than harm (Chou et al., 2010, p. 503). This approach is reflected in the limitations of study size, short observational periods, and patient selection criteria that are not representative of the general population. This affects their ability to evaluate risks in populations not included in the study and long-term harm (Bodeker, 2000, p. 2; Vandenbroucke, 2004, p. 2).

Systematic collation of historical safety assessments could be used together with observational data collated with epidemiological methods from contemporary clinical use, for example from outpatient clinics via the databank PhytoVIS<sup>8</sup> or the European Network for Centres for Pharmacoepidemiology and Pharmacovigilance<sup>9</sup>, as well as state sponsored pharmacovigilance data. Evaluating safety data from various angles will improve the availability of bibliographic safety data on many traditional medicines and may support their pre-marketing approval. Toxicology studies may not be necessary for therapeutic substances with established use and data on effectiveness and safety. They are not always seen as mandatory, for example in Switzerland (Swissmedic, 2018).

### **8.3 Limitations of pharmacopoeias and commentaries as bibliographic evidence**

Pharmacopoeias and their compendia provide important bibliographic proof of the official use of a medicinal plant and its recommended therapeutic applications. However, triangulation of data provided reasons why they cannot replace historical textbooks on the European *materia medica* as an essential documentary body of evidence on the clinical uses of traditional plant medicines. Analysis of data showed that a significant gap can exist between clinically oriented textbooks and a regulator's official assessment of the therapeutic importance or non-importance of a medicinal plant. For instance, despite its ongoing clinical significance in medical patient care over more than two millennia, St. John's Wort was entirely absent in all German pharmacopoeia editions until 1986 when the *Deutsches Arzneibuch* harmonised with the European pharmacopoeia where it was listed

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<sup>8</sup> <http://www.phytovis.de/>

<sup>9</sup> <http://www.encepp.eu/>

(DAB 9, 1986). The regulatory view of St. John's Wort changed only when strong research interest into the therapeutic potential of St. John's Wort began to establish its efficacy in the 1970, resulting in over 150 clinical trials. This delay highlights how non-listing in a pharmacopoeia does not necessarily imply the lack of effectiveness of a medicinal plant. Such a delay may reflect the judgment of the majority of a pharmacopoeia committee at a given time, and this judgement may differ from clinical assessments by those providing patient care. The results of this thesis demonstrated that pharmacopoeias and their commentaries do not incorporate the full spectrum of clinical applications. The regulatory fate of St. John's Wort over the past 150 years is a cautionary tale for traditional medicines that now co-exist under the framework of a modern biomedical healthcare system. Unlike St. John's Wort and regardless of their clinical effectiveness, not all traditional medicines became re-selected as official medicines and thus are not yet integrated into the official healthcare systems of European countries.

Arnica, too, was affected by divergent assessments between the German pharmacopoeia committees and practising physicians, most noticeably after the end of the 19<sup>th</sup> century. While Arnica's legal status as an essential medicine was assured in both the Prussian and German pharmacopoeias, an analysis of its official plant parts revealed that Arnica root was de-listed in the 2<sup>nd</sup> edition of the German pharmacopoeia (1882). This de-listing contrasts with the full range of plant parts, namely aerial parts, flowers, and root, as used by Tabernaemontanus and succeeding physicians. The reason for discontinuing Arnica root as a listed medicine is unclear, but it may have been due to conservation issues or re-assessment of treatment options for diarrhoea and gastro-intestinal infections, the key indications for Arnica root. Consequently, indications related to the gastro-intestinal tract were also absent in the commentaries to the German pharmacopoeia from the second edition onwards (Hager, 1883a). This absence was reversed only when the different active constituent profiles of Arnica root and flower became recognised in the 1<sup>st</sup> edition of the compendium to the *DAB* (HAB 1, 1978).

Comparison of clinical uses and regulatory assessments suggests that contemporary evaluations of traditional use need to cover sufficiently long timeframes. Official approvals can be affected by factors independent of the pharmacological actions of medicinal plants. Analysis of therapeutic recommendations on Arnica showed that commentaries of the Prussian and German pharmacopoeias were initially closely aligned with indications listed in clinical textbooks on the *materia medica*. However, following the end of the 19<sup>th</sup> century,

medicinal plants in pharmacopoeias and indications listed in commentaries are noticeably fewer than in the analysed medical literature. This reduction coincided with regulatory changes to the attributed scope and safety of Arnica stemming from new benefit-risk assessment. During this time, non-clinical technical experts increasingly displaced physicians from the regulatory domain of medicine (Schneider, 1966, p. 192). While commentaries continued to list the main therapeutic uses of Arnica, they did not continue to reflect the broader clinical applications. In the last commentary, the only remaining indications of Arnica pertained to external uses (Hartke, 1993, A54 p.4). This decrease in indications demonstrates that commentaries mirror the controlling regulatory framework of a nation state, rather than the pluralistic clinical strands of phytotherapy. While clinically oriented textbooks on the *materia medica* are affected by regulatory directives too, they nonetheless have been shown to reflect actual clinical practice more comprehensively. Consequently, they are more encompassing sources of traditional evidence for plant medicines.

### **8.3.1 Limitations of regulatory monographs as bibliographic evidence**

Analysis of data showed that a gap can also exist between indications endorsed in regulatory monographs and by those providing patient care. Based on their assessments, the two respective committees of the reviewed European regulatory monographs approved the main traditional indications of Arnica and St. John's Wort but did not consider other indications with an equally long-standing tradition. For instance, medical textbooks continuously recorded the use of St. John's Wort for musculo-skeletal pain from sprains, strains, bruises, and rheumatic disorders at least since the early modern period (see Appendix 14). These traditional indications are absent in the official monographs. Equally, intermittent but persistent indications listed by physicians over an entire 400 years or those that were listed more recently over at least the past 150 years were also not considered in either of the official monographs, except for the indication "temporary mental exhaustion" which is approved in the EU monograph (Committee on Herbal Medicinal Products (HMPC), 2009b, p. 3). With Arnica, the variance between regulatory and clinical assessments arose in the 1980s when European regulators were compelled into a new approach to healthcare based on preventative measures of health and safety. Due to mounting concerns about side-effects and severe adverse events caused by pharmaceutical drugs, the 1980s were a watershed in Europe for the risk assessment of medicines.

Traditional medicines became part of this regulatory review which increased the focus on plant toxicology, potential risks, and side-effects. While no additional risks were noted in the 1980s for Arnica other than those already clinically identified and mitigated via dosage limits and cautions, regulators moved to restrict usage of Arnica to external applications only. This recent regulatory-driven reduction of the official therapeutic scope of *Arnica montana* has caused the biggest variance of historical and contemporary uses over the past 400 years. It might warrant a re-evaluation of the regulatory restrictions by the German and EU regulators, with emphasis on the consistent clinical internal applications within the safety parameters of traditional dosing.

Discrepancies in assessments between regulators and clinicians make it clear that official monographs reflect their specific legal-political framework, one set by the German regulator during the 1980s and 1990s and the other by EMA under the Directive 2004/24/EC, rather than the entirety of long-standing clinical uses. Of the two official monographs, the Commission E monographs provide approvals for more traditional uses than do the more recent EU herbal monographs, reflecting the respective eras in which they were published. Consequently, the strengths and limitations of both sets of monographs need to be considered. It could be unjustified to rule out *a priori* traditional indications which are not listed in these two official monographs, because some additional traditional uses have long been accepted and continue to be applied in clinical practice. For instance, St. John's Wort continues to be recommended in treating varicose veins, respiratory tract infections, and rheumatic disorders (see Table 14). Other historical indications are supported by pharmacological research and clinical reasoning, such as the treatment of biliary disorders, bedwetting in children, or distress during childbirth. Lastly, a small, preliminary body of clinical research has shown the efficacy of a further traditional indication, that of relieving premenstrual tension (Pakgohar, Mehran, Salehi, Akhondzadeh, & Ahmadi, 2004; Stevinson & Ernst, 2000).

In the absence of mechanistic studies or clinical trials, multiple traditional applications for a medicinal plant may at first appear as a “lengthy and indiscriminate laundry lists of effects” (Johnson & Fahey, 2012, p. 778). However, such appraisals might unjustifiably dismiss potentially sound scientific bases for many of these traditional uses. This potential exists because medicinal plants inherently exert complex effects due to their multiple independent mechanisms (Chen et al., 2016; Rezaadoost et al., 2016; Schwabel et al., 2014; van der Greef et al., 2010). Such pleiotropic effects may be accentuated by the synergistic effects of a

plant's multiple constituents (HemaIswarya & Doble, 2006; Herranz-Lopez et al., 2012; Ulrich-Merzenich, Panek, Zeitler, Wagner, & Vetter, 2009). Thus, an evaluation of a traditional indication should take into consideration the polyvalent nature of medicinal plants that result in their broad therapeutic effects. These effects are most comprehensively noted in the historical medical literature and are increasingly also confirmed and explained by modern scientific research methodologies.

#### **8.4 Non-pharmacological reasons influencing the scope of traditional plant medicines in the regulatory literature**

There are further cautions against using pharmacopoeias and regulatory monographs as the sole body of qualitative evidence for traditional plant medicines. These official texts are embedded in their wider socio-economic and legal-political environment and reflect the state-sponsored approach to healthcare at the time of their publishing. They may not necessarily represent the pluralistic strands of medicine in clinical practice. Today's Western science-based medical system is not culturally neutral but rooted in the European scientific revolution (Wartmann, 1993). It is beyond the scope of this present research to detail how the current state-sponsored medical system developed over the past 150 years while progressively aligning with the industrial worldview and its economic market model (Huisman, 2010) or how the increased commercialisation of medicine in the late 19<sup>th</sup> century and the emergence of academic medicine and related professional medical associations advanced the prevalence of new synthetic drugs which gradually displaced traditional medicines (Hionidou, 2016, p. 494; Ijaz & Boon, 2018; MacLennan & Pendry, 2011, pp. 7,11). However, it is important to note that such factors can influence the type of medicines which regulators endorse. Such factors also influence the type of evidence that a state mandates to sponsor a medicine.

Following the 19<sup>th</sup> century shift in clinical reasoning from humoralism to organ- and cell-related thinking in medicine (Uehleke et al., 2012, p. 189), academia increasingly favoured evidence related to pathophysiological explanatory models deduced from experimental science over evidence acquired through empiricism, the repeated and evaluated observations of therapeutic uses in patient care. In a regulatory context, this preference was most noticeably exercised by the committee of the Prussian pharmacopoeia which aligned itself with what it perceived as the peak of natural science (Tschupp, 1998, pp. 121-122). Many long-standing traditional therapeutics were excluded from the modern official

medical repertoire for three key reasons: an initial lack of molecular biological evidence for broadly acting traditional plant medicines, a preference for potent but potentially toxic medicinal plants with their rapid onset of actions, and the increased favouring of new pharmaceutical drugs (Jütte, 1996, p. 166; Rezaadoost et al., 2016, pp. 2-3; Schulz, 1919). Accordingly, commentators on the German pharmacopoeia distanced themselves from empirical uses of medicinal plants during this time (Anselmino & Gilg, 1911a, pp. VI-VII; 1911b, pp. 537-539; 1928, pp. 604-607). They championed a new approach to the European *materia medica*, one that was critical of ‘dated’ medical textbooks. These, they alleged, might contain more ‘harmful than useful’ information and represent an embarrassment to modern medicine (Anselmino & Gilg, 1911a, pp. VI-VII). Consequently, 20<sup>th</sup> century annotations to the German pharmacopoeia increasingly reflect an academic rather than a clinical approach to traditional plant medicines.

Preclinical plausibility as a prerequisite for the continued acceptance of the traditional *materia medica* was not, however, an approach approved by all scientists. Dutch pharmacologist Vogelenzang (1967, pp. 351-352) criticised the 20<sup>th</sup> century trend to modernise pharmacopoeias by deleting those medicinal plants for which the mechanism was unknown. He considered such rationale for de-listings as non-scientific, since ‘obsolete’ meant not sufficiently researched according to modern science rather than not proven to be effective. This analysis showed that St. John’s Wort, a medicinal plant with actions that could initially not be explained via experimental scientific methods, was eliminated from the Prussian pharmacopoeia and not considered in the German pharmacopoeia, yet it continued to be listed in medical textbooks and was later validated via experimental research and clinical trials.

Today, experimental proof of the mechanism of action has been superseded by the EBM principle’s demand of proof of efficacy from clinical trials. From a social science perspective, divergent views on what constitutes evidence reflect paradigmatic preferences rather than validity based on objective rules of science (Cassidy, 1995, p. 19; Churchill, 1999; Evans, 2006, 2008). Ultimately, scientific discourse cannot be divorced from its cultural context or the associated legal-political and economic agenda of an era (Coulter, 2007; Kim A. Jobst, 1998, p. 125). What this thesis has demonstrated is that traditional therapeutics have continued to be used in clinical practice regardless of the various theoretical models that tried to explain their effects.

## 8.5 Implications for New Zealand

Current regulations neither adequately address the place of traditional plant medicines in New Zealand's healthcare system nor protect public health. Therefore, they fail to provide a health policy framework that maximises the contribution of safe and effective traditional medicines to meet primary healthcare needs of New Zealand citizens. This thesis argues that given the important contribution of traditional systems of medicine to national and individual healthcare and the high prevalence of use of traditional plant medicines in New Zealand (Barnes et al., 2016), progress on such regulations should be a matter of urgency.

Bowen and Zwi (2005) argue that the policymaking context is highly political and depends on numerous factors, inputs, and relationships. After the identification of a policy gap, the political agenda of an incumbent government affects the timing of such policy and its implementation. Milio (1985, pp. 273-274) emphasises that timeliness is a key principle for policy success, as improvements in health through primary healthcare interventions take time to become apparent. However, successive New Zealand governments have not made recognisable progress on regulating therapies from traditional systems of medicine over the past decades despite advice from their own Ministerial Advisory Committee on Complementary and Alternative Health (2004) and from the *WHO Traditional Medicine Strategy 2014-2023*, one to which New Zealand is a signatory (World Health Organization, 2013).

Under the current New Zealand healthcare system, pharmaceutical drugs and dietary supplements, the category in which traditional medicines are currently allocated, are divided into two distinct groups, the former being government funded through Pharmac, and the latter privately funded. This system presents an obstacle for patients wishing to use traditional medicines due to out-of-pocket costs, a lack of quality and safety assurance, and the uncertainty of the scope of non-pharmaceutical remedies due to a lack of permitted health claims on labels. The current New Zealand regime contrasts with health policies in European countries where the EU proceeded to protect the status of traditional medicines legally. Under Directive 2004/24/EC, traditional medicines obtained their own regulatory classification as Traditional Herbal Medicinal Products. Switzerland has gone a step further in that since the binding constitutional referendum in 2009, phytotherapy is a treatment option that must be adequately integrated into healthcare services for citizens. This guarantee enables plant medicines to be funded through the public healthcare systems and

provides patient-centred and cost effective treatment options (Saller, 2009; Schweizerischer Bundesrat, 2017; Wolf et al., 2005).

The exclusion of traditional remedies from New Zealand mainstream medicine since the early 20<sup>th</sup> century is therefore out of step with developments in other countries which have now proceeded to grant citizens legal rights to pluralism in medicine. The marginalisation of traditional medicines is perpetuated in the current New Zealand Medicines Act 1981 and the Dietary Supplements Regulations 1985, both of which require updating to accommodate modernisation in New Zealand healthcare. To that end, the replacement of the Medicines Act 1981 is currently under consultation and is an opportunity to address the legal void currently existing around traditional therapeutics, including plant-based medicines.

In its formerly proposed domestic Natural Health and Supplementary Products Bill, New Zealand had moved towards legal acknowledgement of traditional plant medicines by drafting a large list of pre-approved plant species that the Ministry of Health had classified as low risk substances (Ministry of Health, 2017; "Natural Health Products Bill 2011 (2012 No 324-2)"). In the policy advice that preceded this draft, Medsafe issued the following risk considerations for plant-based medicines:

- intrinsic risk – risk arising from ingredients themselves, for example *aristolochia*
- extrinsic risk – risk arising from the way goods are manufactured, for example spiking with pharmaceuticals
- inappropriate use – risk arising from misuse or abuse (Jessamine, 2004, slide 8).

The risk management strategy by Medsafe proposed addressing minimum quality standards, ingredient safety requirements, adverse reaction monitoring in the form of post-market monitoring and surveillance, and appropriate therapeutic claims. If these four key points were integrated into a risk minimising strategy, such a strategy would support the beneficial use of traditional plant medicines and minimise many of the avoidable harms that could arise from it. Assessments for the proposed Permitted Substances List were undertaken in consultation with herbal experts, toxicologists, and pharmacologists who are trained in the intrinsic quality and safety features of plant medicines (Medsafe, n.d., p. 3).

There are some important legacy issues which new regulations on traditional plant medicines will need to address. Schedule 1 of the current Medicines Regulations prevents registered Medical Herbalists and Tohunga from legally accessing several traditionally used

plant species currently regulated as pharmaceutical substances. Pharmacists and physicians are the only professions to have legal access to these medicinal plants even though they are usually not trained in their clinical use. The creation of a practitioner-only category for professionally trained herbal experts, as undertaken in other countries, such as the UK (Linnenbrink, 1990; "The Medicines (Retail Sale or Supply of Herbal Remedies) Order 1977," 1970), would address the misappropriation of traditionally used medicinal plants and provide a legislative framework to put them back into traditional context. This category would be appropriate for more potent medicinal plants (in their whole plant format) that have higher risk profiles than medicinal plants which are milder acting and suitable as OTCs. This recommendation aligns with the WHO policy approach that traditional plant medicines and traditional medicine practitioners should be regulated together (World Health Organization, 2013). As such, Medical Herbalists should be prioritised for admission under statutory regulation.

Another critical issue that needs addressing is how to deal with evidence on traditional medicines. A consultation document relating to the formerly proposed Natural Health and Supplementary Products Bill suggested that health claims for natural health products (NHPs) may be made based on evidence of traditional use (Ministry of Health, 2015, p. 9). The Bill proposed establishing pre-approved bibliographic sources that could be used as evidence for health claims. However, the list did not specify authoritative clinical textbooks on the traditional *materia medica* as sources to be permitted, even though they are—based on this analysis—the most comprehensive and clinically relevant repository of traditional evidence. The findings of this thesis on two traditionally used medicinal plants support the admission of evidence from authoritative textbooks as primary evidence sources.

## **8.6 Strengths, limitations, and research implications of the thesis**

This thesis explored a method to widen the evidence base of traditional plant medicines to support their regulation in the era of contemporary evidence-based health policy. The Historical Assessment Tool was developed to tabulate proof of long-standing indications which are based on empirical observations and evaluated and transmitted by clinical experts. Once clinically oriented and authoritative sources of evidence for a medical tradition are established, the concise tabulation of tradition-of-proof evidence may provide an accelerated pathway for evaluating traditional indications in a regulatory context. The ability to have summarised data of empirical evidence on these therapeutics could reduce

both time and cost for regulators.

The historical research design of this study with its method of systematically triangulating empirical and scientific data is an extension of previous approaches to evaluating traditional knowledge on the European *materia medica* in order to make such data operational in a regulatory context. In a preliminary step, considerable time was spent in archives and libraries to locate historical medical textbooks on the European *materia medica* as well as official pharmacopoeias of Prussia, Germany, and Switzerland, including their commentaries and supplements. This was in addition to authoritative and regulatory monographs, and modern textbooks on European phytotherapy. Such a broad approach was necessary for the selection of sources appropriate for health policy purposes. Additionally, systematic database research was undertaken to locate scientific clinical trials as quantitative sources to cross-validate the qualitative tradition-of-use data.

The comprehensive nature of evaluation of the first exemplar, *Arnica montana*, was required to cross-validate historical medical textbooks as reliable sources of empirical evidence on traditional indications. The simplified approach applied in the evaluation of *Hypericum perforatum* helped to fine tune the method so that it can be recommended as a policy tool to collate proof of traditional evidence for regulatory purposes. By going through the stages of methodically cross-validating various independent data sources, this research sought to develop a reliable framework that could swiftly, summarily, and methodically collate traditional-use-evidence. The results of the data analyses demonstrated that historical and contemporary clinical textbooks are a central bibliographic source of empirical evidence. For the exemplars evaluated, they provided reliable and verifiable data on traditional therapeutic use. The resultant consolidated method may therefore offer a pathway to provide empirical evidence for regulatory purposes.

Aside from its practical use as a health policy tool, the Historical Assessment Tool has further applications. It may provide a research framework for the discovery of potential drug leads, thus helping to save research time and money. It could also be used to validate contemporary phytotherapeutic practice by elevating long-standing clinical knowledge as a reliable form of empirical evidence.

There are several limitations with the research design employed in this thesis. First, the method of data collection was tested on two exemplars only. It is recommended that further

research be undertaken on other exemplars to verify that the outcomes of this research can be replicated. Such broadening of evaluation would strengthen the validity of the method.

Second, this thesis evaluated the German language *materia medica* and collated traditional evidence on long-standing clinical use of therapeutics from Traditional European Medicine. More research is required to determine the suitability of the tested method for traditional-use-evidence pertaining to other written medical traditions of societies prevalent in New Zealand and around the world such as TCM, Ayurveda, Kampo, Traditional Tibetan Medicine, Korean medicine, and other systems of traditional medicine.

Third, there are linguistic and conceptual challenges that need to be addressed so that historical research can reach its potential as a tool for bibliographic substantiation of traditional plant medicines. More work needs to be done to bridge the gap between traditional nosology and the biomedical classification of diseases. Traditional descriptions of diseases prior to the 19<sup>th</sup> century are conceptually different from contemporary Western classifications, and such differences must be considered so that traditional indications can be understood. For the European medical tradition, a study could systematically evaluate the full pharmacological and pharmaceutical content of the *New vollkommen Kräuter-Buch* (Tabernaemontanus, 1664). This early-modern textbook is particularly suited to such an undertaking because the results of this thesis confirmed that the author was accurate in determining the pharmacological actions of Arnica and St. John's Wort, raising the possibility that he was also accurate about the pharmacological actions of other medicinal plants.

Fourth, the Historical Assessment Tool is only suitable for the coding of data from written medical traditions. Future research could therefore develop a data gathering framework for traditional evidence pertaining to traditional uses of medicinal plants in oral traditions. This is urgently needed in New Zealand to progress appropriate regulations that apply to Rongoā Māori (traditional Māori medicine), a system of healing that was and is transmitted orally. Such a framework could potentially also support empirical evidence of other oral medical traditions.

Fifth, one objection that proponents of EBM have raised about the experiential nature of medical practice is that experience can be a repetition of mistakes (Djulbegovic et al., 2000, p. 101). Moreover, traditional knowledge is seen by some as being at risk of bias, and historical experience is therefore questioned as being rigorous enough or even relevant for

present-day practice (Leach, 2016, p. 148). Sackett (1989) proposed a logical, deductive framework for the interpretation of evidence to reduce the impact of un-controlled experience. While eliminating the subjective interpretation of evidence is unrealistic and may not even be desirable (Rawlins, 2008), this thesis employed triangulation of data from various sources to reduce the risk of bias and to strengthen conclusions drawn from historical sources. Assessments on Arnica and St. John's Wort have shown that historical data are reliable and verifiable if such data includes proof of inter-generational records in clinically evaluated textbooks.

Sixth, the premise of triangulation of data is to provide different angles for looking at the same phenomenon, thus adding credibility by strengthening confidence in conclusions drawn (Patton, 2014, p. 661). For this purpose, this thesis triangulated traditional-use-data documented in historical sources on the *materia medica* and contrasted these data with indications on the same exemplars documented in distinctly separate sources such as contemporaneous regulatory pharmacopoeias, their commentaries, regulatory and authoritative herbal monographs, and clinical and experimental research. Such triangulation showed parallel findings between the medical literature and these independent qualitative and quantitative sources. However, some information in the medical textbooks may not have been independent as it is the nature of tradition to be informed by previous evaluations. To reduce the likelihood of including un-evaluated data on the *materia medica* recorded in the medical literature, a selection criterion determined that authors needed to be clinicians who applied plant-based medicines in patient care. The independence of these data could, however, have been further strengthened if clinical records on the same medicinal plants over distinct cultures and languages had also been included. This step was, however, beyond the scope of this thesis.

Seventh, there are unsolved challenges pertaining to safety evaluations of traditional medicines. While the Historical Assessment Tool corroborates reports on observed and documented individual adverse reactions or adverse events from clinical use on a large population over time, these data are incomplete for a contemporary evidence-based healthcare system. More research is required to show how benefit-risk assessments of traditional plant medicines could be approached. Research on safety of traditional medicines would need to consider their actual use in traditional format and posology in order to deliver clinically relevant information. Such investigations are of clinical and regulatory interest and are particularly pressing for vulnerable populations. Analyses on the

scope of Arnica and St. John's Wort listed in the two European regulatory monographs could be a starting point for such research. In addition, it would be worthwhile re-evaluating the current stance on internal use of Arnica in official monographs to determine a rational differentiation between a safe, therapeutic dosage range and an overdose.

Eighth, complementing bibliographic evidence, research using modern observational studies, or pragmatic trials would address knowledge gaps on the effectiveness and safety of traditional plant medicines when used under real-world conditions. External validity of relevance is highly important not only for healthcare professionals but also for policy makers (Rothwell, 2005). Observational research on existing practices also allows for data to be collected without the ethical difficulties of assigning patients to novel, unproven treatments or placebos. While the EBM model considers qualitative research to be a lower level of evidence than clinical trials, an investigation into the estimates of treatment effects in observational studies suggests that they are neither consistently larger nor qualitatively different from those obtained in RCTs (Benson & Hartz, 2000). As noted before, observational studies are also a necessary method to adequately determine risks with an intervention. Such real-world studies would further support the integration of traditional medicines into contemporary healthcare.

Ninth, some researchers assert that desktop research for the development of evidence-based policy is incomplete and needs to be supplemented by expert knowledge and personal contacts (Joffe & Mindell, 2002, p. 137). Some organisations such as the US National Institutes of Health, the US Institute of Medicine, and RAND Corporation view scientific evidence on conventional interventions as insufficient for the decision-making process of an evidence-based healthcare system. It can be argued that this insufficiency also applies to traditional evidence. Any treatment recommendation has to take into consideration appropriateness and necessity (Coulter, Shekelle, Mootz, & Hansen, 1999). Consequently, research organisations propose the vetting of evidence by using expert panels that provide clinical guidance to policy makers, clinicians, and patients (Coulter, Elfenbaum, Jain, & Jonas, 2016; O'Donnell et al., 2017). This is congruent with the approach of the Commission E and of HMPC, and was proposed in New Zealand (Medsafe, n.d., p. 3). It also concurs with the opinion of the former Chairman of the UK National Institute for Health and Clinical Excellence (NICE), who notes that judgments and contextual considerations are an essential component of the health policy decision-making process (Rawlins, 2008, p. 2). This perspective suggests that how evidence is defined—the topic of

this thesis—and how evidence is used in the decision-making process on health policies are both important (Dobrow et al., 2004). Further reviews regarding the utilisation of traditional knowledge at health policy level would be worthwhile (Stephens et al., 2004).

Tenth, long-standing traditional use of plant-based medicines reflects a high level of cultural acceptance and regulations on traditional medicines therefore deal with practices that have established cultural authority. Regulators of traditional systems of medicine should therefore consider regulations that are sensitive to established cultural practice. To support this proposition, a research angle could be to evaluate cost savings in secondary and tertiary healthcare when preventative and primary healthcare with traditional remedies are actively supported. Such research could be extended to quantify the loss of quality of life or life expectancy that occurs when New Zealanders are prevented from fully practicing their traditional medical customs and addressing health issues which are treatable with traditional plant medicines.

Finally, the WHO guidelines on herbal medicines recommend that “each country should seek to identify ten major public health problems amenable to herbal treatment and ten single plants used locally to treat these conditions. The results can usefully be exchanged between countries” (Akerele, 1992, p. 104). New Zealand has a rich biodiversity of medicinal plants—both indigenous and naturalised—which have been shown to possess highly active bio-compounds that could be commercialised (McCallion, 1982; Morgan, 1989; Muir, 1982). This richness has already been demonstrated with Mānuka (*Leptosperum scoparium*) (Cooke & Cooke, 1991; Maddocks-Jennings, Wilkinson, Shillington, & Cavanagh, 2005), now a significant export earner for New Zealand. Therefore, the support of research into traditional plant medicines could help to meet not only local but also global health needs and be commercially beneficial for New Zealand.

The next and final chapter presents the conclusions and policy recommendations arising from this thesis.

## 9 CONCLUSIONS AND RECOMMENDATIONS

Evidence of the effectiveness and safety of therapeutic interventions is paramount to the regulatory integration of traditional medicine into a contemporary evidence-based healthcare system. A presumed lack of evidence is one reason why New Zealand is yet to make progress in regulating traditional plant medicines, despite their prevalent use by its indigenous and immigrant populations. Without adequate regulation, their formal contribution to preventive and primary healthcare cannot be determined, which limits access to medicines of choice. This legal void may also pose a public safety concern, as lack of regulation does not prevent their use.

The findings of this thesis have several implications for the development of health policies. The results of systematic analysis of evidence sources on the European *materia medica* indicate that a body of evidence is available that may help resolve the regulatory difficulty of deciding if there is sufficient proof available to support traditional health claims. The comparison of findings from triangulation of inter-generational clinical expert consensus on two widely used medicinal plants recorded in authoritative medical textbooks and evidence from modern phytotherapeutic use and clinical and experimental research, led to the conclusion that traditional medical knowledge represents a reliable and verifiable source of evidence. It is based on the method of empiricism, a deductive approach to knowledge generation that is central to both traditional and contemporary systems of medicine. In written medical traditions, clinically evaluated observational data are recorded in the clinically orientated professional literature on the *materia medica*. Compared with the official Prussian and German pharmacopoeias, their normative commentaries, modern herbal monographs (i.e. by the Commission E, EMA, WHO, ESCOP, and HagerROM), and scientific research, this body of evidence has shown to be the most comprehensive repository of consistent therapeutic applications, including information on safe use. The analysis infers that empirical knowledge transmitted over several generations of clinicians is reliable and harmonises with modern assessments for the ailments investigated.

Notwithstanding the small number of exemplars analysed—*Arnica montana* and *Hypericum perforatum*—the results of this thesis imply that clinically orientated historical and contemporary textbooks on the European *materia medica* could be admitted as an empirical evidence source for substantiating traditional plant indications. This thesis proposes the Historical Assessment Tool as a pathway for the systematic collation of bibliographic

evidence for traditional health claims. This would enable tradition-of-use data to be duly incorporated into a comprehensive system of evidence in an evidence-based policy framework and make this body of evidence operational.

## **9.1 Health policy recommendations**

The following key recommendations are drawn from the conclusions of this thesis. The recommendations are to support regulation of traditional plant medicines in New Zealand but may also be relevant for other countries who seek to address regulation on traditional therapeutics.

### **9.1.1 Recommendation to advance regulation on traditional plant medicines**

It is recommended that the New Zealand Government addresses the existing health policy gap in relation to traditional medicine. The analysis of the EU approach to regulation of traditional medicine has found that this area of regulation is complex and so may require the establishment of a dedicated authority that includes subject matter experts on all aspects of traditional medicine, namely its products, practices, and professions. Regarding regulation of traditional plant-based products, health policies should include their empirical evidence base, in particular their traditional indications, their traditional guidelines about conditions of use, and safety aspects in the context of traditional knowledge. This evidence base has been recognised by other regulators (European Parliament, 2004; Health Canada, 2012; Swissmedic, 2018; Therapeutic Goods Agency, 2019). A regulatory framework for long-established plant medicines should be appropriate, feasible, practical, and affordable.

### **9.1.2 Recommendation to define traditional plant medicines**

In line with the EU approach for Traditional Herbal Medicinal Products (THMPs), traditional plant medicines should be defined for regulatory clarity (Europäisches Parlament, 2004). It is recommended that traditional plant medicines are classified and regulated in a separate category, reflecting their distinct features and pharmacological purpose. They have distinctly different characteristics from synthetic pharmaceutical drugs. They also have a distinctly different composition and purpose compared to modern dietary supplements that are administered to address nutritional needs. Based on the EU approach to Traditional Herbal Medicinal Products (THMPs), Appendix 16 suggests a definition for traditional plant medicines and highlights their special characteristics that should be

considered for regulations. The proposed definition is built on the EU definition of THMPs, and provides additional clarifications drawn from extensive analysis of traditional plant medicines. This definition does not include other traditional, non-herbal remedies, modern natural health products, or dietary supplements.

### **9.1.3 Recommendation to implement a systematic framework for data collection of bibliographic empirical evidence**

Based on advice of the Ministerial Advisory Committee on Complementary and Alternative Health (2004) systematic systems for the collation of evidence on CAM interventions have previously been used in New Zealand to provide assistance for regulatory frameworks and health policy processes. New Zealand Health Technology Assessment (NZHTA), operating from 1997 to 2007, and the New Zealand Centre for Evidence-based Research into Complementary and Alternative Medicine (ENZCAM), operating from 2005 to 2013, produced university based and independent evidence summaries on natural medicine interventions<sup>10</sup>. With a re-establishment of funding, such centres could be contracted to assist the collation of evidence on traditional plant medicines used by consumers in New Zealand.

As a future structure for data collection and evaluation, the Historical Assessment Tool has been developed to summarily and methodically collate bibliographic traditional-use-evidence of inter-generational clinical knowledge on medicinal plants. The systematic process of searching the literature for empirical evidence is similar to the process of undertaking reviews of the best available evidence using PICO (University of Canberra, 2018) or GRADE (Schünemann, Brożek, Guyatt, & Oxman, 2013). This thesis has demonstrated the tool to be feasible, practical and efficient for the corroboration of bibliographic evidence. It is recommended that the tool be admitted by policy makers for submitting evidence on traditional health claims.

However, the selection of appropriate sources is key for the successful implementation of the tool. The following criteria for data collection of empirical evidence are suggested:

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<sup>10</sup> More information about ENZCAM can be found at <http://www.education.canterbury.ac.nz/healthsciences/enzcam/> and <https://web.archive.org/web/20050104140934/http://www.chmeds.ac.nz/enzcam/index.htm>

- 1) selected historical and contemporary textbooks on traditional plant medicines have been authored by formally trained and qualified experts with long-standing clinical experience in patient care
- 2) selected sources reflect authoritative mainstream clinical texts as determined by their use in professional education, or proof of multiple print editions, or peer recognition via citations by other authoritative authors
- 3) selected sources triangulate independent textbooks at data points about 25 years apart to capture clinical use data for each successive generation of formally trained clinicians
- 4) selected sources represent a minimum dataset in order to comprehensively cover long-standing traditional uses (see Appendix 17 for a template to assist the organisation of these data)
- 5) specific data are collated so that a bibliographic source is admissible. Most importantly, it is a prerequisite for the admission of tradition-of-use data that a medicinal plant is unequivocally identified in the written source (see Appendix 17).

To ensure that the bibliographic data collection on traditional plant medicines meets the policy criteria of feasibility, practicality, and affordability, this thesis recommends that future work need not require as extensive a period as investigated herein to collate data. Results from evaluating exemplars of the German language *materia medica* highlighted that a foundational historical medical textbook from the early modern period, together with authoritative clinical textbooks on phytotherapy from the turn of the 20<sup>th</sup> century onwards, comprehensively cover long-standing traditional uses.

It is suggested that the following authors (listed below) are used as sources of bibliographic evidence for the German language *materia medica*. These clinical textbooks are not the only bibliographic evidence sources on the European *materia medica* that fulfil the proposed selection criteria; rather, they are suggestions of validated options. Each medical tradition would need to agree on its own body of authoritative textbooks that represent regular applications of their traditional medicines. Since the Historical Assessment Tools is only suitable for written traditions, the development of a data gathering framework for oral traditions, for example Rongoā Māori, would require separate and appropriate consideration.

Author	Reason for selection
Tabernaemontanus (1664) and re-prints to this edition (last released in 1731)	Practising physician and enduring influential medical author of the early modern period
Schulz (1919)	Practising pharmacologist and university lecturer; evaluated traditional <i>materia medica</i> from a scientific viewpoint in conjunction with clinical use
Madaus 1938a, 1938b, 1938c	Practising physician; evaluated traditional <i>materia medica</i> based on traditional uses in conjunction with contemporaneous clinical uses and scientific studies; remains in print
Weiss (1985)	Practising physician and post-graduate education lecturer; 1985 edition remains in print.
Saller et al. (1995)	Practising physicians and pharmacists covering expertise in plant medicine, pharmacology, and pharmacy; university lecturers.

It is recommended that regulators approve a traditional indication as a health claim on the basis of traditional evidence if systematic collation of data from authoritative sources demonstrates that the indication meets one of the following two conditions: first, that a traditional plant indication has been consistently recommended over at least two transmission steps (three independent clinically oriented evidence sources); or second, that a traditional indication was intermittently recommended and is clinically plausible today based on contemporary phytotherapeutic use, clinical trials, or relevant experimental research.

## 9.2 Recommendation on safety aspects of traditional plant medicines

It is recommended that regulatory safety assessments of traditional plant medicines relate to their actual clinical uses, traditional types of preparations, and dosage range because historical safety information only relates to these specifications. It becomes problematic if regulatory risk assessments relate to different types of preparations or to synthetic analogues of plant substances. Traditional whole plant preparations have different effects to synthetic isolates and therefore different safety parameters. Similarly, *in vitro* studies need to be carefully analysed for their relevance for traditional *in vivo* applications. It is further suggested that the comparison of the benefits and risks between a plant-based and synthetic drug treatment option is considered in overall regulatory safety assessments.

It is recommended that regulatory safety assessments evaluate history-of-safe-use (innocuousness) in conjunction with modern pharmacovigilance data recorded by national

and international databases (e.g. CARM, WHO) in order to meet requirements of a contemporary evidence-based healthcare system (Abel et al., 2012). Traditional plant medicines permitted as OTC therapeutics should not exceed low to medium risk when used correctly. In line with an approach to protect public health, it is further recommended that manufacturers of traditional plant medicines are subject to reporting obligations for adverse reactions of their products.

It is further recommended that a special practitioner-only category be created for medicinal plants (in their whole-plant format) that are not suitable as OTC remedies but are required by herbal experts in clinical practice. Practitioner access to these stronger traditional therapeutics would help preserve the integrity of traditional systems of medicine. In New Zealand, Schedule 1 of the Medicines Regulations currently prevents registered Medical Herbalists and Tohunga from legally accessing these traditional plant medicines. They are regulated as pharmaceutical substances in conjunction with their synthetic isolates, regardless of their distinctly different risk profiles. The creation of a practitioner-only category would address the misappropriation of medicinal plants and provide a legislative framework to put them back into traditional context. As such, Medical Herbalists should be prioritised for statutory regulation to optimise the accessible delivery of safe and effective traditional medicines for patients, while supporting such traditional treatment options in a system of medical pluralism (Hirschorn, 2005; Ijaz & Boon, 2018; World Health Organization, 2013).

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## APPENDIX 1: DATABASE RESEARCH STRATEGIES

Database search strategies for literature on history of plant medicine and traditional knowledge (TK)

**Database: Embase <1974 to 2013 May 01>**

Search Strategy:

- 1 Tabernaemontanus.af. (6)
- 2 traditional medicine/ or herbal medicine/ (30160)
- 3 ((folk or traditional) adj3 (medicine or remed\* or herbal)).tw. (26424)
- 4 materia medica/ (1220)
- 5 Traditional knowledge.tw. (509)
- 6 Ethnopharmacology/ (1373)
- 7 Ethnobotany/ (1101)
- 8 Pharmacognosy/ (1771)
- 9 Plant preparations/ (7691)
- 10 Phytotherapy/ (14765)
- 11 plants, medicinal/ (62512)
- 12 (Western adj3 (herbal\* or phytotherapy)).tw. (135)
- 13 or/2-12 (120805)
- 14 exp Europe/ (1156936)
- 15 "history of medicine"/ (44881)
- 16 history/ (282713)
- 17 century.tw. (68191)
- 18 paradigm.tw. (72656)
- 19 Chinese medicine/ (20875)
- 20 Chinese.tw. (134054)
- 21 homeopathy/ (8139)
- 22 homoeopath\*.tw. (985)
- 23 Ayurveda.tw. (1434)
- 24 19 or 20 or 21 or 22 or 23 (151449)
- 25 15 or 16 or 17 or 18 (429884)
- 26 13 and 14 and 25 (1421)
- 27 26 not 24 (1345)
- 28 1 or 27 (1350)

\*\*\*\*\*

**Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to Present with Daily Update**

Search Strategy:

- 1 Tabernaemontanus.af. (3)
- 2 Medicine, Traditional/ (8200)
- 3 ethnobotany/ or pharmacognosy/ or herbal medicine/ (2925)
- 4 Materia Medica/ (1579)
- 5 Ethnopharmacology/ (515)
- 6 plant preparations/ (5961)
- 7 phytotherapy/ or eclecticism, historical/ (26841)
- 8 Plants, Medicinal/ (50342)
- 9 ((folk or traditional) adj2 (medicine or remed\* or herbal)).tw. (15145)
- 10 (Western adj2 (herbal\* or phytotherapy)).tw. (47)
- 11 Traditional knowledge.tw. (316)
- 12 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (93680)
- 13 exp Europe/ (1050915)
- 14 history/ or "history of medicine"/ (46296)
- 15 century.tw. (53810)
- 16 paradigm.tw. (56149)
- 17 or/14-16 (154736)
- 18 12 and 13 and 17 (335)
- 19 Drugs, Chinese Herbal/ or Medicine, Chinese Traditional/ or Acupuncture Therapy/ or Medicine, East Asian Traditional/ (44415)
- 20 Chinese.tw. (95121)
- 21 homeopathy/ or mesotherapy/ or mind-body therapies/ or reflexotherapy/ or rejuvenation/ or sensory art therapies/ or speleotherapy/ or spiritual therapies/ (6727)
- 22 homoeopath\*.tw. (610)
- 23 medicine, ayurvedic/ or medicine, east asian traditional/ or shamanism/ (5051)
- 24 19 or 20 or 21 or 22 or 23 (134057)
- 25 18 not 24 (321)

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Database search strategy for Arnica (*Arnica montana*) to cross-validate empirical evidence with contemporary clinical research

**Arnica in database: Embase <1974 to 2014 June 20>**

Search Strategy:

- 1 Arnica montana/ or Arnica/ or Arnica montana extract/ (616)
  - 2 arnica.tw. (425)
  - 3 1 or 2 (756)
  - 4 meta analysis/ (69811)
  - 5 ((meta adj analy\$) or metaanalys\$.tw. (66246)
  - 6 (systematic adj (review\$ or overview\$)).tw. (51546)
  - 7 clinical trial/ (880742)
  - 8 Randomized controlled trial/ (341721)
  - 9 Clinical study/ (90524)
  - 10 Longitudinal study/ (59078)
  - 11 Retrospective study/ (311872)
  - 12 Prospective study/ (228817)
  - 13 Cohort study/ (142723)
  - 14 or/4-13 (1673812)
  - 15 3 and 14 (132)
  - 16 exp history/ or "history of medicine"/ (310826)
  - 17 3 and 16 (9)
  - 18 to.fs. (450593)
  - 19 pd.fs. (1892437)
  - 20 18 or 19 (2242080)
  - 21 3 and 20 (170)
  - 22 15 or 17 or 21 (271)
- \*\*\*\*\*

**Arnica in database: Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) <1946 to June 2014>**

Search Strategy:

- 1 Arnica/ (138)
  - 2 arnica montana.tw. (124)
  - 3 arnica.tw. (275)
  - 4 1 or 2 or 3 (296)
- \*\*\*\*\*

**And so on for:**

Amed, Cochrane Library, Web of Science, CINAHL

Database search strategy for St. John's Wort (*Hypericum perforatum*) to cross-validate empirical evidence with contemporary clinical research

**St. John's Wort in database: Embase <1974 to 2014 June>**

Search Strategy:

- 1 Hypericum perforatum/ (2324)
- 2 St John's Wort.tw. (1956)
- 3 Hypericum perforatum extract/ (3194)
- 4 1 or 2 or 3 (5112)
- 5 meta analysis/ (70589)
- 6 ((meta adj analy\$) or metaanalys\$.tw. (67373)
- 7 (systematic adj (review\$ or overview\$)).tw. (52592)
- 8 clinical trial/ (881449)
- 9 Randomized controlled trial/ (343904)
- 10 Clinical study/ (91065)
- 11 Longitudinal study/ (59775)
- 12 Retrospective study/ (316001)
- 13 Prospective study/ (231918)
- 14 Cohort study/ (145124)
- 15 case control.tw. (83763)
- 16 longitudinal.tw. (154223)
- 17 retrospective.tw. (341171)
- 18 observational.tw. (89883)
- 19 or/5-18 (2041463)
- 20 4 and 19 (1372)
- 21 exp history/ or "history of medicine"/ (311305)
- 22 4 and 21 (35)
- 23 Hypericum perforatum/to, pd [Drug Toxicity, Pharmacology] (164)
- 24 23 or 22 or 20 (1514)
- 25 letter.pt. (821333)
- 26 24 not 25 (1482)

\*\*\*\*\*

**St. John's Wort in database: Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) <1946 to June 2014>**

Search Strategy:

- 1 Hypericum/ (1625)
- 2 St John's Wort.tw. (1355)
- 3 1 or 2 (2119)
- 4 Meta-Analysis as Topic/ (12527)
- 5 meta analy\$.tw. (49637)
- 6 metaanaly\$.tw. (1213)
- 7 Meta-Analysis/ (38469)
- 8 (systematic adj (review\$ or overview\$)).tw. (41815)
- 9 exp Review Literature as Topic/ (6609)
- 10 Randomized controlled trial/ (344493)
- 11 Randomized controlled trials as topic/ (84173)
- 12 exp clinical trial/ (708782)
- 13 controlled clinical trial.pt. (85528)
- 14 Randomized controlled trial.pt. (344493)
- 15 multicenter study.pt. (153386)
- 16 Clinical trial.pt. (475515)
- 17 epidemiologic studies/ (5601)
- 18 exp case control studies/ (591698)
- 19 exp cohort studies/ (1237501)
- 20 case control.tw. (68374)
- 21 longitudinal.tw. (125516)
- 22 retrospective.tw. (242806)
- 23 observational.tw. (63831)
- 24 or/4-23 (2175900)
- 25 3 and 24 (366)
- 26 exp history/ (330847)
- 27 exp history of medicine/ (16302)
- 28 hi.fs. (255045)
- 29 td.fs. (262841)
- 30 26 or 27 or 28 or 29 (592411)
- 31 3 and 30 (31)
- 32 exp Pharmacology/ (142441)
- 33 3 and 32 (58)
- 34 25 or 31 or 33 (434)

\*\*\*\*\*

**And so on for:**

Amed, Cochrane Library, Web of Science, CINAHL

## APPENDIX 2: PHARMACOPOEIAS, COMMENTARIES, MONOGRAPHS, MEDICAL TEXTBOOKS, HAGER: PRELIMINARY AND FINAL SELECTION

### Pharmacopoeias and commentaries

Notes	Title	Edition	Reference
<b>Prussia – Pharmacopoeia Borussica</b>			
Forerunner of <i>Pharmacopoea Germanica</i> , the official pharmacopoeia of the unified German Reich (1871-1945) and succeeding <i>Pharmacopoea Germanica</i> / Deutsches Arzneibuch of Germany	Pharmacopoea Borussica	1799	<b>Arnica</b> Flores: 21 Herba: 29 Radix: 49 Extractum Arnicae e toto: 100  <b>St. John's Wort</b> Herba: 32 Oleum: 123 Unguentum Terebinthinae (unguentum digestivum): 165
	Pharmacopoea Borussica	1804 2. ed.	Not found
	Pharmacopoea Borussica  Pharmacopoea Borussica. Die Preussische Pharmakopoea, übersetzt und erläutert von Friedrich Philipp Dulk.  <i>Professor Dr. Dulk was apothecary and pharmaceutical lecturer at Albertus University, Königsberg (East Prussia)</i>	1804 2. ed.  Commentary 1808 reprinted 1833  Assumed to comment on 2nd edition of <i>Ph. Borussica</i>	<b>Arnica</b> Flores: 103-106 Herba: 106 Radix: 106-107  <b>St. John's Wort</b> Herba: 558-559 Oleum: 559
	Pharmacopoea Borussica  Pharmacopoea Borussica. Die Preussische Pharmakopoea, übersetzt und erläutert von Friedrich Philipp Dulk.  <i>Professor Dr. Dulk was apothecary and pharmaceutical lecturer at Albertus University, Königsberg (East Prussia)</i>	1808 2. ed. Vol. 2  reprinted 1833  Commentary  Assumed to comment on 2nd edition of <i>Ph. Borussica</i>	<b>Arnica</b> Extractum (radicis): 377
	Pharmacopoea Borussica	1813 3. ed.	<b>Arnica</b> Flores: 25 Herba: 35  <b>St. John's Wort</b> Herba: 40

Notes	Title	Edition	Reference
	Pharmacopoea Borussica. Die Preussische Pharmakopoea, übersetzt und erläutert von Carl Wilhelm Juch.  <i>Professor Dr. Carl Wilhelm Juch was a Bavarian "Hofrat" and Professor of Chemistry, Natural History and Nutrition at the Hohe Schule in München.</i>	1813 3. ed.  Commentary 1817  3. expanded and improved edition	<b>Arnica</b> Extractum (e toto): 246  <b>St. John's Wort</b> Oleum coctum hyperici: 316-317
	Pharmacopoea Borussica. Die Preussische Pharmakopoea, übersetzt und erläutert von Friedrich Philipp Dulk  <i>Professor Dr. Dulk was apothecary and pharmaceutical lecturer at Albertus University, Königsberg (East Prussia)</i>	1813 3. ed.  Commentary 1833  3. expanded and improved edition	<b>Arnica</b> Flores: 109-112 Herba: 112 (Wurzelblätter im Mai) Radix: 112  <b>St. John's Wort</b> Herba: 567-568 Oleum: 568
	Pharmacopoea Borussica	1827 4. ed.	<b>Arnica</b> Flores: 15 Herba: 16 Radix: 16 Extractum (radicis): 165 Tinctura (flores): 244  <b>St. John's Wort</b> Herba: 268-269 Oleum: 304 – adulteration with Arkanna root officially recommended!
	Pharmacopoea Borussica. Die Preussische Pharmakopoea, übersetzt und erläutert von Friedrich Philipp Dulk  <i>Professor Dr. Dulk was apothecary and pharmaceutical lecturer at Albertus University, Königsberg (East Prussia)</i>	1827 4. ed.  Commentary 1828  Vol. 1 (einfache Mittel)	<b>Arnica</b> Flores: 89-92 Herba: 92 Radix: 92-94  <b>St. John's Wort</b> Herba: 488, 907 Oleum: 488
	Pharmacopoea Borussica. Die Preussische Pharmakopoea, übersetzt und erläutert von Friedrich Philipp Dulk  <i>Professor Dr. Dulk was apothecary and pharmaceutical lecturer at Albertus University, Königsberg (East Prussia)</i>	1827 4. ed.  Commentary 1828  Vol. 2 (zubereitete und zusammengesetzte)	No entries for <i>Arnica montana</i> and <i>Hypericum perforatum</i>

Notes	Title	Edition	Reference
	<p>Pharmacopoea Borussica oder Preussische Pharmakopoe. Lateinisch und deutsch mit Anmerkungen und Zusätzen. Vierte, völlig umgearbeitete Auflage.</p> <p>Carl Wilhelm Juch Wilhelm Raab</p> <p><i>Professor Dr. Carl Wilhelm Juch was a Bavarian "Hofrat" and Professor of Chemistry, Natural History and Nutrition at the Hohe Schule in München.</i></p> <p><i>Mr Raab was apothecary in Bayreuth.</i></p> <p><i>Further comments were made by apothecary Trautwein, Nürnberg.</i></p>	<p>1827 4. ed.</p> <p>Commentary 1830</p>	<p>The translation of the 4<sup>th</sup> edition of the <i>Ph. Borussica</i> does not add further information. Therefore, this edition was not entered into the Historical Data excel spreadsheet</p>
	<p>Preussische Pharmakopöe. Übersetzung aus der lateinischen Urschrift von H. Straberoh.</p> <p><i>H. Straberoh was a pharamcist.</i></p>	<p>1829 5. ed.</p>	<p><b>Arnica</b> Flores: 16 Herba: 16 Radix: 17</p> <p><b>St. John's Wort</b> Herba: 277-278 Oleum: listed in commentary Dulk</p>
	<p>Pharmacopoea Borussica. Die Preussische Pharmakopoea, übersetzt und erläutert von Friedrich Philipp Dulk</p> <p><i>Professor Dr. Dulk was apothecary and pharmaceutical lecturer at Albertus University, Königsberg (East Prussia)</i></p>	<p>1829 5.ed.</p> <p>Commentary Vol. 1, 1847</p>	<p><b>Arnica</b> Flores: 716-718</p>
		<p>1829 5.ed.</p> <p>Commentary Vol. 2, 1848</p>	<p><b>St. John's Wort</b> Herba: 46-47 Oleum: 47</p>
	<p>Preussische Pharmakopöe. Nach der sechsten Ausgabe der Pharmacopoea Borussica übersetzt von Professor Dr. Gurlt</p> <p><i>Professor Dr. Ernst Julius Gurlt was a surgeon and associate professor at the University of Berlin.</i></p>	<p>1847 6. ed.</p> <p>(1846 first official print)</p>	<p><b>Arnica</b> Flores: 94 Herba: not listed Radix: 188 Tinctura: 244-246</p> <p><b>St. John's Wort</b> Herba: not listed Oleum: not listed</p>
	<p>Commentar zur Preußischen Pharmacopoe nebst Übersetzung des Textes. Nach der sechsten Auflage der Pharmacopoea Borussica bearbeitet von Dr. Friedrich Mohr für Apotheker, Aerzte und Medicinal-Beamte.</p> <p><i>Dr. Mohr was an apothecary and pharmaceutical assessor at the Royal Prussian Medical Association ("Königliches Preussisches Medicinal=Collegium)</i></p>	<p>1847 6. ed.</p> <p>Commentary Vol. 1, 1848</p>	<p><b>Arnica</b> Flores: 443</p> <p><b>St. John's Wort</b> Not listed</p>

Notes	Title	Edition	Reference
		1847 6. ed.  Commentary Vol. 2, 1849	<b>Arnica</b> Radix: 245 Tinctura: 411 (made with flowers)
	Preussische Pharmakopöe. Pharmacopoea Borussica. Siebente Ausgabe.	1862 7. ed.	<b>Arnica</b> Flores: 80  <b>St. John's Wort</b> Not listed
	Friedrich Mohr Commentar zur preussischen Pharmacopoe nebst Übersetzung des Textes. Dritte umgearbeitete Auflage.  <i>Dr. Mohr was an apothecary and pharmaceutical assessor at the Royal Prussian Medical Association ("Königliches Preussisches Medicinal=Collegium)</i>  <i>Very short – no added insights</i>	1862 7. ed.  Commentary 1863	<b>Arnica</b> Flores: 281  <b>St. John's Wort</b> Not listed
	Hermann Hager Kommentar zu der siebenten Ausgabe der Pharmacopoea Borussica mit besonderer Berücksichtigung der neusten Pharmakopöen des Königreichs Hannover und des Kurfürstenthums Hessen.  <i>Dr. Hermann Hager, was a Prussian apothecary, pharmacist, chemist, pharmacologist and writer of pharmaceutical commentaries and textbooks.</i>	1862 7. ed.  Commentary 1865	<b>Arnica</b> Flores: 691-692 (re Arnica fly/irritating hair on leaves)  Further: Extractum Arnicae Florum: 582 (Ph. Hann.) Extractum Arnicae radicis: 582-583 (Ph. Hann et Ph. Hass.) Radix: 1133-1134 (Ph. Hann et Ph. Hass.)  <b>St. John's Wort</b> Not listed
<b>Germany – Pharmacopoeia Germanica</b>			
Provisional pharmacopoeia in preparation of the unification of the German Reich	Pharmacopoea Germaniae	1865	<b>Arnica</b> 110, 224, 289  <b>St. John's Wort</b> Not listed
Official pharmacopoeias of the unified German Reich (1871-1945) and subsequent Pharmacopoea Germanica / Deutsches Arzneibuch (DAB)	Pharmacopoeia Germanica.  Übersetzt von Hermann Hager	1872 1. ed.	<b>Arnica</b> Flores: 146 Radix: 278-279 Tinctura flori: 350  <b>St. John's Wort</b> Not listed

Notes	Title	Edition	Reference
	<p>Commentar zur Pharmacopoea Germanica.</p> <p>Herausgegeben von Dr. Hermann Hager</p> <p><i>Dr. Hermann Hager, was a Prussian apothecary, pharmacist, chemist, pharmacologist and writer of pharmaceutical commentaries and textbooks.</i></p>	<p>1872 1. ed.</p> <p>Commentary Vol. 1, 1874</p>	<p><b>Arnica</b> Not listed</p> <p><b>St. John's Wort</b> Not listed</p>
		<p>1872 1. ed.</p> <p>Commentary Vol. 2, 1874</p>	<p><b>Arnica</b> Flores:21-22 Radix: 565-566 Tinctura: 789</p> <p><b>St. John's Wort</b> Not listed</p>
	<p>Commentar zur Pharmacopoea Germanica.</p> <p>Professor Dr. Ludwig Andreas Buchner und Professor Dr. Herman von Boeck.</p> <p><i>Professor Dr. Buchner was a physician, professor of pharmacy and doctor of philosophy</i></p> <p><i>Professor Dr. von Boeck was a professor of pharmacology</i></p>	<p>1872 1. ed.</p> <p>Commentary Vol. 1, 1878</p>	<p><b>Arnica</b> Not listed</p> <p><b>St. John's Wort</b> Not listed</p>
	<p>Commentar zur Pharmacopoea Germanica.</p> <p>Professor Dr. Ludwig Andreas Buchner und Professor Dr. Herman von Boeck.</p> <p><i>Professor Dr. Buchner was a physician, professor of pharmacy and doctor of philosophy</i></p> <p><i>Professor Dr. von Boeck was a professor of pharmacology</i></p>	<p>1872 1. ed.</p> <p>Commentary Vol. 2, 1884</p>	<p><b>Arnica</b> Radix: 530-532 (prevalence of Arnica popular in folk medicine but less so now with physicians)</p> <p><b>St. John's Wort</b> Not listed</p>
	<p>Pharmacopoea Germanica. Editio altera. Deutscher, der lateinischen Ausgabe zu Grunde liegender Entwurf</p>	<p>1882 2. ed.</p>	<p><b>Arnica</b> Flores: 107-108 Radix: not listed anymore for first time. Consequently, not listed in commentaries either Tinctura: 272 <b>St. John's Wort</b> Not listed</p>
	<p>Commentar zur Pharmacopoea Germanica. Herausgegeben von Dr. Hermann Hager</p> <p><i>Dr. Hermann Hager, was a Prussian apothecary, pharmacist, chemist, pharmacologist and writer of pharmaceutical commentaries and textbooks.</i></p>	<p>1882 2. ed.</p> <p>Commentary Vol. 1, 1883</p>	<p><b>Arnica</b> Flores: 750-752</p> <p><b>St. John's Wort</b> Not listed</p>
	<p>Commentar zur Pharmacopoea Germanica. Herausgegeben von Dr. Hermann Hager</p> <p><i>Dr. Hermann Hager, was a Prussian apothecary, pharmacist, chemist,</i></p>	<p>1882 2. ed.</p> <p>Commentary Vol. 2, 1884</p>	<p><b>Arnica</b> Tinctura: 706</p> <p><b>St. John's Wort</b> Not listed</p>

Notes	Title	Edition	Reference
	<i>pharmacologist and writer of pharmaceutical commentaries and textbooks.</i>		
	Kommentar zur zweiten Auflage der Pharmacopoea Germanica.  <i>O. Schlickum was a German apothecary and writer of pharmaceutical commentaries and textbooks</i>	1882 2. ed.  Commentary 1883	<b>Arnica</b> Flores: 178-179 Tinctura: 468  <b>St. John's Wort</b> Not listed
	Arzneibuch für das Deutsche Reich. Dritte Ausgabe.	1890 3. ed.	<b>Arnica</b> Flores: 125 Tinctura: 307  <b>St. John's Wort</b> Not listed
	Commentar zum Arzneibuch für das Deutsche Reich (Pharmacopoea Germanica, editio III.) : mit vergleichender Berücksichtigung der früheren deutschen u.a. Pharmakopöen von Dr. Bruno Hirsch und Dr. Alfred Schneider  <i>Dr. B. Hirsch was apothecary in Berlin and Dr. A. Schneider was military apothecary („Korps-Stabsapotheker“) in Dresden</i>	1890 3. ed.  Commentary 1891	<b>Arnica</b> Flores: 306 <i>(Blütenböden und Hüllkelch sollten mitverwendet werden (=gleicher Geruch und Geschmack = gleiche Inhaltsstoffe wie Blüten)</i> Flores Arnicae cum receptaculis (calicibus) Tinctura: 650 keine Änderungen  <b>St. John's Wort</b> Not listed
	Kommentar zum Arzneibuch für das Deutsche Reich, Dritte Ausgabe (Pharmacopoea Germanica, editio III.). Herausgegeben von H. Hager, B. Fischer und C. Hartwich.  <i>Drs. H. Hager, H. (Frankfurt am Main), B. Fischer (Breslau), C. Hartwich (Zürich) were apothecaries and writers of pharmaceutical commentaries and textbooks</i>	1890 3. ed.  Commentary  Vol. 1, 1891	<b>Arnica</b> Flores: 635, 662-664,  <b>St. John's Wort</b> Not listed <i>(“Johannisblume“ referred to Arnica not to St. John's Wort)</i>
		1890 3.ed.  Commentary Vol.2, 1892	<b>Arnica</b> Flores: 635  <b>St. John's Wort</b> Not listed
	Arzneimittel, welche in dem Arzneibuch für das Deutsche Reich, 3. Ausg., (Pharmacopoea Germania, editio 3) nicht enthalten sind. Deutscher Apotheker-Verein.  Supplement complementing the official <i>Ph. Germanica</i> . Not a commentary and no indications of use.	1891  1. Supplement to Ph. Ger. 3	<b>Arnica</b> Charta: 57 Rhizoma: 219 <i>Not listed under poison</i>  <b>St. John's Wort</b> Herba: 145 <i>Not listed under poison</i>
	Arzneimittel, welche in dem Arzneibuch für das Deutsche Reich, 3. Ausg., (Pharmacopoea Germania, editio 3), Neudruck 1895 nicht enthalten sind. Deutscher Apotheker-Verein.  Supplement complementing the <i>Ph. Germanica</i> . Not a commentary and no indications of use.	1897  2. Supplement to Ph. Ger. 3	<b>Arnica</b> Charta: 62 Rhizoma: 250 <i>Not listed under poison</i>  <b>St. John's Wort</b> Herba: 160 <i>Not listed under poison</i>

Notes	Title	Edition	Reference
	Arzneibuch für das Deutsche Reich. Vierte Ausgabe.	1900 4. ed.	<b>Arnica</b> Flores: 160-161 Tinctura: 371-372  <b>St. John's Wort</b> Not listed
	Kommentar zum Arzneibuch für das Deutsche Reich, 4. Ausgabe (Pharmacopoea Germanica, editio IV.): Ergänzungsband zum Kommentar für die III. Ausgabe des Arzneibuchs, enthaltend Nachträge und die Veränderungen der IV. Ausgabe des Arzneibuchs, herausgegeben von B. Fischer und C. Hartwich.  Drs. B. Fischer (Breslau) and C. Hartwich (Zürich) were apothecaries and writers of pharmaceutical commentaries and textbooks	1900 4. ed.  Commentary 1901	<b>Arnica</b> Flores: 127-128 Tinctura: 283  <b>St. John's Wort</b> Not listed
	Kommentar zum Arzneibuch für das Deutsche Reich. Mit Zugrundelegung des amtlichen Textes, sowie einer Anleitung zur Massanalyse im Anschluss an den Schlickumschen Kommentar. Bearbeitet von Dr. C Jehn und Dr. E. Crato. Dr. Jehn and Crato were both German apothecary	1900 4. ed.  Commentary 1901	<b>Arnica</b> Flores: 290-291 Tinctura: 676  <b>St. John's Wort</b> Not listed
	Handkommentar zum Arzneibuch für das Deutsche Reich, vierte Ausgabe , Pharmacopoea Germanica, editio IV. 3. Auflage des Hirsch'Schneider'schen Kommentars zum Deutschen Arzneibuch. Mit vergleichender Berücksichtigung der früheren deutschen und anderen Pharmakopöen bearbeitet von Dr. Alfred Schneider und Dr. Paul Süß.  <i>Dr. A. Schneider was military apothecary („Korps-Stabsapotheker“) and Dr. P. Süß was apothecary and Assistant at the „Hygienisches Institut der Technischen Hochschule“</i>	1900 4. ed.  Commentary 1902	<b>Arnica</b> Flores: 421-422 Tinctura: 965-966  <b>St. John's Wort</b> Not listed
	Ergänzungsbuch zum Arzneibuch für das Deutsche Reich. (Arzneimittel, welche in dem Arzneibuch für das Deutsche Reich nicht enthalten sind). Dritte Ausgabe.  Deutscher Apotheker-Verein (editor).	1906  3. Supplement to Ph. Ger.	<b>Arnica</b> Charta: 63 Rhizoma: 300  <b>St. John's Wort</b> Herba: 182
	Arzneibuch für das Deutsche Reich. 5. Ausgabe.	1910 5. ed.	<b>Arnica</b> Flores: 217 Tinctura: 519  <b>St. John's Wort</b> Not listed

Notes	Title	Edition	Reference
	Kommentar zum Deutschen Arzneibuch. 5. Ausgabe 1910. Auf Grundlage der Hager-Fischer-Hartwichschen Kommentare der früheren Arzneibücher in 2 Bänden. Herausgegeben von Dr. O. Anselmino und Dr. Ernst Gilg.  <i>Dr. O. Anselmino was private lecturer at the University of Greifswald and Dr. E. Gilg was professor of botany and pharmacognosy at the University of Berlin and „Kustos“ at the „Königliches Botanisches Museum“ in Berlin</i>	1910 5. ed.  Commentary Vol. 1, 1911	<b>Arnica</b> Flores: 537-539  <b>St. John's Wort</b> Not listed
	Kommentar zum Deutschen Arzneibuch. 5. Ausgabe 1910. Auf Grundlage der Hager-Fischer-Hartwichschen Kommentare der früheren Arzneibücher in 2 Bänden. Herausgegeben von Dr. O. Anselmino und Dr. Ernst Gilg.  <i>Dr. O. Anselmino was private lecturer at the University of Greifswald and Dr. E. Gilg was professor of botany and pharmacognosy at the University of Berlin and „Kustos“ at the „Königliches Botanisches Museum“ in Berlin</i>	1910 5. ed.  Commentary Vol. 2, 1911	<b>Arnica</b> Tinctura: 464  <b>St. John's Wort</b> Not listed
	Ergänzungsbuch zum Arzneibuch für das Deutsche Reich. (Arzneimittel, welche in dem Arzneibuch für das Deutsche Reich nicht enthalten sind). Vierte Ausgabe.  Deutscher Apotheker-Verein.	1916  4 <sup>th</sup> Supplement to Ph. Ger.	<b>Arnica</b> Rhizoma: 325-326  <b>St. John's Wort</b> Herba: 194
	Arzneibuch für das Deutsche Reich. 6. Ausgabe.  <i>With index for first time!</i>	1926 DAB 6	<b>Arnica</b> Flores: 259-260 Tinctura: 692  <b>St. John's Wort</b> Not listed
	Arzneibuch für das Deutsche Reich. 6. Ausgabe.  <i>With index for first time!</i>	1926 DAB 6 Reprint and Addendum 1947	<b>Arnica</b> Flores: 137-138 Tinctura: 370  <b>St. John's Wort</b> Not listed
	Kommentar zum Deutschen Arzneibuch 6. Ausgabe, Erster Band, 1926. Herausgegeben von Dr. O. Anselmino und Dr. Ernst Gilg.  <i>Dr. O. Anselmino was private lecturer at the University of Greifswald and Dr. E. Gilg was professor of botany and pharmacognosy at the University of Berlin and „Kustos“ at the „Königliches Botanisches Museum“ in Berlin</i>	1926 DAB 6  Commentary Vol. 1, 1928	<b>Arnica</b> Flores: 604-607  <b>St. John's Wort</b> Not listed

Notes	Title	Edition	Reference
	Kommentar zum Deutschen Arzneibuch 6. Ausgabe, Zweiter Band, 1926. Herausgegeben von Dr. O. Anselmino und Dr. Ernst Gilg.  <i>Dr. O. Anselmino was private lecturer at the University of Greifswald and Dr. E. Gilg was professor of botany and pharmacognosy at the University of Berlin and „Kustos“ at the „Königliches Botanisches Museum“ in Berlin</i>	1926 DAB 6  Commentary Vol. 2, 1928	<b>Arnica</b> Tinctura: 596-597  <b>St. John's Wort</b> Not listed
	Ergänzungsbuch zum Deutschen Arzneibuch (Arzneimittel, die im Deutschen Arzneibuch nicht enthalten sind). Fünfte Ausgabe (Erg.-B. 5).  Deutscher Apotheker-Verein (editor)	1930  5 <sup>th</sup> Supplement to DAB	<b>Arnica</b> Radix: 363-364  <b>St. John's Wort</b> Herba: 225
	Ergänzungsbuch zum Deutschen Arzneibuch (Arzneimittel, die im Deutschen Arzneibuch nicht enthalten sind). Sechste Ausgabe (Erg.-B. 6)  Deutscher Apotheker-Verein (editor)	1948  6 <sup>th</sup> Supplement to DAB  Reprint of first edition from 1941	<b>Arnica</b> Tinctura destillata: 482 Radix: discontinued  <b>St. John's Wort</b> Flores recentes: 170 (new) Herba: 254-255 Oleum: 366-367 (new)
	Deutsches Arzneibuch. 7. Ausgabe	1968 DAB 7	<b>Arnica</b> Flores (summitates): 343-345 (not <i>flores</i> anymore) Tinctura: 346  <b>St John's Wort</b> Not listed
	Deutsches Arzneibuch. 7. Ausgabe. Kommentar von Prof. Dr. Dr. h.c. H. Böhme und Prof. Dr. K. Hartke, Universität Marburg.  <i>Prof. Dr. Horst Böhme was a German pharmacist and chemist and professor of pharmaceutical chemistry and rector at the University of Marburg. Prof. Dr. K. Hartke was a pharmacist</i>	1968 DAB 7  Commentary 1969	<b>Arnica</b> Flores(summitates): 509-512 (not <i>flores</i> anymore) Tinctura: 513  <b>St John's Wort</b> Not listed
	Deutsches Arzneibuch. 8. Ausgabe	1978 DAB 8	<b>Arnica</b> Flores (summitates): 116-118 Tinctura: 119  <b>St John's Wort</b> Not listed
	Deutsches Arzneibuch. 8. Ausgabe. Kommentar. Kommentar von Prof. Dr. Dr. h.c. H. Böhme und Prof. Dr. K. Hartke, Universität Marburg.  <i>Prof. Dr. Horst Böhme was a pharmacist and chemist and professor of pharmaceutical chemistry and rector at the University of Marburg, Germany. Prof. Dr. K. Hartke was a pharmacist and professor at the University of Marburg, Germany.</i>	1978 DAB 8  Commentary 1981  2. ed. 1983 (identical)	<b>Arnica</b> Flores (summitates): 161-165 Tinctura: 166-167  <b>St John's Wort</b> Not listed

Notes	Title	Edition	Reference
	Homöopathisches Arzneibuch	1978 1. Ausgabe  HAB 1	<b>Arnica</b> Radix: 198-201 Flores, herba (summitates): 202-205 Planta tota: 205-210  <b>St. John's Wort</b> Planta tota: 545-546 Flores, herba (summitates): 547-548
	Homöopathisches Arzneibuch	1981 1. Nachtrag	<b>Arnica</b> Radix: 27-30  <b>St. John's Wort</b> No addition
	Homöopathisches Arzneibuch	1983 2. Nachtrag	<b>Arnica</b> Planta tota: 47  <b>St. John's Wort</b> Planta tota: 109-110
	Homöopathisches Arzneibuch	1985 3. Nachtrag	<b>Arnica</b> Flores, herba (summitates): 83-86  <b>St. John's Wort</b> Flores, herba (summitates): 237-238
	Deutsches Arzneibuch. 9. Ausgabe	1986 DAB 9	<b>Arnica</b> Flores: 527-529 Tinctura: 529-530  <b>St. John's Wort</b> Not listed
	DAB 9-Kommentar. Deutsches Arzneibuch, 9. Ausgabe 1986, mit wissenschaftlichen Erläuterungen. Prof. Dr. K. Hartke, Universität Marburg (Gesamtherausgeber) und Prof. Dr. Dr. E. Mutschler (Herausgeber des Pharmakologischen Teils).  <i>Prof. Dr. K. Hartke was a pharmacist and professor at the University of Marburg, Germany. Prof. Dr. Dr. E. Mutschler was a pharmacologist at the University of Frankfurt, Germany.</i>	1986 DAB 9  Commentary Vol. 2., 1986	<b>Arnica</b> Flores: 872-876 Tinctura: 877  <b>St. John's Wort</b> Not listed
	Deutsches Arzneibuch, 10. Ausgabe, 2. Nachtrag	1993 DAB 10	<b>Arnica</b> Flores: A (no page numbers) Tinctura: A (no page numbers)
	DAB 10-Kommentar für Studierende. Wissenschaftliche Erläuterungen zum Deutschen Arzneibuch, 10. Ausgabe 1991 (1993). Prof. Dr. K. Hartke, Universität Marburg (Gesamtherausgeber).  <i>Prof. Dr. K. Hartke was a pharmacist and professor at the University of Marburg, Germany.</i>	1993 DAB 10  Commentary 1993	<b>Arnica</b> Flores: A 54 Tinctura: A 55  <b>St. John's Wort</b> Not listed

Notes	Title	Edition	Reference
	DAB 1999	1999 DAB 1999 (1999-2002)	<b>Arnica</b> Flores: not listed Tinctura: A  <b>St. John's Wort</b> Not listed
	Deutsches Arzneibuch 2012.  <i>Covers the period from 1999-2012.</i>  <i>All regular entries are in Ph. Europea. The regional pharmacopoeiae now only list amendments to these officially binding European entries.</i>	2012 ed. DAB 2012	<b>Arnica</b> No amendments  <b>St. John's Wort</b> No amendments
	DAB 2012 was at the cutoff date for data collection (June 2014) the latest available regional pharmacopoeia. This data was subsequently checked against the two latest <i>Ph. Europea</i> 2014 and 2017.		
<b>European Community (EU) – Pharmacopoeia Europea</b>			
	Europäisches Arzneibuch	2014 8. ed.	<b>Arnica</b> Flores: 1151-1153 Tinctura: 1153  <b>St. John's Wort</b> Herba: 1391-1392 Hyperici herbae extractum siccum quantificatum: 1393-1394
	Europäisches Arzneibuch (englische Ausgabe)	2016 9. ed.	<b>Arnica</b> Flores: 1251-1253 Tinctura: 1253  <b>St. John's Wort</b> Herba: 1526 Hyperici herbae extractum siccum quantificatum: 1527-1529
<b>Switzerland – Pharmacopoeia Helvetica</b>			
Unofficial pharmacopoeia of Switzerland	Pharmacopoea Helvetica  Praefatus est Albertus de Haller  <i>The author, Dr. Albrecht von Haller, was a Swiss physician, anatomist, physiologist, natural scientist and writer of medical textbooks</i>	1771	<b>Arnica</b> 26, 18-19  <b>St. John's Wort</b> (I)85-86  (II) 38, 39, 40, 67, 106-107, 108, 110, 111, 150, 151, 155, 201, 203, 235, 274,-275, 280-281, 306, 315, 334

Notes	Title	Edition	Reference
The first official pharmacopoeia of Switzerland  The Swiss pharmacopoeia was also used as a base for East European pharmacopoeias	Pharmacopoeia Helvetica  Scafhusiae (ex officina Brodtmanniana). No location	1865 1. ed.	<b>Arnica</b> 74, 236  <b>St. John's Wort</b> Not listed  <i>(but exotic medicinal plants such as Ginger, Ipecacuanha, Myrrh, Lobelia are listed)</i>
	Pharmacopoea Helvetica, 1872, Editio Altera.	1872 2. ed.	<b>Arnica</b> Flores: 53 Rhizoma: 111  <b>St. John's Wort</b> Not listed
	Pharmacopoea Helveticae Supplementum.	1876  Supplement of 2. ed.	<b>Arnica</b> Extractum: 40  <b>St. John's Wort</b> Not listed
	Pharmacopoea Helveticae. Editio Tertia	1893 3. ed.	<b>Arnica</b> Flos: 127 Tinctura: 279  <b>St. John's Wort</b> Not listed
	Commentar zur Pharmacopoea Helvetica. Editio Tertia  <i>Dr. Carl Dünninger, Pharmacist</i>	1893 3. ed.  Commentary 1896	<b>Arnica</b> Tinctura: 358  <b>St. John's Wort</b> Not listed
	Pharmacopoea Helveticae. Editio Quarta. Deutsche Ausgabe  <i>Preface explains history of Ph. Helvetica</i>	1907 4. ed.	<b>Arnica</b> Flores: 185 Tinctura: 450  <b>St. John's Wort</b> Not listed
	Kommentar zur Pharmacopoea Helvetica. Editio Quarta.  <i>Dr. Eugen Beuttner (1860 – 1950) was a Swiss apothecary, pharmaceutical author and commentator of the Swiss pharmacopoeia.</i>	1907 4. ed.  Commentary 1909	<b>Arnica</b> Flores: 188 Tinctura: 388  <b>St. John's Wort</b> Not listed
	Pharmacopoea Helvetica. Editio Quinta. Deutsche Ausgabe	1933 5. ed.	<b>Arnica</b> Flores: 389-390 Tinctura: 938  <b>St. John's Wort</b> Not listed

Notes	Title	Edition	Reference
	Kommentar zur Pharmacopoea Helvetica, Editio Quinta.  <i>Prof. Robert Eder, pharmaceutical Chemistry</i>  <i>Prof. Jakob Büchi, pharmaceutical Chemistry and galenical chemistry</i>  <i>Prof. Hans Flück, Pharmacognosy</i>  <i>Hans Käsermann, Chair ,Eidgenössisches Pharmakopöelaboratorium</i>	1933 5. ed.  Commentary 1947	<b>Arnica</b> Flos: 384 Tinctura: 832  <b>St. John's Wort</b> Not listed
	Kommentar zur Pharmacopoea Helvetica, Editio Quinta. Supplemente I und II	1933 5. ed.  Commentary 1956	No comments listed for Arnica and St. John's Wort
	Kommentar zur Pharmacopoea Helvetica, Editio Quinta. Supplement III	1933 5. ed.  Commentary 1963	No comments listed for Arnica and St. John's Wort
	Pharmacopoea Helvetica Editio Sexta. Deutsche Ausgabe.  <i>Edited by Prof. Jakob Büchi, pharmaceutical Chemistry and galenical chemistry</i>	1979 6. ed. Vol. 2	<b>Arnica</b> Flores: 553  <b>St. John's Wort</b> Not listed
		1979 6. ed. Vol. 3	<b>Arnica</b> Tinctura: 613
	Kommentar zur Pharmacopoea Helvetica Editio Sexta  <i>Prof. Jakob Büchi, pharmaceutical Chemistry and galenical chemistry</i>  <i>Prof. Hans Flück, Pharmacognosy</i>  <i>Prof. Hans Mühlemann Galenical pharmacy</i>  <i>Prof. André Mirimanoff Pharmacognosy and galenical pharmacy</i>  <i>Lux Anker Chair ,Eidgenössisches Pharmakopöelaboratorium</i>	1975	<b>Arnica</b> Flores: 375-376 Tinctura: 765  <b>St. John's Wort</b> Not listed
	Pharmacopoea Helvetica Editio Septima. Deutsche Ausgabe. 1995	1991 7. ed. A-C	<b>Arnica</b> Flores: no page number Tinctura: no page number
		1992 D-K	<b>St. John's Wort</b> Herba: no page number - newly listed!
	Pharmacopoea Helvetica 8. Ausgabe	1997 8. ed.	<b>Arnica</b> Flores: 177 Tinctura: 178 Monograph totally revised based on DAB 10  <b>St. John's Wort</b> Herba: 299-300

Notes	Title	Edition	Reference
	Pharmacopoea Helvetica 9. Ausgabe	2003 9. ed.	<b>Arnica</b> Tinctura 161-162 Flores: e1220 – Ph Eur. 4  <b>St. John’s Wort</b> Summitates cum floribus recentes: 259 (for immediate processing into oil) Herba: e2157 - Ph Eur. 4 Oleum: 260
	Pharmacopoea Helveticae 10. Ausgabe	2006 10. ed	<b>Arnica</b> Flores: Ph. Europea 5th ed. e1426 Tinctura: Ph. Europea e5.1 ed. 3836  <b>St. John’s Wort</b> Hyperici sumitates cum floribus recentes: 251 Herba: Ph. Europea 5th ed. 2481 Oleum: 252
	Pharmacopoea Helveticae 11. Ausgabe	2012	<b>Arnica</b> Flores: Ph. Europea 7th ed. e1626 Tinctura: Ph. Europea 7th. ed. 1628  <b>St. John’s Wort</b> Herba: Ph. Europea 7th. ed. e1756 Hyperici herbae extractum siccum quantificantum: Ph. Europea 7th. ed. e1757 Hyperici sumitates cum floribus recentes: 311 Oleum: 312
	Ph. Helvetica 11 (2012) was at the cutoff date for data collection (June 2014) the latest available regional pharmacopoeia. This data was subsequently checked against the two latest <i>Ph. Europea</i> 2014 and 2017.		

## Monographs

<b>Official monographs</b>			
Germany	Kommission E Monografien Bundesanzeiger 228	1984	<b>Arnica</b> Flores (no page number)  <b>St. John's Wort</b> Herba (no page number)
28 Member States of the European Community (EU)	European Medicines Agency (EMA) Community Herbal Monographs	2014	Arnica online: <a href="http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/herbal/medicines/herbal_med_000022.jsp&amp;mid=WC0b01ac058001fa1d">http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/herbal/medicines/herbal_med_000022.jsp&amp;mid=WC0b01ac058001fa1d</a>
		2009	<b>St. John's Wort</b> Online: <a href="http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/herbal/medicines/herbal_med_000117.jsp&amp;mid=WC0b01ac058001fa1d">http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/herbal/medicines/herbal_med_000117.jsp&amp;mid=WC0b01ac058001fa1d</a>
<b>Authoritative monographs</b>			
Authored by governing body of national European professional organisations for phytotherapy	European Scientific Cooperative on Phytotherapy (ESCOP) Monographs	2003 2. ed.	<b>Arnica</b> 43-47  <b>St. John's Wort</b> 257-81
International	WHO Monographs on selected medicinal plants. Volume 3	2007	<b>Arnica</b> Flores: 77-87
International	WHO Monographs on selected medicinal plants. Volume 2	2004	<b>St. John's Wort</b> Herba: 149-171
Germany EU	HagerROM 2012 Hagers Enzyklopädie der Arzneistoffe und Drogen	2012	<b>Arnica</b> 1-24  <b>St. John's Wort</b> 1-43

## Medical and modern phytotherapeutic textbooks

*Final selected was based on authors with therapeutic experience. The selection reflects approximately one textbook every 25 years (one for every generation). Textbooks by authors without therapeutic patient experience were excluded. Data were entered into Historical Data Excel spreadsheet for final analysis. The Neu vollkommen Kräuterbuch by Tabernaemontanus was used as pars pro toto for medical practice in the early modern period. The last reprint of this textbook was in 1731. For this reason, the data collection on successive medical textbooks started in the last third of the 18<sup>th</sup> century. This coincides with the start of the data collection of the Prussian and Swiss pharmacopoeias (only the Prussian pharmacopoeia was used in the final analysis).*

Author(s)	Selected	Title	Edition	Biographical data	Reference
<b>Tabernaemontanus</b> Jakob Theodor  <i>Physician, apothecary, botanist, balneotherapist. Personal physician to Philip II, Count of Nassau-Saarbrücken and to Marquard von Hattstein, bishop of Speyer. "Stadtphysicus" (town physician) to the free imperial city of Worms, Germany</i>	Yes	Neu vollkommen Kräuterbuch: darinnen uber 3000 Kräuter, mit schönen und kunstlichen Figuren, auch deren Unterscheid und Wirckung, sampt ihren Namen in mancherley Spraachen beschrieben: Deßgleichen auch, wie dieselbige in allerhand Kranckheiten, beyde der Menschen und des Viehs, sollen angewendet und gebraucht werden, angezeigt wird.	1664  Last re-print 1731	1522-1590	<b>Arnica</b> 714-715  <b>St. John's Wort</b> 1249-1252
<b>Stahl</b> Georg Ernst  <i>Physician, chemist, philosopher (vitalist); proponent against heroic medicines. Chair of medicine at the University of Halle, president of Collegium-Medicum in Berlin. Personal physician to Duke Johann Ernst of Sachsen-Weimar and King Friedrich Wilhelm I. of Prussia</i>  <i>Made transition from alchemy to chemistry</i>	No	Materia medica: das ist: Zubereitung, Krafft und Würckung, derer sonderlich durch chymische Kunst erfundenen Artzneyen	1744	1659-1734	<b>Arnica</b> Not listed  <b>St. John's Wort</b> 104

Author(s)	Selected	Title	Edition	Biographical data	Reference
<p><b>Plenck</b> Josephus Andreas Jacobus</p> <p><i>Physician, pharmacologist, chemist, botanist, dermatologist and surgeon. Appointed by Maria Theresia, archduchess of Austria and Queen of Hungary, as Professor for Surgery and Obstetrics to the University of Tyrnau (Slovakia. Professor of Chemistry and Botany at the Military-Medical Academy of Wien.</i></p>	No	Joseph Jacob Plenks Chirurgische Pharmakologie: oder Lehre von den Arzneymitteln, welche zur Heilung äußerer Krankheiten pflegen angewendet zu werden	1787	1735-1807	<p><b>Arnica</b> 163, 381-382</p> <p><b>St. John's Wort</b> Not listed</p>
		<p>Icones plantarum medicinalium</p> <p><i>First time plant names according to Linneus</i></p>	<p>1788 – 1803</p> <p>7 volumes</p>		<p><b>Arnica</b> Vol. 7: 13-14</p> <p><b>St. John's Wort</b> Vol. 6: 57</p>
<p><b>Löseke</b> Johann Ludwig Leberecht</p> <p><i>Physician; practising in Halle (born in Plötzky, Anhalt)</i></p> <p><b>Gmelin</b> Johann Friedrich</p> <p><i>Physician, chemist, natural scientist (Germany)</i></p>	Yes	Materia medica oder Abhandlung von den auserlesenen Arzneymitteln: nach derselben Ursprung, Güte, Bestandtheilen, Maße und Art zu wirken nebst Vorschriften wie dieselben aus der Apotheke zu verordnen sind (6. ed.).	1790 (6. ed)	<p>1724-1757</p> <p>1748-1804</p>	<p><b>Arnica</b> 170-171</p> <p><b>St John's Wort</b> 341</p>
<p><b>Hufeland</b> Christoph Wilhelm</p> <p><i>Physician, Professor of Medicine, University of Jena, Director of Medical Hospital Charité, Berlin "Hofarzt" (personal physician) of Friedrich Wilhelm III of Prussia and personal physician of Johann Wolfgang Goethe, German poet and natural scientist, as well as of other celebrities</i></p>	No	System der praktischen Heilkunde. Allgemeine Therapeutik	1802	1762-1836	<p><b>Arnica</b> 81,118,128, 78, 98, 109, 148, 220</p> <p><b>St. John's Wort</b> not listed</p>
		System der praktischen Heilkunde. Spezielle Therapeutik	1803		<p><b>Arnica</b> not listed</p> <p><b>St. John's Wort</b> not listed</p>
		Conspectus Materiae medicae secundum Ordines naturales in Usum Auditorium	1820		<p><b>Arnica</b> 25</p> <p><b>St. John's Wort</b> 17</p>

Author(s)	Selected	Title	Edition	Biographical data	Reference
<b>Richter</b> Georg August  <i>Military physician. Professor of Practical Medicine („praktische Heilkunde“), University of Königsberg</i>	Yes	Ausführliche Arzneimittellehre. Handbuch für praktische Aerzte	1827 Vol. 2	1778-1832	<b>Arnica</b> Flores, herba et radix 140-153  <b>St. John's Wort</b> Herba 293-294
<b>Kosteletzky</b> Vincent Franz  <i>Botanist, Professor of Pharmacognosy</i>	No	Allgemeine medizinisch-pharmazeutische Flora: enthaltend die systematische Aufzählung und Beschreibung sämtlicher bis jetzt bekannt gewordenen Gewächse aller Welttheile in ihrer Beziehung auf Diätetik, Therapie und Pharmazie, nach den natürlichen Familien des Gewächsreiches geordnet	1831 6 volumes	1801-1887	<b>Arnica</b> 711-713 (Vol.2) copied  <b>St. John's Wort</b> 1963-1966 (Vol. 5)
<b>Most</b> Georg Friedrich  <i>Physician, ophthalmologist, obstetrician, Lecturer of Medicine, University of Rostock, Doctor of Philosophy</i>	No	Ausführliche Encyclopädie der gesammten Staatsarzneikunde: für Gesetzgeber, Rechtsgelehrte, Polizeibeamte, Militärärzte, gerichtliche Ärzte, Wundärzte, Apotheker und Veterinärärzte	1838	1794-1832	<b>Arnica / Fallkraut</b> 23, 457 (A-K) 622 (L-Z) 685, 837 (Supplement)  <b>St. John's Wort</b> Not listed
<b>Casper</b> Johann Ludwig  <i>Physician, Professor of Medicine and Coroner, City of Berlin</i>	No	Wochenschrift für die gesamte Heilkunde	1841	1796-1864	Book on constitutional therapy – no <i>Materia medica</i>
<b>Venus</b> Carl Johann Alexander  <i>Physician, translator of French medical textbooks</i>	No	Grundriss der medicinischen Receptirkunst und der systematisch-practischen Arzneimittlehre	1841	1806-?	<b>Arnica</b> Flores: 148-149  Radix et flores: 256  <b>St. John's Wort</b> Not listed
<b>Rademacher</b> Johann Gottfried  <i>Physician, student of Hufeland. Stadtphysicus (town physician) of Goch</i>	No	Rechtfertigung der von den Gelehrten misskannten, verstandesrechten Erfahrungsheillehre der alten scheidekünstigen Geheimärzte und treue Mittheilung des Ergebnisses einer 25jährigen Erprobung dieser Lehre am Krankenbette  <i>Contains many case studies</i>	1848 Vol. 1	1772-1850	<b>Arnica</b> (Wolferleiblume) 843-845  <b>St. John's Wort</b> 661, 672, 683
			Vol. 2		<b>St. John's Wort</b> 661

Author(s)	Selected	Title	Edition	Biographical data	Reference
<p><b>Strumpf</b> Ferdinand Ludwig</p> <p><i>Physician. Practising in Berlin (since 1840), previously "Stadtphysicus" (town physician) of Stassfurt. Prussian "Hofrath" (civil service title) since 1835</i></p> <p><i>Descendent of renowned Professor of Chemistry and Botany in Halle, Karl Christoph Strumpf, to whom Linnaeus dedicated the genus "Strumpfia".</i></p>	Yes	Systematisches Handbuch der Arzneimittellehre	1855 Vol. 2	n.a.	<p><b>Arnica</b> Flores, herba, radix 46-56</p> <p><b>St. John's Wort</b> Herba, semen cum floribus 35-37</p>
<p><b>Lessing</b> Michael Benedict</p> <p><i>Physician in Berlin, surgeon. "Geheimer Hofrath" (honorary member of academia). Published a three book series on Paracelsus's life and work and medical textbook for students</i></p>	No	Handbuch der speciellen praktischen Arzneimittellehre	1863	1809-1884	<p><b>Arnica</b> 62-63</p> <p><b>St. John's Wort</b> Not listed</p>
		Kurzer Abriss der Materia Medica. Ein Repetitorium	1866		<p><b>Arnica</b> 155, 179- 181, 271- 272</p> <p><b>St. John's Wort</b> Not listed</p>
<p><b>Hager</b> Herrmann</p> <p><i>Apothecary, chemist and pharmacologist and writer of pharmaceutical commentaries and textbooks</i></p>	Yes	Handbuch der pharmaceutischen Praxis: für Apotheker, Ärzte, Droguisten und Medicinalbeamte.	1876 (1) 1. ed.	1816-1897	<p><b>Arnica</b> 462-467</p> <p><b>St. John's Wort</b> 217</p>
			1878 (2) 2. ed.		<p><b>St. John's Wort</b> 170-172</p>
			1883 (supp.)  1. ed.		<p><b>Arnica</b> 115</p> <p><b>St. John's Wort</b> Not listed</p>
<p><b>Köhler</b> Hermann Adolph</p> <p><i>Physician, chemist, extraordinary Professor of Pharmacology</i></p>	No	Grundriss der Materia medica für praktische Ärzte und Studierende: mit besonderer Rücksichtnahme auf die Pharmacopoea Germanica  <i>Editor. G. Pabst</i>	1878	1834-1879	<p><b>Arnica</b> 183-184</p> <p><b>St. John's Wort</b> Not listed</p>

Author(s)	Selected	Title	Edition	Biographical data	Reference
		Köhler's Medizinal-Pflanzen. Atlas zur Pharmacopoeia germanica, austriaca, belgica, danica, helvetica, hungarica, rossica, suecica, Neerlandica, British Pharmacopoeia, zum Codex medicamentarius, sowie zur Pharmacopoeia of the United States of America.  <i>This book belonged to Insel Hospital Apothecary, Berne, Switzerland</i>	1887 (4 vols.)  Vol. 1		<b>Arnica</b> 12-13  <a href="https://www.biodiversitylibrary.org/item/10836#page/39/mode/lup">https://www.biodiversitylibrary.org/item/10836#page/39/mode/lup</a>
<b>Flückiger</b> Friedrich August  <i>Apothecary. Associate Professor of Pharmacy and Pharmacognosy University of Bern; Professor of Pharmacy, University of Strassburg</i>  <b>Tschirch</b> Alexander  <i>Apothecary. Professor of Pharmacy and Pharmacognosy, University of Bern</i>	No	Grundlagen der Pharmakognosie	1885	1828-1894        1856-1939	<b>Arnica</b> 29, 69, 111, 188, 209, 222, 225 ( <i>pharmacognosy only</i> )  <b>St. John's Wort</b> Not listed
<b>Bernatzik</b> Wenzel  Physician and military physician. Professor of Theoretical Medicine at the "Institut für feldärztliche Zöglinge", Vienna. Professor of Pharmacology (Arzneimittellehre) and Pathology at the Josef Academy (Josephinum), Vienna. Member of the governing council (Regierungsrath)  <b>Vogl</b> August Emil  <i>Physician, Surgeon. Professor of Pharmacology and Pharmacognosy, University of Vienna. "Hofrath" (honorary member of academia)</i>	No	Lehrbuch der Arzneimittellehre. Mit gleichmässiger Berücksichtigung der österreichischen und deutschen Pharmacopoe.  Zweite, vermehrte und mit Rücksicht auf die neue österreichische Pharmacopoe vom Jahr 1889 (Edit. VII) umgearbeitete Auflage.	1891  2. ed.	1821-1902           1833-1909	<b>Arnica</b> Flos: 582-583  Radix: 549, 582-583  <b>St. John's Wort</b> Not listed
<b>Husemann</b> Theodor Gottfried  <i>Physician. Professor of Medicine and Pharmacology, University of Göttingen</i>	No	Handbuch der Arzneimittellehre. Mit besonderer Rücksichtnahme auf die neuesten Pharmakopöen für Studierende und Aerzte.	1892  3. ed.	1833 - 1901	<b>Arnica</b> Flos, radix: 499-500  <b>St. John's Wort</b> Not listed

Author(s)	Selected	Title	Edition	Biographical data	Reference
<b>Dragendorff</b> Georg Noël  <i>Physician. Pharmacist, pharmacologist. Professor of Pharmacy University of Dorpat</i>	No	Die Heilpflanzen verschiedener Völker und Zeiten.	1898	1836-1898	<b>Arnica</b> 683  <b>St. John's Wort</b> 349-350 (487 – is wrong index)
<b>Zörnig</b> Heinrich  <i>Apothecary, Pharmacist. Curator at "Königliches pflanzenphysiologisches Institut", München. Co-editor of Hager's Handbuch</i>	No	Arzneidrogen: als Nachschlagebuch für den Gebrauch der Apotheker, Ärzte, Veterinärärzte, Drogisten und Studierenden der Pharmazie. Die in Deutschland, Österreich und der Schweiz offizinellen Drogen.	1909	1866-?	<b>Arnica</b> Flos: 111-113, 144-145 Radix: 443-444  <b>St. John's Wort</b> Not listed  <i>(p. 111: Johannisblume was Arnica montana; p. 264: Johannisgürtelkraut was Artemisia vulgaris)</i>
<b>Poulsso</b> Edvart  <i>Physician, Pharmacist. Professor of Chemistry, University of Oslo</i>	No	Lehrbuch der Pharmakologie.	1909	1858-1935	<b>Arnica</b> Flos: 285  <b>St. John's Wort</b> Not listed
<b>Tschirch</b> Alexander  <i>Apothecary, Pharmacist and pharmacognosist. Professor of Pharmacy and Pharmacognosy, University of Berne</i>	No	Handbuch der Pharmakognosie	1909-1923  Vol. 1.1	1856-1939	<b>Arnica</b> 34, 67, 70  <b>St. John's Wort</b> 70, 96, 100-102
			Vol. 1.2		<b>St. John's Wort</b> 581, 587, 649, 650, 655, 658, 661, 799
			Vol. 2.1		<b>Arnica</b> 523
			Vol. 2.2		<b>Arnica</b> 1174-1184, 1560
			Vol. 3.1		<b>Arnica</b> 127, 244

Author(s)	Selected	Title	Edition	Biographical data	Reference data
<b>Schulz</b> Hugo  <i>Physician, Pharmacologist and toxicologist. Professor of Pharmacology, University of Greifswald</i>	Yes	Vorlesungen über Wirkung und Anwendung der deutschen Arzneipflanzen	1919	1853-1932	<b>Arnica</b> 293-299  <b>St. John's Wort</b> 228-229
<b>Dornblüth</b> <b>Otto</b>  <i>Physician; "Sanitäts-Rat" (administrative service title)</i>  <b>Bachem</b> Carl  <i>Physician. Professor of Medicine, University of Bonn</i>	No	Arzneimittel der heutigen Medizin: mit therapeutischen Notizen. Zusammengestellt für praktische Ärzte und Studierende der Medizin	1919	1860-1922  n.a.	<b>Arnica</b> Flos: 53  <b>St. John's Wort</b> Not listed
<b>Ziegler</b> Otto  <i>Chemist. "Studientrat" in München (honorary academic title for teaching)</i>  <b>Petzold</b> Arthur  <i>Chemist. Author of textbooks on chemistry. Owner of a drugstore ("Drogerie") in Charlottenburg. Politician and Member of German "Reichstag"</i>		Drogenkunde. Ein Hilfsbuch für den Unterricht and den Drogeisten-Fachschulen und zum Selbstunterricht, sowie ein Auskunftsbuch für die Praxis des Drogisten	1929	n.a.  n.a.	<b>Arnica</b> Flos: 113-114 Radix: 265  <b>St. John's Wort</b> 104
<b>Madaus</b> Gerhard  <i>Physician. Medicine manufacturer. Author of medical texts on plant medicine integrating a scientific and ethnomedical approach</i>	Yes	Lehrbuch der biologischen Heilmittel, Abteilung I. (Heilpflanzen)	1938  Vol. 1-3	1890-1942	<b>Arnica</b> 585-597 (Vol.1)  <b>St. John's Wort</b> 1587-1594 (Vol. 2)
<b>Fischer</b> Eugen  <i>Physician, Medical anthropologist</i>	No	Unsere Heilpflanzen in neuer Wertung und Geltung. Praktischer Ratgeber für den Anbau, das Sammeln und die Verwendung einheimischer Heil- und Gewürzpflanzen	1941	1874-1967	<b>Arnica</b> Flos, herba, radix: 57-60  <b>St. John's Wort</b> Herba: 160-163 Oleum: 161

Author(s)	Selected	Title	Edition	Biographical data	Reference data
<b>Flück</b> Hans  <i>Pharmacist. Professor of Pharmacognosy, Institut ETH Zürich. Member Commission Pharmacopoeia Helvetica and Pharmacopoeia Europea</i>  <a href="http://www.hls-dhs-dss.ch/textes/d/D43657.php">http://www.hls-dhs-dss.ch/textes/d/D43657.php</a>	No	Unsere Heilpflanzen	1941	1901-1985	<b>Arnica</b> 141  <b>St. John's Wort</b> 70
<b>Weiss,</b> Rudolf Fritz  <i>Physician. Lecturer on Phytotherapy, University of Berlin; Honorary Professor, University of Tübingen. Permanent Member of Kommission E 1978-1990</i>	No	Die Pflanzenheilkunde in der ärztlichen Praxis. Vorlesungen an der Berliner Akademie für ärztliche Fortbildung	1944	1895-1991	<b>Arnica</b> Flos, radix: 92-93, 115, 180-182, 222-224  <b>St. John's Wort</b> Herba cum summitates floribus (recentes): 162, 193-194, 215, 224
	Yes	Lehrbuch der Phytotherapie	1974, 3. ed.		<b>Arnica</b> Flos, radix: 131, 176-177, 279, 335, 341-342, 345  <b>St. John's Wort</b> Herba cum summitates floribus (recentes): 254, 296-298 Oleum: 56, 334, 342
	No	Lehrbuch der Phytotherapie  <i>(Last edition with Weiss as sole author. This edition was translated into English under the title: Weiss's Herbal Medicine. Classic Edition 2001).</i>	1985, 6. ed.		<b>Arnica</b> Herba, radix: 153, 161, 214-215, 342, 411, 421, 424  <b>St. John's Wort</b> Herba: 311-312, 345, 362-364, 411

Author(s)	Selected	Title	Edition	Biographical data	Reference
<b>Fischer</b> Georg  <i>Physician, Surgeon</i>	No	Heilkräuter und Arzneipflanzen. Benennung, Vorkommen, Inhalt, Heilwirkung und Anwendung der Heilpflanzen der europäischen, subtropischen, tropischen und überseeischen Flora	1947 2. ed.	1836-1921	<b>Arnica</b> Flos, herba, radix: 18  <b>St. John's Wort</b> Herba: 100-101
<b>Kroeber</b> Ludwig  <i>Apothecary, Pharmacist. "Apothekerdirektor" (administrative service title). Director of hospital apothecary München Schwabing (large hospital in Bayern)</i>	Yes	Das Neuzeitliche Kräuterbuch. Die Arzneipflanzen Deutschlands in alter und neuer Betrachtung.  Vierte, neu bearbeitete Auflage.	1948 4. ed. Vol. 1  (1. ed. 1934)	1872-1951	<b>Arnica</b> Flos, radix: 37-42  <b>St. John's Wort</b> Herba cum summi-tates (recentes): 192-196
<b>Neumann</b> Robert  <i>Physician. Professor University of Tübingen</i>	No	Materia Medica 1955 Dem praktischen Arzt gewidmet	1955	n.d.	<b>Arnica</b> mi 27/2  <b>St. John's Wort</b> gu 22/18
<b>Zimmermann</b> Walther  <i>Physician. Head physician („Chefarzt“) of "Krankenhaus für Naturheilwesen", München-Harlaching, the most prominent hospital of natural therapies in Germany</i>	No	Praktische Phytotherapie. Die Arzneipflanze in der Medizin	1994	1923-2003	<b>Arnica</b> 34-35, 42, 57, 62-63, 67, 72, 87, 99, 110, 117, 125, 126, 149, 182, 189, 191, 309, 375, 381, 384, 391  <b>St. John's Wort</b> 43, 181, 189, 198, 210, 213-214, 218, 275, 382, 391

Author(s)	Selected	Title	Edition	Biographical data	Reference
<p><b>Saller Reinhard</b></p> <p><i>Physician. Professor and Director of Institute of Complementary Medicine - Department of Internal Medicine - University Hospital Zürich</i></p> <p><b>Reichling Jürgen</b></p> <p><i>Pharmacist, Pharmacologist. Professor of Institute of Pharmacy and Molecular Biotechnology, University of Heidelberg</i></p> <p><b>Hellenbrecht Dieter</b></p> <p><i>Physician. Professor of Institute of Pharmacology at Goethe University of Frankfurt am Main</i></p>	Yes	Phytotherapie. Klinische, pharmakologische und pharmazeutische Grundlagen	1995	1947-   1943-   1939-1994	<p><b>Arnica</b> 49-55, 405</p> <p><b>St. John's Wort</b> 208-216, 431-432</p>
<p><b>Wichtl Max</b></p> <p><i>Pharmacist, chemist, botanist. Professor for Pharmacognosy, University of Wien and Philipps University of Marburg Member Kommission E</i></p>	No	Teedrogen und andere Phytopharmaka	1997  3. ed.	1925 -	<p><b>Arnica</b> Flos, herba, radix: 78-82</p> <p><b>St. John's Wort</b> Herba cum summitates floribus (recentes): 309-312</p>
<p><b>Schulz Volker</b></p> <p><i>Physician, Internist. Honorary professor</i></p> <p><b>Hänsel Rudolf</b></p> <p><i>Pharmacist. Professor of Pharmacognosy and Phytochemistry, Freie Universität Berlin</i></p>	No	Rationale Phytotherapie. Ratgeber für die ärztliche Praxis	1999	n.a.   n.a.	<p><b>Arnica</b> 324-325</p> <p><b>St. John's Wort</b> 16, 59-78</p>

Author(s)	Selected	Title	Edition	Biographical data	Reference data
<p><b>Wagner</b> Hildebert</p> <p><i>Pharmacologist, Professor of Pharmaceutical Biology, Maximilian Universität München</i></p> <p><b>Wiesnauer</b> Markus</p> <p><i>Physician</i></p>	No	Phytotherapie. Phytopharmaka und pflanzliche Homöopathika	2003	1929-  1959-	<p><b>Arnica</b> Flos: 43, 81, 182, 269, 306, 331, 378, 388, 390-391, 396 Radix: 29</p> <p><b>St. John's Wort</b> Herba cum summitates (recentes): 182, 204, 233-239, 378-379, 388, 393-394, 396, 444</p>
<p><b>Bäumler</b> Siegfried</p> <p><i>Physician, internist, physician of natural medicine ("Arzt für Naturheilverfahren")</i></p>	Yes	Heilpflanzen Praxis Heute. Porträts, Rezepturen, Anwendung	2007	n.a.	<p><b>Arnica</b> Flos: 61-63, 526, 572, 616, 633, 639-640, 646, 664-665, 668, 715, 721-723, 731, 736, 780, 782, 785, 792, 868</p> <p><b>St. John's Wort</b> Herba cum summitates floribus (recentes): 221-224, 522, 740, 782-784, 795, 812-813, 839, 841-844, 848-850, 852-854, 860</p>

**Hermann Hager's collated pharmacology textbooks  
(excluding pharmacopoeia commentaries)**

Author / Editors	Title	Date		Reference
<b>Hager</b> Herrmann (1816-1897)  <i>Dr. Hermann Hager, was a Prussian apothecary, pharmacist, chemist, pharmacologist and writer of pharmaceutical commentaries and textbooks</i>	Handbuch der pharmaceutischen Praxis: für Apotheker, Ärzte, Droguisten und Medicinalbeamte.	1876 (1)  1. ed.		<b>Arnica</b> 462-467  <b>St. John's Wort</b> 217
		1878 (2)  1. ed.		<b>St. John's Wort</b> 170-172
		1883 (supp.)  1. ed.		<b>Arnica</b> 115  <b>St. John's Wort</b> Not listed
<b>Hager</b>  <b>Editors:</b> <b>Lenz W.&amp; Arends G.</b>	Hagers Handbuch der Pharmazeutischen Praxis. Für Apotheker, Ärzte, Drogisten und Medicinalbeamte.	1900 (1)  2. ed.		<b>Arnica</b> 383-386
		1902 (2)  2. ed.		<b>Arnica</b> 111  <b>St. John's Wort</b> 98
		1908 (supp)  2. ed.		<b>Arnica</b> 90-91, 274
<b>Hager</b>  <b>Editors:</b> <b>Frerichs, G., Arends G. &amp; Zörnig, H.</b>  Note: predominantly preparations from fresh- plant tinctures	<b>Hagers Handbuch der Pharmazeutischen Praxis für Apotheker, Arzneimittelhersteller, Drogisten, Ärzte und Medizinalbeamte.</b>	1925 Vol. 1 A-I  3. ed.		<b>St. John's Wort</b> 1505- 1506
		1927 Vol. 2 K-Z  3. ed.		<b>Arnica</b> 547-550
Note: preparation guidelines only; no references to applications		1958 Ergänzungsband 1  3. ed.	Covers time from 1944 to end of 1956.	<b>Arnica</b> 753-754  <b>St. John's Wort</b> 1193- 1194
		1958 Ergänzungsband 2  3. ed.	Covers time from 1944 to end of 1956	Not listed

Author / Editors	Title	Date		Reference
<b>Hager</b> <b>Editors:</b> <b>List, P.H. &amp;</b> <b>Hörhammer, L.</b>	<b>Hagers Handbuch der Pharmazeutischen Praxis. Für Apotheker, Arzneimittelhersteller, Ärzte und Medizinalbeamte.</b>	Vol. 3 4. ed.	1969	<b>Arnica</b> 214-223
		Vol. 5 4. ed.		<b>St. John's Wort</b> 214-219
		Vol. 7a 4. ed.		<b>Arnica</b> Nachtrag
<b>Hager</b> <b>Editors:</b> <b>Hänsel, R.</b> <b>Keller, K.</b> <b>Rimpler, H.</b> <b>Schneider G.</b>	<b>Hagers Handbuch der Pharmazeutischen Praxis. Drogen.</b>	1991-1993 Vol. 1 5. ed.		<b>Arnica</b> 570-572, 670-671
		Vol. 2 5. ed.		<b>Arnica</b> 275, 1017 <b>St. John's Wort</b> 1017
		Vol. 3 5. ed.		<b>Arnica</b> 249, 650, 1024
		Vol. 4 5. ed.		<b>Arnica</b> 342-357, 382, 604-603 <b>Yarrow</b> 45-54
		Vol. 5 5. ed.		<b>Arnica</b> 440-441 <b>St. John's Wort</b> 475-495 (148: Johanniswedel = <i>Filipendula ulmaria</i> )
		Vol. 6 5. ed.		Arnidiol – not relevant 898, 1017
		Folgeband 2 5. ed.		<b>Arnica</b> 375, 440
<b>HagerRom 2000</b> <b>Editors:</b> <b>Ebel, S.</b> <b>Blaschek, W.</b> <b>Hackenthal, E.</b>				<b>Arnica</b> Monograph <b>St. John's Wort</b> Monograph
<b>HagerRom 2001</b> <b>Editors:</b> <b>Blaschek, W.</b> <b>Ebel, S.</b> <b>Hackenthal, E.</b> <b>Holzgrabe, U.</b> <b>Keller, K.</b> <b>Reichling, J.</b>	<b>HagerRom 2001. Hagers Handbuch der Drogen und Arzneistoffe</b>	Yearly updated editions		<b>Arnica</b> Monograph <b>St. John's Wort</b> Monograph

Author / Editors	Title	Date		Reference
<b>Blaschek, W.</b> <b>Ebel, S.</b> <b>Hackenthal, E.</b> <b>Holzgrabe, U.</b> <b>Keller, K.</b> <b>Reichling, J.</b> <b>Schulz, V.</b>	<b>HagerRom 2006 Hagers</b> <b>Handbuch der Drogen und</b> <b>Arzneistoffe</b>	Yearly updated editions  <i>additonal</i> <i>editors</i>		<b>Arnica</b> Monograph  <b>St. John's</b> <b>Wort</b> Monograph

## Encyclopaedias

Author	Title	Edition	Biographical data	Availability
<b>Zedler</b> Johann Heinrich  Book dealer, publisher	Universallexicon	1732-1754	1706-1751	<a href="https://www.zedler-lexikon.de/">https://www.zedler-lexikon.de/</a>
<b>Krünitz</b> Johann Georg  Physician  Encyclopaedist	Oekonomische Encyklopädie, oder allgemeines System der Staats-, Stadt-, Haus- und Landwirthschaft	1773-1858	1728-1796	<a href="http://www.kruenitz1.uni-trier.de/">http://www.kruenitz1.uni-trier.de/</a>  <a href="http://www.e-rara.ch/zut/content/titelinfo/10812037">http://www.e-rara.ch/zut/content/titelinfo/10812037</a>

## APPENDIX 3: TRANSCRIPT OF *ARNICA MONTANA* MONOGRAPH IN TABERNAEMONTANUS

This appendix is the German language transcript of Tabernaemontanus' monograph on *Arnica montana* (1664). The pharmaceutical and pharmacological data is translated into English in Appendix 4.

### Das XXII. Capitel.

VON MUTTERWURTZ.

Mutterkraut Chalta [*Caltha*] alpina.



Figure 8. *Arnica montana* in Tabernaemontanus 1664, p. 714.

	Originaltext	Moderne Übersetzung
Mutterwurz	Djeses Kraut beschreibet LOBELIUS in seinen OBSERVATIONIBUS und ADVERSARIIS NOVIS / daß es ein schönes Gewächs sey / seine Wurtzel vergleicht sich der Wurtzel des grossen Baldrians / außgenommen daß sie kleiner ist / und mit vielen Faseln behencket / bey nahe dem DORONICO gleich / eines räsén / scharffen / durchtringenden / bittern / und doch wurtzigen Geschmacks / dem NARDO gantz gleich / auß welcher Wurtzel ein Stengel herfür tritt / einer elen hoch / bißweilen auch nidriger / an welches Gipfel ein gestirnte goldgelbe Blum herfür kommt / gantz lustig und schön anzusehen / der Rindsaugblumen oder Johansblumen fast gleich. Seine blätter sind lang / breit und bleichgelb / mit vielen Aederlein durchzogen / der Entzian so gleich und ähnlich / daß sie in der erst vor die Entzian möchte angesehen werden. GESNERUS und DODONEUS vergleicht sie den Wegrichsblättern / mit welchen sie auch gar übereinkommen. LOBELIUS schreibet / daß er es in AGRO	Über diese Pflanze schreibt Lobelius <sup>11</sup> in seinen OBSERVATIONES und ADVERSARIA NOVA, dass sie schön sei. Ihre Wurzel ähnelt der des großen Baldrians <sup>12</sup> . Allerdings ist sie kleiner und hat zahlreiche Seitenwurzeln, ähnlich wie die Gemswurz <sup>13</sup> . Sie schmeckt rösch <sup>14</sup> , scharf, durchdringend, bitter und dabei doch würzig wie die Narde <sup>15</sup> . Aus ihrer Wurzel wächst ein Stengel hervor, der ungefähr 54 cm <sup>16</sup> hoch, manchmal aber auch niedriger sein kann. An der Spitze des Stengels erscheint jeweils eine sternförmig strahlende <sup>17</sup> goldgelbe Blüte, die sehr anmutig <sup>18</sup> und schön aussieht und eine starke Ähnlichkeit mit der Blüte der Färberkamille <sup>19</sup> oder der Wucherblume <sup>20</sup> besitzt. Die Blätter der Pflanze sind lang, breit und blass, mit vielen Gefäßen durchzogen. Sie ähneln denen des Enzians <sup>21</sup> so sehr, dass man sie zunächst leicht für Enzianblätter halten könnte.

<sup>11</sup> Matthias Lobelius, eigtl. M. de l'Obel (1538 - 1616), niederländischer Botaniker

<sup>12</sup> „grosser Baldrian“: großer Baldrian - *Valeriana phu L.*, aus dem Kaukasus; MARZELL, IV, Sp. 1000

<sup>13</sup> „Doronicum“: Gemswurz - *Doronicum L.*; MARZELL, II, Sp. 153f

<sup>14</sup> „räsén“: zu rösch, ‚frisch‘; KLUGE, S. 770<sup>b</sup>

<sup>15</sup> „Nardus“: als Narde wurden verschiedene aromatisch riechende Pflanzen bezeichnet (u.a. Deutsche Narde - *Lavandula latifolia Medic.*, Römische Narde - *Valeriana celtica L.*, Speik - *Nardostachys jatamansi (Jones) DC. = Valeriana spica (L.) Vahl.*) ; vgl. MILDENBERGER (1997), III, S. 1288 - 1290, und siehe auch MARZELL, III, Sp. 291

<sup>16</sup> eine Elle entspricht ungefähr 54 cm; MULSOW (1910), S. 33; MEYER III, Sp. 804: Frankfurter Elle

<sup>17</sup> „gestirnt“: mit einem Blütenstern versehen; DWB, IV / I / II = 5, Sp. 4241

<sup>18</sup> „lustig“: anmutig; DWB VI = 12, Sp. 1340-1342

<sup>19</sup> „Rindsaugblume“: Färberkamille - *Anthemis tinctoria L.*; MARZELL, I, Sp. 324

<sup>20</sup> „Johansblume“: Wucherblume - *Chrysanthemum leucanthemum L.*; MARZELL, I, Sp. 964

<sup>21</sup> „Entzian“: gelber Enzian - *Gentiana lutea L.*; MARZELL, II, Sp. 626

	Originaltext	Moderne Übersetzung
	NARBONENSI habe angetroffen / es wächst auch in den feuchten Wiesen / auff den hohen Gebirgen. [In Schweitzerland und Elsaß]	Gessner <sup>22</sup> und Dodoens <sup>23</sup> vergleichen sie mit den Blättern des Wegerichs <sup>24</sup> , mit denen sie ebenfalls große Ähnlichkeit besitzen. Lobelius schreibt, dass er die Pflanze im südlichen Languedoc <sup>25</sup> gefunden habe. Sie wächst auch auf hochgelegenen feuchten Wiesen. [so auch in der Schweiz und im Elsass]
	<b>Von den Namen.</b>  Mutterwurtz wird [von Pnegellern in den Bürden wilder Wegerich] Lateinisch genannt CALTHA ALPINA, dieweil es für ein Art der Ringelblumen gehalten wird: RONDELETIUS hält es für ein Geschlecht des NARDI GALLICAE, andere sagen / es sey ein SPECIES des NARDI CELTICAE, GESNERUS nennet es CALTHAM ALPINAM.	<b>Von den Namen.</b>  Arnika wird [von Pnegellern in den Bürden wilder Wegerich <sup>26</sup> ] lateinisch als Caltha alpina bezeichnet, weil man sie für eine Art der Ringelblumen hält. <sup>27</sup> Rondelet <sup>28</sup> ordnet sie der Gallischen Narde zu, andere der Keltischen Narde. <sup>29</sup> Gessner nennt sie Caltha alpina.
	[Bey den Sachsen und Seestätten wird es Wolvey geheissen bey dem gemeinen Mann: aber von den MEDICIS, ARNICA, DORONICUM PLANTAGINIS FOLIO ALTERUM, C.B. 5. GERMANICUM & 6.	[Die Sachsen und die Küstenbewohner nennen sie volkstümlich Wolvey <sup>30</sup> . Die Ärzte dagegen verwenden die Namen ARNICA, DORONICUM PLANTAGINIS FOLIO ALTERUM, C.B. 5. GERMANICUM & 6. PANNONICUM, CLUS. <sup>31</sup> HIST. ALISMA,

<sup>22</sup> Konrad Gessner (1516 - 1565), eidgenössischer Naturforscher und Arzt

<sup>23</sup> Rembert Dodoens (1516 - 1585), kaiserlicher Leibarzt flämischer Herkunft in Wien, Internist in Leiden, erhielt den Reichsadel

<sup>24</sup> „Wegerich“: großer Wegerich - *Plantago major* L.; MARZELL, III, Sp. 815

<sup>25</sup> „Narbonensis“: ehemals römische Provinz im jenseits der Alpen gelegenen Gallien (GEORGES [1913], II, 1090); zur territorialen Verflechtung von Stadt, Erzbistum und Grafschaft Narbonne siehe LexMA VI, Sp. 1020-1023

<sup>26</sup> „wilder Wegerich“: MARZELL, I, Sp. 407 hat nur „Welscher Wegerich“; „Pregeller“ bleibt zunächst ungedeutet; für „Bürde“ liegt die Deutung ‚Bündel‘ nahe, vgl. FrnhdWb IV, Sp. 1406; vielleicht verballhornt aus „von den Bergellern in den <Grauen> Bünden“

<sup>27</sup> „Ringelblume“: vgl. MARZELL, I, Sp. 400: *Caltha alpina* als alter Name für *Arnica montana* L.; sowie MARZELL, I, Sp. 715: *Caltha* für *Calendula officinalis* L.

<sup>28</sup> Guillaume Rondelet (1507 - 1566), französischer Naturforscher

<sup>29</sup> „Nardus celtica“: vgl. MARZELL, IV, Sp. 986, *Nardus gallica* bzw. *Nardus celtica* als alte Namen für den Echten Speik (*Valeriana celtica* L.)

<sup>30</sup> „Wolvey“: verballhornt aus ‚Wohlverleih‘, zusammengesetzt aus ‚Wohl‘ und ‚Verleih, ‚Wellness-Spender‘; MARZELL, I, Sp. 400f; zur Wortbildung KEIL / MÜLLER (1997)

<sup>31</sup> Carolus Clusius, Charles de l'Écluse (1526-1609), flandrischer Altphilologe, Jurist und Arzt, Hugenotte, dann bekennender Lutheraner, Freund

	Originaltext	Moderne Übersetzung
	PANNONICUM, CLUS. HIST. ALISMA, MATTH. CAST. CAM. EYST. ALPINUM, GES. HORT, THAL. CALTHA ALPINA, GES. HERR. CALENDULA ALPINA, GER. NARDUS CELTICA ALTERA, AD. LOB. LUGD. CHRYSANTHEMUM LATIFOL. DOD. LUGD. GER. DAMASONIUM SIVE ALISMA, LUGD. PTARMICA MONTANA, LUGD.]	MATTH. <sup>32</sup> CAST. CAM. EYST. ALPINUM, GES. HORT, THAL. CALTHA ALPINA, GES. HERR. CALENDULA ALPINA, GER. NARDUS CELTICA ALTERA, AD. LOB. LUGD. CHRYSANTHEMUM LATIFOL. DOD. LUGD. GER. DAMASONIUM SIVE ALISMA, LUGD. PTARMICA MONTANA, LUGD.]
Harn treiben	<b>Von der Natur und Wirckung.</b>  LOBELIUS schreibt / daß es den Harn sehr und gewaltig forttreibe / was sein Complexion sey / ist zuvor angezeiget.	<b>Von der Natur und Wirkung</b>  Lobelius schreibt, dass die Pflanze stark harntreibend wirke. Ihre Komplexion ist zuvor angegeben.
Niessen machen	[GESNERUS meldet / daß die Wurtzel niessen mache. Bey den Sachsen braucht es das gemein Volck / denen so hoch hinunder gefallen / oder so sich sonst etwan mit Arbeit verletzt haben: Nemmen ein Handvoll / sieden es in Bier / trincken des Morgens einen Trunck warm davon / decken sich zu / und schwitzen: Wo sie sich dann verletzt haben / empfinden sie an dem verletzten Ort großen Schmerzen / auff zwo oder drey Stund / und werden also curiert: Haben sie sich aber nicht verletzt / empfinden sie keine Veränderung.	[Nach Gessner löst die Wurzel Niesreiz aus. Die Sachsen verwenden die Pflanze volkstümlich zur Behandlung von Sturzverletzungen oder sonstigen Arbeitsunfällen. Dazu wird eine Handvoll davon in Bier gekocht. Diesen Absud trinkt man morgens warm. Anschließend deckt man sich warm zu, um die Schweißbildung zu fördern. Verletzte spüren an den betroffenen Körperstellen während der folgenden 2 oder 3 Stunden zunächst starke Schmerzen, danach setzt die Heilung ein. Dagegen nehmen Personen ohne Verletzungen keine Veränderung wahr.
	Auch zu Dantzic in Preussen ist es sehr in grossem Brauch / und obwol bey ihnen es nicht wächst / wird es doch auß Nider Sachsen in Fässern dahin gebracht.]	Auch zu Danzig in Westpreußen wird die Pflanze oft verwendet, obwohl sie dort nicht wächst. Sie wird deshalb in Fässern aus Niedersachsen dorthin geliefert.]

Rembert Dodoens', wirkte bzw. wurde ausgebildet in Montpellier, Marburg, Wittenberg, Frankfurt a. M., Leiden, kaiserlicher Leibarzt in Wien, richtete den Wiener botanischen Garten ein, wurde berühmt durch seine Beschreibung der österreichisch-ungarischen Flora.

<sup>32</sup> Pietro Andrea Mattioli (1501-1577), kaiserlicher Leibarzt in Prag, stammte aus Siena, wirkte seit 1527 als Arzt zu Cles in Nonsberg / Sulzberg (Tirol), wo er seinen Dioskurides-Kommentar erarbeitete (1554), der schon 1563 als 'New Kräuterbuch' in deutscher Übersetzung erschien.

	<b>Originaltext</b>	<b>Moderne Übersetzung</b>
	[Von diesem Kraut wird auch gehandelt unten in der 11. Section am 20. Cap. unter dem Namen: groß Lucians Kraut / das erste / welches nichts anders dann diß Mutterwurtz.]	[Diese Pflanze wird auch weiter unten in der 11. Abteilung des 20. Kapitels <sup>33</sup> unter dem Namen 'Groß Lucians Kraut' <sup>34</sup> (erster Abschnitt) beschrieben. Diese ist identisch mit der hier behandelten Arnika.]

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<sup>33</sup> Dies ist ein Druckfehler. Die Beschreibung des „Groß Lucians Kraut“ befindet sich im Kapitel 23.

<sup>34</sup> vgl. MARZELL (1958), I, Sp. 408

## APPENDIX 4: APPROXIMATION TO THE PHARMACEUTICAL AND PHARMACOLOGICAL PROFILE OF *ARNICA MONTANA*, TABERNAEMONTANUS 1664

Label	Contemporary English	Contemporary German	Original Text	Use-categories
<b>Contemporary name</b>	Arnica			
<b>Botanical name</b>	<i>Arnica montana</i>	<i>Arnica montana</i>	<i>Caltha alpina, Chalta alpina, Arnica, Doronicum plantaginis folio alterum, Alisma, Calendula alpina, Nardus celtica altera, Chrysanthemum latifol., Damasonium sive alisma, Ptarmica montana</i>	
<b>Historical names</b>	n.a.	Arnica	Mutterwurz, Mutterkraut, Wilder Wegerich, Wolveley	
<b>Constitutional effect</b>	warm and dry (listed in contemporaneous literature (Gerard, 1633 (1975), p. 740).			
<b>Organoleptic properties</b>	it tastes fresh, sharp, penetrating, bitter, aromatic	sie schmeckt rösch, scharf, durchdringend, bitter und dabei doch würzig	eines räsens, scharffen, durchdringenden, bitteren und doch wurzigen Geschmacks	
<b>Plant part used</b>	aerial parts, flower, root	Kraut, Blüten, Wurzel	Kraut, Blum, Wurzel	

Label	Contemporary English	Contemporary German	Original Text	Use-categories
<b>Preparations Internal use</b>	<b>Decoctions:</b> not defined decoction (used as a diuretic)  beer decoction of root	<b>Absud:</b> Absud (als Diuretikum gebraucht – nicht näher definiert)  Bierabsud der Wurzel	„es“ <sup>35</sup> (den Harn...forttreibe)  Sieden es in Bier [Wurzel]	
<b>Preparations External use</b>	<b>Drug:</b> snuff	<b>Droge:</b> Schnupftabak	Wurtzel niessen mache	
<b>Actions internally</b>	diuretic  tissue healing  analgesic  uterine healing	diuretisch  heilend  schmerzlindernd  Uterus heilend	daß es den Harn sehr und gewaltig forttreibe  denen so hoch hinunder gefallen oder so sons etwann mit Arbeit verletzt haben...und werden also curiert  empfinden sie an dem verletzten Ort großen Schmerzen...und werden also curiert  dient auch wider den Gebrechen der Mutter <sup>36</sup>	uro  musc-skel  nerve  gyn

<sup>35</sup> The extraction method is not defined here. Since this preparation was used for diuresis it is most likely that it was a water extraction. The authoritative German apothecary textbook from 1783, printed a little more than 50 years after the last edition of Tabernaemontanus' textbook (1731), provides guidelines for a water extraction of Arnica with the whole plant (herb, flowers, root): "...man giebt gemeiniglich die ganze Pflanze, als Blumen, Wurzeln und Kraut in einen Absud..." (one usually uses the whole plant including flowers, roots, and herb and makes a decoction) (Pfungsten, 1783, p. 99).

<sup>36</sup> Insert by the Bauhin editors (Tabernaemontanus, 1664, p. 1116)

Label	Contemporary English	Contemporary German	Original Text	Use-categories
	emmenagogue anti-diarrhoea decontaminating / detoxifying	menstruationsfördernd stopfend entgiftend	treibt die Monzeit <sup>37</sup> stopffet den Stulgang <sup>38</sup> Es meldet Camerarius, daß die Bauern dem Viehe gesotten zu trinken geben / wann sie vermeinen daß sie etwas vergiftes gessen haben. <sup>39</sup>	gyn gastro-intest liver-spleen
<b>Actions externally</b>	sneezing effect (drainage, tonic)	Niesreiz auslösend (reinigend, Tonikum)	daß die Wurtzel niessen mache	tonic cleanse

<sup>37</sup> Inserted by the Bauhin editors (Tabernaemontanus, 1664, p. 1116).

<sup>38</sup> Insert by the Bauhin editors (Tabernaemontanus, 1664, p. 1116).

<sup>39</sup> Insert by the Bauhin editors (Tabernaemontanus, 1664, p. 1116)

Label	Contemporary English	Contemporary German	Original Text	Use-categories
<b>Medicinal uses Internally</b>	bring on menstruation (amenorrhoea)	Amenorrhö	treibt die Monzeit	gyn
	diuresis (powerful)	(zur starken) Diurese	daß es den Harn sehr und gewaltig forttreibe	uro
	diarrhoea	Durchfall	stopft den Stulgang	gastro-intest
	injuries	Arbeitsverletzungen heilen	mit Arbeit verletzt haben...und werden also curiert	musc-skel
	pain	Schmerzen	Schmertzten...curiert	musc-skel
	poisoning	Vergiftung	etwas vergifttes gessen	liver-spleen
	uterine complaints	Gebärmutterbeschwerden	Gebrechen der Mutter	gyn
<b>Medicinal uses Externally</b>	snuff	Schnupftabak	Wurtzel niessen mache	tonic cleanse
<b>Dosage internal use</b>	<b>Extractions:</b> plant extract; dose unknown  <b>Beer extraction:</b> a handful [of root] boiled in beer; drink warm each morning, cover up and sweat	<b>Extraktion:</b> Pflanzenextrakt. Dosis unbekannt  <b>Bier Extrakt:</b> eine Handvoll [der Wurzel] in Bier sieden; davon warm morgens trinken, sich zudecken und schwitzen	„es“  Nemmen ein Handvoll / sieden es in Bier / trincken des Morgens einen Trunck warm davon / decken sich zu / und schwitzen	

Label	Contemporary English	Contemporary German	Original Text	Use-categories
<b>Dosage external use</b>	<b>Snuff</b> (usually dosage to fill cavity of the nose)	<b>Schnupftabak</b> (üblicherweise Dosis um ein Nasenloch zu füllen)		
<b>Contraindications</b>	None mentioned	Keine genannt		
<b>Warnings and Precautions</b>	None mentioned	Keine genannt		
<b>Pregnancy and Lactation</b>	No contraindication mentioned explicitly for use during pregnancy or breastfeeding or in the section “uterus tonic”	Keine Kontraindikation genannt expressis verbis für Gebrauch während Schwangerschaft oder Stillen oder in der Sektion „Uterus stärkend“		
<b>Side effects</b>	None mentioned	Keine genannt		

Annotations by the Bauhin editors are marked in the 4<sup>th</sup> edition of *Neu vollkommen Kräuter-Buch* by square brackets.

## APPENDIX 5: INDICATIONS FOR *ARNICA MONTANA* IN MEDICAL TEXTBOOKS

Use-categories	Tabernaemontanus 1664	Löseke 1790	Richter 1827	Strumpf 1855	Hager 1876	Schulz 1919	Madaus 1938	Kroeber 1948	Weiss 1974	Saller et al 1995	Bäumler 2007
card-vasc	0	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
		circulatory stimulant to treat oedema, knots, spasms, liver and spleen congestion, rheumatism, gout, respiratory tract infections, tuberculosis, malaria, paralysis, blindness	circulatory and lymph flow stimulant to treat oedema, haematoma, swelling of glands, injuries, after stroke, haemorrhoids and other issues	circulatory and lymph flow stimulant to treat oedema, swelling of glands	circulatory stimulant to treat paralysis, cerebral concussion	circulatory stimulant on vascular system  to treat oedema  <i>after stroke</i>	circulatory stimulant to treat oedema, spasms, rheumatism, gout, respiratory tract infection, paralysis, stroke	circulatory stimulant	circulatory stimulant to treat neuralgia, badly healing wounds, rheumatism, respiratory tract infection, infected throat	<i>circulatory stimulant for heart and circulation</i>	circulatory stimulant
		circulatory insufficiency	circulatory insufficiency	circulatory insufficiency	circulatory insufficiency	circulatory insufficiency	circulatory insufficiency	circulatory insufficiency	circulatory insufficiency		circulatory insufficiency
			bleeding (coughing, vomiting blood, uterus, menorrhagia)	bleeding		bleeding (bronchi, kidneys; inner eye)	bleeding (uterus, kidneys, nose)	bleeding (chest and abdominal cavity, brain, eyes, skin)			
						cardiac stimulant in low blood pressure	coronary insufficiency (Angina pectoris, atherosclerosis, adipositas cordis, cyanosis, weakness of heart muscle)	coronary insufficiency (Angina pectoris, atherosclerosis, shock, weakness of heart muscle)	coronary insufficiency / Angina pectoris		coronary insufficiency (Angina pectoris)

Use-categories	Tabernaemontanus 1664	Löseke 1790	Richter 1827	Strumpf 1855	Hager 1876	Schulz 1919	Madaus 1938	Kroeber 1948	Weiss 1974	Saller et al 1995	Bäumler 2007
								varicose veins		<i>varicose veins</i>	varicose veins
										phlebitis	phlebitis
<b>gastro-intest</b>	✓	✓	✓	✓	✓	0	✓	✓	0	0	0
	diarrhoea	constipation	diarrhoea	diarrhoea	diarrhoea			diarrhoea			
		putrefaction (infection with fever)	typhus / dysentery and other gastro-intestinal infections	typhus / dysentery and other gastro-intestinal infections	gastro-intestinal infections		gastro-intestinal infections	typhus and other gastro-intestinal infections			
<b>gyn</b>	✓	✓	✓	✓	0	(✓)	✓	0	0	(✓)	(✓)
	to bring on menstruation (amenorrhoea)	to bring on menstruation (amenorrhoea)	to bring on menstruation (amenorrhoea)	to bring on menstruation (amenorrhoea)		<i>to induce abortion (deliberate overdose)</i>				<i>to induce abortion (deliberate overdose)</i>	
	uterus complaints	puerperium (uterus cleansing)	puerperium (uterus cleansing)	puerperium (uterus cleansing)			uterus bleeding uterus complaints				<i>uterus complaints</i>
		knots in breasts									
<b>head</b>	0	✓	✓	✓	✓	✓	✓	✓	0	0	0
		black star (blindness)				eye injury	<i>eye rinse</i>	inner / outer eye bleeding			
			cerebral concussion haematoma / oedema in brain	cerebral concussion inflammation of brain, dizziness, memory loss or paralysis after concussion	cerebral concussion		cerebral concussion spasms and cyanosis in newborns due to intracranial bleeding	bleeding in brain			
			after stroke			<i>after stroke</i>	after stroke				
							nosebleed				
							tooth pain				
		hair colouring					<i>hair colouring</i>				

Use-categories	Tabernaemontanus 1664	Löseke 1790	Richter 1827	Strumpf 1855	Hager 1876	Schulz 1919	Madaus 1938	Kroeber 1948	Weiss 1974	Saller et al 1995	Bäumler 2007
<b>infection</b>	0	✓	✓	✓	✓	0	✓	0	0	(✓)	✓
		malaria	malaria	malaria			infections resulting in fever			<i>infections resulting in fever</i>	infections
			infections resulting in fever	infections resulting in fever	infections resulting in fever or putrefaction						
<b>liver-spleen</b>	✓	✓	0	0	0	0	0	0	0	0	0
	poisoning	poisoning bitter tonic jaundice									
<b>musc-skel</b>	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	injuries	inner and outer injuries	inner and outer injuries	inner and outer injuries	inner and outer injuries <i>inner and outer injuries</i>	injuries	inner and outer injuries	inner and outer injuries	injuries	injuries	inner and outer injuries
		haematoma	haematoma, swelling, inflammation	haematoma	haematoma	contusion	haematoma	haematoma, bruises, oedema	haematoma, bruises	haematoma, bruises, oedema	haematoma, haematoma from fractures, bruises
			sprains and strains	sprains and strains	sprains and strains	sprains and strains	sprains and strains, contusions, inflammation	sprains and strains, inflammation	sprains and strains	sprains and strains	sprains and strains
						torn or overexerted muscles, ligaments, also in animals	torn muscles, ligaments		torn muscles, ligaments	<i>torn muscles</i>	torn muscles, ligaments
		gout, rheumatism		gout, rheumatism			gout, rheumatism	<i>rheumatism</i>	rheumatism	gout, rheumatism	rheumatic muscle and joint problems (Commission E.)
		stiffness of joints				joint issues due to overexertion	sciatica, lumbago joint inflammation			<i>sciatica</i>	
		spasms					spasms				

Use-categories	Tabernaemontanus 1664	Löseke 1790	Richter 1827	Strumpf 1855	Hager 1876	Schulz 1919	Madaus 1938	Kroeber 1948	Weiss 1974	Saller et al 1995	Bäumler 2007
						strained vocal cords					
							contusions after passing of kidney stones				
							bone injuries <i>Bursitis praepatellaris</i>				
<b>nerve</b>	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	pain	pain due to injuries	pain due to injuries	pain due to injuries	pain due to injuries	pain due to injuries, overexertion	pain due to injuries to muscles, inflammation or infection	pain due to inner and outer injuries, inflammation, bleeding, swelling	pain due to sprains and strains, bruises, rheumatism	pain due to injuries, sprains and strains, bruises, haematoma, sciatica	pain due to injuries, sprains and strains, haematoma, oedema
						neuralgias	neuralgias		neuralgias		
		nerve injuries / function		nerve injury; inflammation			nerve injuries		nerve injuries	nerve injuries	
		paralysis	nerve stimulation in paralysis / after stroke	nerve stimulation in paralysis / after stroke / in oedema, spasms	nerve stimulation in paralysis/cerebral concussion		nerve stimulation in paralysis paralysis after contusions				
			epilepsy		epilepsy		epilepsy				
<b>respiratory</b>	0	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
		lower respiratory tract infections, tuberculosis, pneumonia, pleurisy	lower respiratory tract infections	lower respiratory tract infections		lower respiratory tract infections such as whooping cough and pneumonia	lower respiratory tract infections, influenza	bronchitis			
		breathing difficulties	breathing difficulties	breathing difficulties	accelerates respiration		breathing difficulties	breathing difficulties			

Use-categories	Tabernaemontanus 1664	Löseke 1790	Richter 1827	Strumpf 1855	Hager 1876	Schulz 1919	Madaus 1938	Kroeber 1948	Weiss 1974	Saller et al 1995	Bäumler 2007
		cough	cough, asthma (with phlegm)	cough			asthma, whooping cough	asthma, whooping cough, emphysema	chronic smoker's catarrh		
							sore throat tonsillitis		sore throat tonsillitis	sore throat	sore throat tonsillitis, peritonsillar abscess
							hoarseness		chronic pharyngitis		
<b>skin-mucous</b>	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	for sneezing (cleansing of mucous membranes)		<i>for sneezing (cleansing of mucous membranes)</i>								
			ulcers ulcers of male genitals	ulcers malignant ulcers	ulcers		ulcers	ulcer	ulcer		ulcer
					infected lesions	wounds	wounds	wounds bleeding wounds	wounds	<i>wounds</i>	wounds
						boils	boils	boils	boils	boils	boils
							infections (viral - herpes)				
						burns					
				mouth and throat (gargle)			mouth and throat (inflammation)		mouth and throat (inflammation)	mouth and throat (inflammation)	mouth and throat (inflammation); stomatitis
										inflammation from insect bites	inflammation from insect bites
										phlebitis	
<b>tonic</b>	✓	✓	✓	✓	(✓)	✓	✓	✓	✓	(✓)	✓
	for sneezing (tonic)	for sneezing (tonic)	for sneezing (tonic)	for sneezing (tonic)	<i>for sneezing (tonic)</i>		<i>for sneezing (tonic)</i>				

Use-categories	Tabernaemontanus 1664	Löseke 1790	Richter 1827	Strumpf 1855	Hager 1876	Schulz 1919	Madaus 1938	Kroeber 1948	Weiss 1974	Saller et al 1995	Bäumler 2007
					<i>smoking</i>		<i>smoking</i>				
						cardiac stimulant	debility	exhaustion		<i>exhaustion</i>	debility from overexertion
						<i>fortifying stimulant in pneumonia</i>	debility from Angina pectoris, Adipositas cordis, weak heart muscle		debility from ageing heart, Angina pectoris, weakness of the heart	<i>tonic for heart and circulation</i>	debility from Angina pectoris
								shock recovery			
<b>uro</b>	✓	✓	✓	0	✓	0	✓	0	0	0	0
	diuresis	diuresis	diuresis		diuresis						
		gravel					kidney stones (recovery from passing)				
<p><i>Dark green rows refer to continued use</i>  <i>Light green rows refer to intermittent but present-day-use</i>  <i>Grey rows refer to present-day discontinuation</i>  <i>Indications in italics and brackets (✓) reference historical uses or folk medicine uses</i></p>											

## APPENDIX 6: DETAILED ANALYSIS OF THERAPEUTIC INDICATIONS FOR *ARNICA MONTANA* RECORDED IN HISTORICAL MEDICAL TEXTBOOKS

This appendix provides a detailed discussion on the recommended medicinal uses of Arnica over the past 400 years. For an overview, the indications are tabulated in Appendix 5.

Documented indications for using *Arnica montana* have been identified in the treatment of 12 different body systems:

- **Musculo-skeletal and nervous system**

The treatments of complaints of the musculo-skeletal and nervous systems involving various types of injuries and pain syndromes have been consistently listed in the medical literature since at least the early modern period.

Main indications in the musc-skel use-category are as follows:

- inner and outer injuries (noted since Tabernaemontanus 1664)
- haematoma (noted since Löseke 1799)
- sprains and strains (noted since Richter 1827)
- torn muscles and ligaments (noted since Schulz 1919)
- gout and rheumatism (intermittent since Löseke 1799)
- stiffness of joints (intermittent since Löseke 1799).

Main indications in the nerve use-category are as follows:

- pain related to musculo-skeletal complaints (noted variously since Tabernaemontanus 1664)
- nerve injuries (intermittently noted since Löseke 1799 until Saller et al 1995).

Treatment of paralysis with Arnica as noted from Löseke 1799 until Madaus 1938 was discontinued after WW2, most likely due to better treatment options. This discontinuation does not preclude the use of Arnica as an adjunctive treatment for symptoms related to this condition.

- **Tonic**

While indications belonging to the tonic use-category have been consistently listed across the past 400 years, Arnica was applied in different ways to achieve the stimulant effect. From the mid-17<sup>th</sup> to the beginning of the 20<sup>th</sup> century the tonic effect was achieved by either habitual snuffing or smoking of Arnica, whereas from the turn of the 20<sup>th</sup> century onwards the tonic effect in debility and exhaustion from various sources was achieved by ingesting a tincture, distillate (*Schnapps* preparation), powder, or water extract.

Main indications in the tonic use-category are as follows:

- as a stimulating snuff or tobacco (noted from Tabernaemontanus 1664 until Hager 1876)
- in debility due to exhaustion or heart complaints (since Schulz 1919).

- **Cardio-vascular and respiratory systems**

Indications relating to cardio-vascular and respiratory use-categories have been noted consistently since the end of the 18<sup>th</sup> century. Awareness of the circulatory stimulant action of Arnica was raised with the conclusive confirmation of blood circulation by the English physician William Harvey in 1628. Subsequently, new physiological understandings expanded on prior traditional uses of Arnica to include indications that benefit from a stimulation of circulation and lymph flow. Continued research into Arnica's sympathicotonic, vasodilating, spasmolytic, and circulatory stimulant properties led to the inclusion of Arnica's medicinal use in coronary insufficiency, varicose veins, and phlebitis from the middle of the 20<sup>th</sup> century onwards.

Main indications in the card-vasc use-category are as follows:

- circulatory insufficiency (noted since Löseke 1799)
- congestion, swelling, paralysis, and respiratory tract infections (noted since Löseke 1799)
- bleeding (noted since Richter 1827 until Kroeber 1948)
- varicose veins (noted since Kroeber 1948)
- phlebitis (noted since Saller et al 1995).

Main indications in the respiratory use-category are as follows:

- lower respiratory tract infections (noted since Löseke 1799 until Kroeber 1948)
- breathing difficulties (noted since Löseke 1799 until Kroeber 1948)
- cough of various origins (noted since Löseke 1799 until Weiss 1974)
- sore throat (noted since Madaus 1938).

- **Skin-mucous membranes**

Indications relating to the skin-mucous membranes category have shown consistency since the middle of the 19<sup>th</sup> century. These indications were confirmed by experimental research conducted since the 19<sup>th</sup> century, providing scientific proof of Arnica's antiseptic properties.

Main indications in the skin-mucous use-category are as follows:

- ulcers (noted since Richter 1827)
- wounds (noted since Hager 1876)
- boils (noted since Schulz 1919)
- inflammation of the mouth and throat (noted since Strumpf 1855).

Additionally, Arnica snuffs were noted from Tabernaemontanus (1664) until Hager (1876). The purpose of Arnica snuffs was not only a stimulating effect, but also the cleansing of the mucous membranes in the nasal cavity.

- **Infection**

The treatment of non-specific systemic infections resulting in fever with *Arnica montana* preparations was listed from the end of the 18<sup>th</sup> century until WW2. The co-treatment of infections with Arnica was discussed once again by Bäumlner (2007). From a contemporary perspective, there are at least two different mechanisms that may support this traditional application. *In vitro* assays have demonstrated Arnica's topical antimicrobial actions against several gram-positive and gram-negative bacteria as well as fungi (ESCOP, 2003a, p. 44). It is possible that these antimicrobial properties also come to effect with internal use. In addition, infections can cause a cardiac decompensation. Human and animal experiments have

established that Arnica improves cardiac output and oxygenation (Erley, 1965, p. 236).

Within this infection use-category, there are some interesting shifts to note. Arnica came to prominence in the 18<sup>th</sup> century when it was tried as a European malaria treatment in place of imported Cinchona bark (*Cinchona officinalis*), an alkaloid rich medicine from the tropical Andean forests. Malaria, caused by protozoal parasites transmitted by mosquitos that thrive in wetlands, was widespread in swampy areas of Central Europe from antiquity to the 20<sup>th</sup> century (Adams, Alther, et al., 2011, pp. 278-288). The most likely explanation for the discontinuation of Arnica in the treatment of malaria by the mid-1800s is that Arnica was an experimental stand-in drug only when Cinchona was either unavailable or became unaffordable. Cinchona bark or its alkaloid quinine, which was first isolated in 1820 (Willcox, Bodeker, Rasoanaivo, & Addae-Kyereme, 2004), is more effective than Arnica in the treatment of malaria and remained first choice. In addition, during the 19<sup>th</sup> century, Central European wetlands were drained, thus reducing or eliminating the habitat for the malaria vector. The reduction of malaria decreased the need for experimentation with local treatment options, such as with Arnica. This example illustrates that the therapeutic use of Arnica was not randomly transmitted but came through a process of trial and error where effective treatments were passed on whilst ineffective or unnecessary treatments were eliminated.

- **Gastro-intestinal system**

Several factors may explain why indications relating to the gastro-intestinal system were consistently recommended in medical textbooks until the middle of the 20<sup>th</sup> century at which point the use of Arnica for such conditions was discontinued. Arnica root, the plant part used for the treatment of gastro-intestinal infections, was de-listed as an official plant part from the 2<sup>nd</sup> edition of the German pharmacopoeia (Pharmacopoea Germanica, 1882) onwards, possibly due to a conservation issue. This de-listing made access to Arnica root for the treatment of gastro-intestinal infections and diarrhoea more difficult. When Arnica became a protected species due to overharvesting, the root (the plant part used for the treatment of such complaints) became unavailable (Engels & Brinckmann, 2015). This coincided with

the availability of synthetic antibiotics, which became the drug of choice for the treatment of bacterial infections.

Main indications in the gastro-intest use-category are as follows:

- diarrhoea (noted since Tabernaemontanus 1664 until Kroeber 1948)
- ‘putrefaction’ (*Faulfieber*), typhus, dysentery, and other gastro-intestinal infections (noted since Löseke 1799 until Kroeber 1948).

- **Head**

Arnica was used for treating head injuries, cerebral concussion, bleeding in the brain, and paralysis after concussion from the first quarter of the 19<sup>th</sup> century onwards. It enjoyed renewed fame during 20<sup>th</sup> century war periods. With advances in trauma care, Arnica became redundant for treating haematoma and bleeding in the brain in the latter part of the 20<sup>th</sup> century; this is reflected in the discontinuation of Arnica’s specific recommendation in the treatment of head injuries. However, this did not affect the general recommendation of use of Arnica for injury recovery after traumatic events.

Main indications in the head use-category are as follows:

- eye complaints such as reduced vision, injury to the eye, or bleeding (noted since Löseke 1799 until Kroeber 1948)
- cerebral concussion (noted since Richter 1827 until Kroeber 1948)
- post stroke (noted since Richter 1827 until Madaus 1938).

- **Gynaecology**

Arnica was used medicinally as a uterine remedy at least since the 17<sup>th</sup> century to the middle of the 19<sup>th</sup> century after which such use was mainly continued in lay care.

Main indications in the gyn use-category are as follows:

- to promote menstruation in amenorrhoea and infertility (noted since Tabernaemontanus 1664 until Strumpf 1855)
- to cleanse the uterus after birth (noted since Tabernaemontanus 1664 until Stumpf 1855; also listed in Madaus 1938).

Overdoses of Arnica were also noted for the induction of abortion; however, this was a folk medicine use rather than a clinical use.

- **Liver-spleen**

The use of Arnica as a liver-spleen remedy was permanently discontinued by the end of the 18<sup>th</sup> century. This coincided with paradigmatic changes to the understanding of the human body from a humoral perspective to a pathophysiological view of illness. The remedial treatment of poisoning with Arnica most likely related to the concept of humoral detoxification.

The main indications in the liver-spleen category are as follows:

- poisoning (noted since Tabernaemontanus 1664 until Löseke 1799)
- bitter tonic (noted since Tabernaemontanus 1664 until Löseke 1799).

- **Urinary tract**

Arnica was noted by Tabernaemontanus (1664) to promote diuresis and was also used in formulations to treat urinary calculi (Löseke 1799). However, this use became de-listed in textbooks after Hager (1876).

## APPENDIX 7: INDICATIONS FOR *ARNICA MONTANA* IN THE COMMENTARIES TO THE PRUSSIAN PHARMACOPOEIA

Use-categories	Tabernaemontanus 1664	Dulk 1808 comm. to 2 <sup>nd</sup> ed. of <i>Ph. Borussica</i>	Dulk 1813 (comm. to 3 <sup>rd</sup> ed. of <i>Ph. Borussica</i> )	Dulk 1828 comm. to 4 <sup>th</sup> ed. of <i>Ph. Borussica</i>	Dulk 1829 comm. to 5 <sup>th</sup> ed. of <i>Ph. Borussica</i>	Mohr 1847 comm. to 6 <sup>th</sup> ed. of <i>Ph. Borussica</i>	Hager 1865 comm. to 7 <sup>th</sup> ed. of <i>Ph. Borussica</i>
<b>card-vasc</b>	0	0	0	0	0	<b>NO INDICATIONS</b>	✓
							circulatory stimulant to treat paralysis from injuries to the head and bone marrow, cerebral concussion, epilepsy
							circulatory insufficiency
							diaphoretic
<b>gastro-intest</b>	✓	✓	✓	✓	✓		0
	diarrhoea	diarrhoea	diarrhoea	diarrhoea	diarrhoea		
<b>gyn</b>	✓	0	0	0	0		0
	to bring on menstruation (amenorrhoea)						
	uterus complaints						
<b>head</b>	0	0	0	0	0		✓
							cerebral concussion
<b>infection</b>	0	✓	✓	✓	✓		✓
		antiseptic remedy	antiseptic remedy	antiseptic remedy	antiseptic remedy		infections resulting in fever or putrefaction
<b>liver-spleen</b>	✓	0	0	0	0		0
	poisoning						
<b>musc-skel</b>	✓	✓	✓	✓	✓		✓
	injuries	injuries	injuries	injuries	injuries		injuries

Use-categories	Tabernaemontanus 1664	Dulk 1808 comm. to 2 <sup>nd</sup> ed. of <i>Ph. Borussica</i>	Dulk 1813 (comm. to 3 <sup>rd</sup> ed. of <i>Ph. Borussica</i> )	Dulk 1828 comm. to 4 <sup>th</sup> ed. of <i>Ph. Borussica</i>	Dulk 1829 comm. to 5 <sup>th</sup> ed. of <i>Ph. Borussica</i>	Mohr 1847 comm. to 6 <sup>th</sup> ed. of <i>Ph. Borussica</i>	Hager 1865 comm. to 7 <sup>th</sup> ed. of <i>Ph. Borussica</i>
		bruises	bruises	bruises	bruises		bruises, haematomas
		rheumatism	rheumatism	rheumatism	rheumatism		
<b>nerve</b>	✓	✓	✓	✓	✓		✓
	pain						
		nerve stimulation	nerve stimulation	nerve stimulation	nerve stimulation		nerve stimulation after cerebral concussion, brain or bone marrow injuries, epilepsy, in putrefaction (septicaemia)
		paralysis	paralysis	paralysis	paralysis		paralysis
		rheumatism	rheumatism	rheumatism	rheumatism		
<b>respiratory</b>	0	0	0	0	0		✓
							breathing difficulties
<b>skin-mucous</b>	✓	✓	✓	✓	✓		✓
	for sneezing (cleansing of mucous membranes)	for sneezing (cleansing of mucous membranes)	for sneezing (cleansing of mucous membranes)	for sneezing (cleansing of mucous membranes)	for sneezing (cleansing of mucous membranes)		<i>for sneezing (cleansing of mucous membranes)</i>
		wounds	wounds	wounds	wounds		
							ulcers
<b>tonic</b>	✓	✓	✓	✓	✓		(✓)
	for sneezing (tonic)	for sneezing (tonic)	for sneezing (tonic)	for sneezing (tonic)	for sneezing (tonic)		<i>for sneezing (tonic)</i>
							<i>for smoking</i>
<b>uro</b>	✓	0	0	0	0		✓
	diuresis						diuresis

## APPENDIX 8: INDICATIONS FOR *ARNICA MONTANA* IN THE COMMENTARIES TO THE GERMAN PHARMACOPOEIA 1<sup>ST</sup> TO 10<sup>TH</sup> EDITION

Use-categories	Tabernaemontanus 1664	Hager 1874 1 <sup>st</sup> ed.	Hager 1883 2 <sup>nd</sup> ed.	Schlickum 1882 2 <sup>nd</sup> ed.	Hager 1891/1892 3 <sup>rd</sup> ed.	Fischer & Hartwich 1901 4 <sup>th</sup> ed. <i>as per 3<sup>rd</sup> ed.</i>	Jehn & Crato 1901 4 <sup>th</sup> ed.	Schneider & Süß 1902 4 <sup>th</sup> ed.	Anselmino & Gilg 1911 5 <sup>th</sup> ed.	Anselmino & Gilg 1928 6 <sup>th</sup> ed.	Böhme & Hartke 1969 7 <sup>th</sup> ed.	Böhme & Hartke 1981 8 <sup>th</sup> ed.	Hartke & Mutschler 1986 9 <sup>th</sup> ed.	Hartke 1993 10 <sup>th</sup> ed.
card- vasc	0	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	0	0
		circulatory stimulant to treat paralysis from injuries to the head and bone marrow, cerebral concussion, epilepsy, septicaemia	circula-tory stimulant to treat paralysis from injuries to the head and bone marrow, cerebral concussion, epilepsy, septicaemia	circulator y stimulant	circula-tory stimulant to treat paralysis from injuries to the head and bone marrow, cerebral concussion, epilepsy, septicaemia	circulatory stimulant to treat paralysis from injuries to the head and bone marrow, cerebral concussion, epilepsy, septicaemia	circula-tory stimulant	circula-tory stimulant in fever; in stroke; as a diaphoretic	circula-tory stimulant, excitant	circula-tory stimulantexcitant	circula-tory stimulant	circulator y stimulant to heart and brain		
			cardio-vascular weakness		cardio-vascular weakness	cardio-vascular weakness						cardio-vascular weakness		
			shock		shock	shock								
												local circulator y stimulant bleeding		
gastro- intest	✓	✓	0	0	0	0	0	0	0	0	0	0	0	0
	diarrhoea	diarrhoea												

Use-categories	Tabernaemontanus 1664	Hager 1874 1 <sup>st</sup> ed.	Hager 1883 2 <sup>nd</sup> ed.	Schlickum 1882 2 <sup>nd</sup> ed.	Hager 1891/1892 3 <sup>rd</sup> ed.	Fischer & Hartwich 1901 4 <sup>th</sup> ed. <i>as per 3<sup>rd</sup> ed.</i>	Jehn & Crato 1901 4 <sup>th</sup> ed.	Schneider & Stüss 1902 4 <sup>th</sup> ed.	Anselmino & Gilg 1911 5 <sup>th</sup> ed.	Anselmino & Gilg 1928 6 <sup>th</sup> ed.	Böhme & Hartke 1969 7 <sup>th</sup> ed.	Böhme & Hartke 1981 8 <sup>th</sup> ed.	Hartke & Mutschler 1986 9 <sup>th</sup> ed.	Hartke 1993 10 <sup>th</sup> ed.
		gastro- intestinal infections												
<b>gyn</b>	✓	0	0	0	0	0	0	0	0	0	0	(✓)	0	0
	to bring on menstrua- tion (ameno- rrhoea)													
	uterine complaints											<i>abortive</i>		
<b>head</b>	0	✓	✓	0	✓	✓	0	✓	0	0	0	0	0	0
		cerebral concussion	cerebral concuss-ion		cerebral concuss-ion	cerebral concussion								
								stroke						
												circulator y insuff- iciency in the brain		
<b>infectio n</b>	0	✓	✓	0	✓	✓	0	✓	0	0	0	0	0	0
		infections resulting in fever or putrefaction	infections resulting in fever or putrefac- tion		infections resulting in fever or putrefac- tion	infections resulting in fever or putrefaction		infec-tions result- ing in fever or putre- faction						
<b>liver- spleen</b>	✓	0	0	0	0	0	0	0	0	0	0	0	0	0
	poisoning													
<b>musc- skel</b>	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Use-categories	Tabernaemontanus 1664	Hager 1874 1 <sup>st</sup> ed.	Hager 1883 2 <sup>nd</sup> ed.	Schlickum 1882 2 <sup>nd</sup> ed.	Hager 1891/1892 3 <sup>rd</sup> ed.	Fischer & Hartwich 1901 4 <sup>th</sup> ed. <i>as per 3<sup>rd</sup> ed.</i>	Jehn & Crato 1901 4 <sup>th</sup> ed.	Schneider & Stüss 1902 4 <sup>th</sup> ed.	Anselmino & Gilg 1911 5 <sup>th</sup> ed.	Anselmino & Gilg 1928 6 <sup>th</sup> ed.	Böhme & Hartke 1969 7 <sup>th</sup> ed.	Böhme & Hartke 1981 8 <sup>th</sup> ed.	Hartke & Mutschler 1986 9 <sup>th</sup> ed.	Hartke 1993 10 <sup>th</sup> ed.
	injuries	internal and external injuries	internal and external injuries	sprains and strains	internal and external injuries	internal and external injuries	sprains and strains	sprains and strains	sprains and strains	sprains and strains	sprains and strains	sprains and strains; blunt injuries	sprains and strains	sprains and strains; blunt injuries
		bruises haematoma	bruises haema-toma		bruises haema-toma	bruises haema-toma		bruises haematoma	bruises, haematoma	bruises, haematoma	bruises, haematoma, oedema	bruises, haematoma oedema		bruises, haematoma oedema
		rheumatism	rheumatism									rheumatism		
													muscle pain	muscle pain
														joint pain
<b>nerve</b>	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	pain	pain from internal and external injuries	pain from internal and external injuries	pain from sprains and strains	pain from internal and external injuries	pain from internal and external injuries	pain from sprains and strains	pain from sprains and strains neuralgias	pain from sprains and strains	pain from sprains and strains	pain from sprains and strains	pain from sprains and strains; blunt injuries	pain from sprains and strains	muscle and joint pain
		nerve stimulation after cerebral concussion, brain or bone marrow injuries, epilepsy, in putrefaction / septicaemia	nerve stimulation after cerebral concussion, brain or bone marrow injuries, epilepsy, in putrefaction / septicaemia	nerve stimulant	nerve stimulation after cerebral concussion, brain or bone marrow injuries, epilepsy, in putrefaction / septicaemia	nerve stimulation after cerebral concussion, brain or bone marrow injuries, epilepsy, in putrefaction / septicaemia	nerve stimulant	nerve stimulation in epilepsy, septicaemia  nerve complaints						
		paralysis	paralysis		paralysis	paralysis								

Use-categories	Tabernaemontanus 1664	Hager 1874 1 <sup>st</sup> ed.	Hager 1883 2 <sup>nd</sup> ed.	Schlickum 1882 2 <sup>nd</sup> ed.	Hager 1891/1892 3 <sup>rd</sup> ed.	Fischer & Hartwich 1901 4 <sup>th</sup> ed. <i>as per 3<sup>rd</sup> ed.</i>	Jehn & Crato 1901 4 <sup>th</sup> ed.	Schneider & Stüss 1902 4 <sup>th</sup> ed.	Anselmino & Gilg 1911 5 <sup>th</sup> ed.	Anselmino & Gilg 1928 6 <sup>th</sup> ed.	Böhme & Hartke 1969 7 <sup>th</sup> ed.	Böhme & Hartke 1981 8 <sup>th</sup> ed.	Hartke & Mutschler 1986 9 <sup>th</sup> ed.	Hartke 1993 10 <sup>th</sup> ed.
		rheumatism	rheuma- tism									rheuma- tism		
<b>respira- tory</b>	0	✓	✓	0	✓	✓	0	0	0	0	0	0	0	0
		breathing difficulties	breathing difficulties		breathing difficulties	breathing difficulties								
<b>skin- mucous</b>	✓	✓	✓	0	✓	✓	0	✓	✓	✓	✓	✓	0	0
	for sneezing - cleansing of mucous membra- nes	for sneezing -cleansing of mucous membra- nes			for sneezing- cleansing of mucous membra- nes	for sneezing- cleansing of mucous membra- nes		for snee- zing- clean-sing of mucous mem- branes						
		ulcers	ulcers		ulcers	ulcers								
								wounds	wounds	wounds		wounds		
											inflamma- tion of the mucous mem- branes of the mouth	inflamma- tion of the mucous mem- branes of the mouth		
<b>tonic</b>	✓	✓	✓	0	✓	✓	0	✓	✓	✓	0	0	0	0
	for sneezing (tonic)	for sneezing (tonic)			for sneezing (tonic)	for sneezing (tonic)		for sneezing (tonic)						
	for smoking	for smoking			for smoking	for smoking		for smoking						
			shock from sudden collapse, fall, suggillation		shock from sudden collapse, fall, suggillation	shock from sudden collapse, fall, suggillation								
								tonic	tonic / exci-tant	tonic / (excitant				
<b>uro</b>	✓	✓	✓	0	✓	✓	0	✓	0	0	0	0	0	0
	diuresis	diuresis			diuresis	diuresis		diuresis						

## **APPENDIX 9: EVALUATION OF INDICATIONS LISTED IN THE COMMENTARIES TO THE GERMAN PHARMACOPOEIA**

Commentaries to the German pharmacopoeia are used as an independent source to triangulate therapeutic use data recorded in medical textbooks. This body of literature is also a potential source of bibliographic evidence for verifying claims on traditional clinical applications of medicinal plants. Alongside Appendix 8 which tabulates the indications of Arnica as endorsed in the commentaries to the German pharmacopoeia, this appendix provides a comprehensive evaluation of these indications in the context in which they were embedded.

The 19<sup>th</sup> century commentaries provide evidence of congruency between the normative but not legally binding commentaries to the German pharmacopoeia and contemporaneous clinically based medical textbooks. Apart from the gastro-intest use-category, both bodies of literature list indications in nine use-categories (card-vasc, head, infection, musc-skel, nerve, respiratory system, skin-mucous, tonic, and urinary tract) as displayed in Appendices 5 and 8. These nine use-categories expand on body systems addressed by Tabernaemontanus in the following areas; the stimulating effect of Arnica on the cardiovascular and respiratory system, its benefits in trauma to the head, and its anti-infective effects on systemic and topical infections.

The various commentaries reveal considerable differences in depth of therapeutic information offered. While some commentaries are extensive (Hager, 1874, 1883a; Hager et al., 1891), another of the same period is short (Schlickum, 1883, pp. 178-179) and one does not offer therapeutic guidance at all (Hirsch & Schneider, 1891). Since Hager (1865) was the commentator of the last edition of the Prussian pharmacopoeia, a text which became the founding text for the *Ph. Germania*, his commentaries mirror initially the same indications.

The 2<sup>nd</sup> commentary by Hager (1883a) demonstrates that tradition is not static but expands when new insights are gained. This commentary lists three new indications; rheumatic complaints, cardiovascular weakness, and shock. For the last, it recommends a preparation with ½ teaspoon of a 1:10 Arnica tincture in ½ a glass of sugar water, drunk at once for the treatment of shock from sudden collapse, fall, or contusion. Unlike the 1<sup>st</sup> commentary, the

2<sup>nd</sup> commentary does not list the treatment of gastro-intestinal infections with Arnica root because the German pharmacopoeia de-listed this plant part as an official drug.

By the turn of the 20<sup>th</sup> century, divergent views between academic scholars and clinicians become apparent. Compared with the clinician authored medical literature, annotations to the German pharmacopoeia now display a reductionist trend in their endorsements of indications of *Arnica montana* (Anselmino & Gilg, 1911c, 1911d, 1928). It is beyond the scope of this research to discuss how the privileging of the new natural-science based medical paradigm, commercial competition, and politically enforced regulatory requirements shaped the development of drug approvals, licensing guidelines, and funding. It is, however, important to understand that the evaluations of the therapeutic value of Arnica and other drugs reflect broader contextual factors within their time. They cannot be considered as an assessment purely based on a neutral scientific position. Rapid changes in pharmaceutical manufacturing captivated European healthcare during this time, and almost all newly developed and registered medicines became chemically synthesised (Müller-Jahncke & Friedrich, 1996). The rapid rise of industrial pharmaceutical manufacturing threatened the commercial viability of local compounding pharmacists, their image as traditionalists, and their skill base (Anselmino & Gilg, 1911a, p. VI). By the turn of the 20<sup>th</sup> century, long-standing, traditional plant drugs that were mainstream medicines until then became a target of commercial rivalry. In response to intense competition from industrially mass-produced pharmaceutical drugs and in an attempt to gain legitimacy and a greater share of the market, local pharmacists developed a strategy to frame their image as that of modern scientists (Huisman, 1999; Quirke & Slinn, 2010, p. 21). Over time, a focused narrative framed traditional plant medicines and other non-pharmaceutical approaches to health as ‘unscientific’ or ‘quackery’, a situation that persists to this day (Holmes et al., 2006; Schwager, 2012; Walach, 2009).

It is in this context that the commentators on the 5<sup>th</sup> German pharmacopoeia distance themselves from the broader, empirically-based use of Arnica applied by contemporaneous physicians. They reduce the indications of Arnica to its use as a circulatory stimulant, as a treatment for bruises, haematoma, sprains and strains, as a topical disinfectant in wounds, and as an internal tonic (use-categories card-vasc, musc-skel, nerve, skin-mucous, and tonic) (Anselmino & Gilg, 1911d, pp. 537-539; 1928, pp. 604-607). As non-clinicians, the commentators omit all traditional indications relating to Arnica’s nerve and respiratory stimulant actions, to its use in the recovery for head injuries, to its treatment of systemic

infections, and to its diuretic effects. The authors acknowledge Arnica's essential oil and bitter principles but are unaware of other complex mechanisms involved in the diverse therapeutic effects of Arnica.

Even though indications were reduced in the commentaries to the German pharmacopoeia during the first decades of the 20th century, Arnica continued to be used in patient care and attracted scientific curiosity. Experimental *in vitro* and animal studies in chemistry, pharmacology, and toxicology from the 1930s onwards contributed to an increasing evidence base for the clinical use of Arnica (Faber, 1953a; Kreitmair, 1952; Kroeber, 1949a; Labadie, 1968; Stirnadel, 1959). This increase is reflected in the partial re-introduction to the German pharmacopoeia of traditional indications in the 7<sup>th</sup> and 8<sup>th</sup> commentary by two professors of pharmacy, H. Böhme and K. Hartke from the University of Marburg (1969, 1981).

In their commentary to *DAB 7*, Böhme and Hartke (1969, pp. 509-512) discuss Arnica as a circulatory stimulant based on the presence of distinct active constituents in Arnica flower; these had been scientifically shown to activate blood circulation in skin and mucous membranes. This stimulant effect had previously been recorded in the medical literature based on empirical observations. The authors further endorse topical uses of Arnica preparations with a 2% infusion or with a 20-25% cream (prepared with a 1:10 tincture) to recover from injury, bruises and haematomas, to decrease fluid in oedema, to support the healing of sprains, and to accelerate wound healing. These are long-standing historical indications. Based on pharmacological evidence, the authors further recommend a gargle or paint with either a 2% Arnica infusion or a 1:10 Arnica tincture (diluted five to ten times with water) for the treatment of inflammation of the mucous membranes in the mouth, another clinical indication previously noted in the medical literature (Fischer, 1941, p. 59; Schulz, 1919, p. 298).

The authors claim, however, that the use of Arnica in cardio-vascular weakness and asthma is not defensible with modern pharmacology (Böhme & Hartke, 1969, p. 512). This comment highlights divergent views between an academic approach to the European *materia medica* and clinical practice at the time (Weiss, 1974, p. 177). In contrast to the 1969 commentary, post WW2 medical textbooks continued to list clinical uses of Arnica preparations for conditions such as coronary heart insufficiency, *Angina pectoris*, asthma, arteriosclerosis, and emphysema (Kroeber, 1949a; Stirnadel, 1959).

In the commentary to *DAB 8*, Böhme and Hartke (1981, pp. 161-167) come to accept the empirically observed systemic circulatory stimulant effect of Arnica on the cardio-vascular system and the brain as well as its local stimulant action. Their re-assessment is informed by new experimental research into the active constituent profile of Arnica, which discovered the flavonoids astragalín and isoquercitrín with plausible systemic or local circulation actions. The 8<sup>th</sup> commentary (1981) also re-lists the traditional indication of rheumatism, an indication that was recorded in the 1<sup>st</sup> and 2<sup>nd</sup> commentary to the German pharmacopoeia (Hager, 1873, 1874; 1883a, p. 752) but that became de-listed when the mechanism of therapeutic action could not be explained by modern science methodologies. By the 1980s, research into the molecular mode of actions of Arnica elucidated its mechanism of inhibition on the transcription factors NF- $\kappa$ B and NF-AT at micromolar concentrations. Both transcription factors regulate how genes encode many inflammatory mediators (Merfort, 2003). The anti-inflammatory effect of this mechanism in rheumatism is now also established with clinical trials (Cameron et al., 2009; Knuesel et al., 2002; Widrig et al., 2007).

Parallel to the re-introduction of traditional clinical indications, the commentary to *DAB 8* (1981) highlights the risk profile of *Arnica montana*. The commentators caution against excessive doses of Arnica preparations, both internally and externally. Excessive external doses are said to lead to significant inflammation, including blisters and even necrosis, whilst excessive internal doses are said to irritate the mucous membranes of the gastrointestinal system, which can cause nausea, vomiting, and diarrhoea. Such toxic side-effects based on overdoses had been previously noted in medical textbooks. The commentators to *DAB 8* confirm symptoms of transient central nervous system dysfunction such as significant irritability and paralysis when Arnica is taken at extreme high doses for abortive purposes. The commentary lists the safe internal dose as 0.3-0.5g (20-30 drops) of tincture or an infusion of 200mg of flowers in 200ml hot water, taken by tablespoon full 10ml at a time. A 2% Arnica flower infusion is recorded as a safe external application (Böhme & Hartke, 1981, p. 165).

While the commentary to the 8<sup>th</sup> German pharmacopoeia continues to endorse the internal use of Arnica within a safe therapeutic dosage range, German commentaries beyond the 1980s depart from such a favourable benefit-risk assessment. This departure reflects a period when official risk assessments of plant medicines changed overall (Zepernick et al., 1983). Until the 1980s, several European pharmacopoeia monographs and their

commentaries consistently endorsed both the internal and external use of Arnica preparations as exemplified in the German (*DAB 8, 2. AB-DDR*), Swiss (*Ph. Helv. VI.*), Austrian (*ÖAB*), and French (*FP 56*) pharmacopoeias (Blaschek et al., 2012; Zepernick et al., 1983, pp. 56-59). Research during the 1980s did not add new information regarding Arnica's constituents, its proposed modes of actions, or its therapeutic effects, but a new approach to risk prompted some national regulators to recommend against most Arnica preparations for internal use (Wijnsma et al., 1995, p. 54; Zepernick et al., 1983, pp. 56-59). Since the 1980s, the only approved internal preparations are listed in *HAB I* (1981), the homoeopathic compendium to the German pharmacopoeia. These preparations are traditional mother tinctures (strength 1:10) of various plant parts which are applied either undiluted as phytotherapeutic preparations or diluted as homoeopathic preparations.

The commentary to the Arnica monograph in *DAB 9*, written by toxicologist Schäfer-Korting (Hartke et al., 1987, p. 876), signals an unprecedented departure from previous expert consensus. She sees the therapeutic action of Arnica as *ungewiss* (doubtful). Despite the availability of consistent empirical evidence that was noted in medical and pharmaceutical textbooks (see Appendix 5) and evidence from experimental research and clinical patient research (see Appendix 11), Schäfer-Korting drastically reduces the indications for Arnica tincture to two areas of topical treatment: sprains and muscular pain. Without elaborating on dosage, she advises against internal use of Arnica due to 'intoxication' (Hartke et al., 1987, p. 876). Contradicting the assessment of the Commission E on *Arnica montana* which permitted Arnica's use as a disinfectant on small wounds of the skin, Schäfer-Korting recommends the use of Arnica preparations for unbroken skin only.

The commentary to *DAB 10* (1993) reverses some of the narrowing of indications noted in the commentary to *DAB 9*. However, without elaborating on dosage, it recommends that systemic, internal applications are to be excluded from clinical practice. Therefore, by the end of the 20<sup>th</sup> century, indications relating to the external use of Arnica in the treatment of musculo-skeletal injury and pain remained the only indications endorsed in the commentary to the German pharmacopoeia. There are no amendments for Arnica noted in *DAB 2012*.

In conclusion, commentaries to the German pharmacopoeia independently validate the main indications of Arnica recorded in the mainstream medical literature. They could be used as an additional source of bibliographic evidence for traditional health claims. Their limitations are that their assessments are academic rather than clinical and represent the

regulator. Therefore, they should not be used as the sole source of evidence on traditional medicinal plant uses since they do not represent the broader clinical applications in clinical patient care.

## APPENDIX 10: INDICATIONS FOR *ARNICA MONTANA* IN OFFICIAL AND AUTHORITATIVE MONOGRAPHS COMPARED WITH THE MEDICAL LITERATURE

Use-categories	Indications – medical literature 400 years	Indications – medical literature > 30 years	Commission E 1984 approved claims	EMA 2014 approved claims	ESCOP 2003 endorsed claims	WHO 2007 endorsed claims	HagerROM 2012 endorsed claims
<b>card-vasc</b>	0	✓	✓	0	(✓)	✓	✓
		varicose veins / phlebitis (topical) (since Kroeber 1948)	superficial phlebitis		positive RCT on varicose veins (not listed under indication)	superficial phlebitis	superficial phlebitis
		cardiac stimulant (since Schulz 1919) – official until mid-1980s				cardiovascular disease	cardiovascular diseases (myocarditis, atherosclerosis, Angina pectoris)
		circulatory stimulant (since Löseke 1790) – official until mid-1980s					cardiovascular weakness
		circulatory insufficiency (since Löseke 1790) – official until mid-1980s					circulatory insufficiency frostbites
							illness of the arterial and venous system (mother tincture with root HAB 4a)
<b>gastro-intest</b>	intermittent	0	0	0	0	✓	0
	diarrhoea (until Kroeber 1948)					indigestion	

Use-categories	Indications – medical literature 400 years	Indications – medical literature > 30 years	Commission E 1984 approved claims	EMA 2014 approved claims	ESCOP 2003 endorsed claims	WHO 2007 endorsed claims	HagerROM 2012 endorsed claims
<b>gyn</b>	intermittent	0	0	0	0	✓	(✓)
	to bring on menstruation (until Strumpf 1855)					emmenagogue	
	uterus complaints (until Madaus 1938)						(heavy) bleeding during birth
							(heavy) bleeding during peri-menopause
<b>head</b>	intermittent	0	0	0	0	0	0
	cerebral concussion (from Richter 1927-Kroeber 1948)						
<b>infection</b>	intermittent	0	0	0	0	0	(✓)
	infections resulting in fever (until Madaus 1938)						fever (herb)
	infections resulting in fever (until Madaus 1938)						infectious diseases (root)
<b>liver-spleen</b>	pre-modern	0	0	0	0	0	0
	poisoning, bitter tonic, jaundice (until Löseke 1790)						
<b>musc-skel</b>	✓	✓	✓	✓	✓	✓	✓
	injuries, sprains and strains		injury and accidents	sprains	sprains	minor injuries and accidents	injury and accidents

Use-categories	Indications – medical literature 400 years	Indications – medical literature > 30 years	Commission E 1984 approved claims	EMA 2014 approved claims	ESCOP 2003 endorsed claims	WHO 2007 endorsed claims	HagerROM 2012 endorsed claims
	torn muscles and ligaments, bruises, oedema, haematoma		consequences of accidents, i.e. haematoma, dislocations, contusions, oedema due to fracture	bruises	bruises	bruises, ecchymoses, haematomas and petechiae	consequences of accidents, e.g. haematoma, dislocations, contusions, oedema due to fracture <i>sprains, contusions</i>
	rheumatism ( <i>since Löseke 1790</i> )	rheumatic muscle and joint problems	rheumatic muscle and joint problems		rheumatic complaints	rheumatism	rheumatic muscle and joint problems
				muscular pain			myalgia (mother tincture with root HAB 4a)
<b>nerve</b>	✓	✓	✓	✓	✓	✓	✓
	pain related to musculo-skeletal system and nerves		pain due to injury and accidents	pain due to sprains	sprains	pain due to minor injuries and accidents	pain due to injury and accidents
					pain due to rheumatic complaints	pain due to rheumatism	pain due to injury and accidents
					<i>pain in primary varicose veins (indication not listed)</i>		
				muscular pain	<i>RCT on muscle aches (indication not listed)</i>		myalgia (mother tincture with root HAB 4a)
			pain due to haematoma and oedema	pain due to bruises		pain due to bruises, ecchymoses, haematomas and petechiae	pain due to haematoma and oedema
<b>respiratory</b>	intermittent	✓	✓	0	0	✓	✓

Use-categories	Indications – medical literature 400 years	Indications – medical literature > 30 years	Commission E 1984 approved claims	EMA 2014 approved claims	ESCOP 2003 endorsed claims	WHO 2007 endorsed claims	HagerROM 2012 endorsed claims
	cough <i>(since Löseke 1790 until Weiss 1974)</i>						
	lower respiratory tract infections <i>(since Löseke 1790 until Kroeber 1938)</i>						
		sore throat <i>(since Madaus 1938)</i>	inflammation of mucous membranes of mouth and throat			inflammation of the oral mucous membranes	inflammation of mucous membranes of mouth and throat
<b>skin-mucous</b>	intermittent	✓	✓	0	✓	✓	✓
	sneezing - cleansing of mucous membranes <i>(until Madaus 1938)</i>						
		ulcers, infected lesions or wounds <i>(since Richter 1827)</i>					<i>wounds (herb)</i>  <i>bleeding from internal or external wounds (root)</i>
		boils <i>(since Schulz 1919)</i>	furunculosis				furunculosis
		mouth and throat gargle <i>(since Strumpf 1855)</i>	inflammation of mucous membranes of mouth and throat		gingivitis aphthous ulcers	inflammation of the oral mucous membranes	inflammation of the oral and throat region
		varicose veins / phlebitis (topical) <i>(since Kroeber 1948)</i>	superficial phlebitis			inflammation of superficial phlebitis	superficial phlebitis
			inflammation caused by insect bites		inflammation caused by insect bites	inflammation of insect bites	inflammation caused by insect bites

Use-categories	Indications – medical literature 400 years	Indications – medical literature > 30 years	Commission E 1984 approved claims	EMA 2014 approved claims	ESCOP 2003 endorsed claims	WHO 2007 endorsed claims	HagerROM 2012 endorsed claims
							<i>in cosmetics as an antimicrobial in face creams, tooth paste, hair waters</i>
							<i>hair waters to prevent hair loss</i>
<b>tonic</b>	✓	✓	0	0	0	0	(✓)
	for sneezing – tonic action <i>(until Madaus 1938)</i>						<i>severe exhaustion and cardio-vascular weakness</i>
	cardiac stimulant <i>(since Schulz 1919)</i>						<i>oil for liquors (Benediktiner, Karthäuser)</i>
<b>uro</b>	Intermittent	0	0	0	0	0	0
	Diuresis <i>(until Madaus 1938)</i>						

*Dark green rows refer to continued use  
 Light green rows refer to intermittent but present-day-use  
 Grey rows refer to present-day discontinuation  
 Indications in italics and brackets (✓) reference historical uses or folk medicine uses*

The *Kommission E Monografie (Commission E Monograph)* is a regulatory monograph by the former German *Bundesgesundheitsamt (BGA)* (German Ministry of Health) that provided approved claims for sale of plant-based medicines based on empirical and scientific evidence.

The *European Union Herbal Monograph* is a regulatory monograph authored by the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) based on consensus of 28 EU Member States. The Arnica monograph evaluated was a ‘traditional use’ monograph.

The ESCOP, WHO and HagerROM monographs are authoritative expert monographs and provide broader perspectives on clinical use of a medicinal plant.

## **APPENDIX 11: *ARNICA MONTANA* DATABASE RESEARCH EXCEL SPREADSHEET**

This spreadsheet is attached separately.

## APPENDIX 12: TRANSCRIPT OF *HYPERICUM PERFORATUM* MONOGRAPH IN TABERNAEMONTANUS (1664)

This appendix is the German language transcript of Tabernaemontanus' monograph on *Hypericum spp.* The pharmaceutical and pharmacological data is translated into English in Appendix 13.

**Das CXL III. Capitel.**  
**VON SANCT JOHANNESKRAUT**  
**1. Sanct Johanneskraut.**  
**Hypericon.**

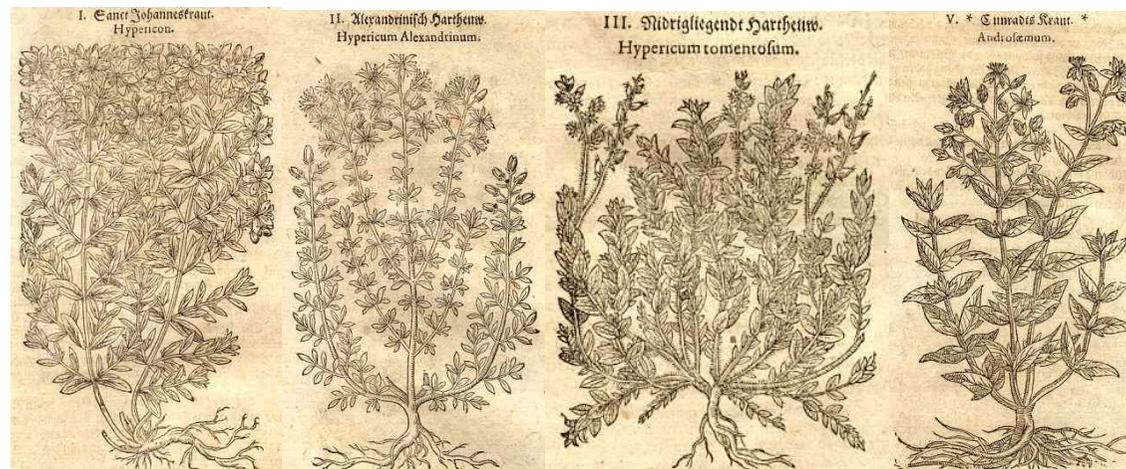


Figure 9. *Hypericum perforatum* in Tabernaemontanus 1664, pp. 1249-1250

<Buch 2, Sektion 11, Kapitel 143, S.1249B-1252A>

	Originaltext	Moderne Übersetzung
I. Sanct Johanskraut	<p>Sanct Johanneskraut (I.) hat ein harte holtzechte Wurtzel / welche sich hin und wider im Land weit außbreitet / auß der Wurtzel entstehen viel runde / holtzechte / braunrothe Stengel / welche einer Elen hoch wachsen / mit andern Nebenästlein besetzt / an welches Gieppfel kleine Blümlein erscheinen / mit fünff gelben Blättlein geziehret / mit härichten Fäsichen / wenn man diese Blumen zwischen den Fingern zerreibet / wie auch seine Blätter / so geben sie / wie DODONÆUS schreibet / einen schwarzrothen / oder vielmehr einen braunroten Safft / wie ein Blut. Die Blätter seyn etwas breyt / auch länger dann rund / den Dostenblättern oder Gauchheyl bey nahe gleich / und so man sie gegen dem Tag oder das Liecht helt / sihet man viel kleiner Löchlein darinn / als wären sie mit Nadeln durchstochen. Nach den Blumen wachsen kleine Schörtlein / welche forn spitzig seyn / und an dem Stiel runde und etwas weit einem Gerstenkorn ähnlich / in welchen sehr kleiner Saame verschlossen ist / welcher</p>	<p>I. Sankt Johanniskraut besitzt eine zum Verholzen neigende Wurzel, die sich gelegentlich weitflächig ausbreitet; aus der Wurzel sprießen mehrere runde, verholzende rotbraune Stengel, die bis zu einer Höhe von 60 bis 70 Zentimetern aufwachsen, sich astig verzweigen, am Ende kleine Blüten mit fünf gelben Kronblättern tragen, die mit haarigen Fäserchen besetzt sind. Wenn man diese Blüten, wie auch die Blätter, zwischen den Fingern zerreibt, dann geben sie, wie Rembert Dodoens schreibt, einen dunkelroten oder braunroten Saft wie Blut. Die Blätter sind breit und eher länglich als rund, den Blättern des Thymianostes<sup>40</sup> oder Ackergauchheils<sup>41</sup> nahezu gleich, und wenn man sie gegen das Tages- oder Kerzenlicht hält, sieht man in ihnen viele kleine Löchlein, als wären sie mit Nadeln perforiert worden<sup>42</sup>. Aus den Blüten wachsen kleine Schoten, die spitz zulaufen, am Stiel breiter sind und einem Gerstenkorn ähnlich sehen; sie umschließen winzig</p>

<sup>40</sup> *Origanum vulgare* L.; MARZELL (2000), III, 449ff.

<sup>41</sup> *Anagallis arvensis* L.; MARZELL (2000), I, 253ff.

<sup>42</sup> Zu den Perforationssagen sieh HWdAgl. (1927-1942), III, 1485ff.

	Originaltext	Moderne Übersetzung
	erstlich roht / darnach schwartz wird / am Geschmack dem Hartz gleich / wie DODONÆUS vermeldet.	kleinen Samen, der zunächst rot ist, dann schwarz wird und wie Koniferenharz schmeckt, wie Dodoens berichtet <sup>43</sup> .
II. Alexandrinisch Hartheuw	II. Von dem andern Geschlecht schreibt LOBELIUS, daß seine Blätter viel kleiner seyen / dann am ersten Geschlecht / sonst sey es mit seinen gelben Blümlein demselbigen durchauß gleich.	II. Von der anderen Art schreibt Matthias Lobelius van Rijssel <sup>44</sup> , dass ihre Blätter erheblich kleiner seien; ansonsten würde sie mit ihren gelben Blüten der erstbeschriebenen Art durchaus gleichen <sup>45</sup> .
III. Nidrigligend Hartheuw.	III Das dritte Geschlecht HYPERICON TOMENTOSUM, genennt / hat ein hartes holtzechtes Würtzlein / mit viel Zaseln / deren sich etliche über die Erden außbreyten / über die Wurtzel kommen viel rauhe Zweiglein / welche sich über die Erden außbreiten / mit viel kleinen Blettlein besetzt / wie an dem gemeinen Sanct Johanskraut / außgenommen daß sie graw und wollecht seyn: Seine blümlein seyn von Farben gelb / doch etwas bleicher dann am andern Geschlecht.	III. Die dritte Art, die sich <i>Hypericum tomentosum</i> nennt <sup>46</sup> , verfügt über eine kleine, harte, verholzende Wurzel mit zahlreichen Wurzelfäserchen <sup>47</sup> , von denen einige über dem Boden verlaufen. Die Stengel sind zahlreich, niederliegend und rauh; sie zeigen einen Besatz mit vielen kleinen Blättern wie beim echten Sankt Johanniskraut, mit dem Unterschied allerdings, dass sie grau und wollig erscheinen. Die Blüten sind zwar ebenfalls gelb, wirken aber blasser als bei der anderen Art.
	Dem Johanskraut werden noch zwey andere Geschlecht zugeschrieben / so von dem Authore noch nit seyn / nemlich Hartheuw und Conradskraut / von welchen man	Unter „Johanskraut“ werden noch zwei weitere Arten aufgelistet, die dem Autor <sup>48</sup> noch nicht bekannt sind, nämlich

<sup>43</sup> „het welke ghewreven zijnde nae den Harst schijnt te riecken“, DODOENS (1644), S. 101b. Dies wurde bereits bei Dioskurides vermerkt, DIOSCURIDES (1610) III, S.242.

<sup>44</sup> In seiner *Plantarum seu stirpium historia* von 1576.

<sup>45</sup> Das hier als andere, sehr ähnliche Art geführte (und in der Bild-Beischrift als „*Hypericum Alexandrinum*“) ausgewiesene *Hypericum quadrangulum* L. = *Hypericum maculatum* GRANTZ wurde in der Volksbotanik vom Sankt Johanniskraut *Hypericum perforatum* L. nicht unterschieden; vgl. MARZELL (2000), II, 937f.

<sup>46</sup> Vermutlich *Hypericum elodes* L. (= *Elodes palustris* SPACH.) oder *Hypericum humifusum* L. „Tomentosum“ bezieht sich auf den ‚wollig‘- filzigen Besatz der Stengel und Blätter; vgl. GEORGES (1879/80), II, Sp. 2824; Dfg. 587a „*tomentum*“, und sieh auch DRAGENDORFF (1898), S. 437f.

<sup>47</sup> Zur Bedeutung der ‚kleinen Fasern an der Pflanzenwurzel‘ sieh DWB, XV = 31, Sp. 314.

<sup>48</sup> Der Erstautor des Werkes, Tabernaemontanus.

	Originaltext	Moderne Übersetzung
	bey dem DIOSCORIDE und DODONÆO lesen kan / sie seyn aber diesem Johanskraut fast gleich / allein daß das Harthew ständlecher ist / auch grösser Stengel und Aest hat / welche braunrot seyn. In dem Conradskraut kommen / als neben den grossen Blättern / andere kleine Blättlein herfür.	Hartheu <sup>49</sup> und Konradskraut <sup>50</sup> , über die man indessen bei Dioskurides <sup>51</sup> und Dodoens <sup>52</sup> etwas nachlesen kann; sie sind freilich mit dem echten Sankt Johanniskraut nahezu identisch, ausgenommen dass das Hartheu stabiler <sup>53</sup> ist und höher aufragende Stengel und Seitentriebe besitzt, die rotbraun gefärbt sind. Beim Konradskraut sprießen neben den großen auch noch kleinere Blätter hervor.
IV. Hartheuw	IV. [Das Hartheuw hat ein weißlecht Wurtzeln / in viel Zaseln zertheilet / so nicht tieff in der Erden stecken / auß welcher die Stengel herfür schiessen / so braunrot und grösser dann am St. Johanskraut: die Blätter sind dünn / mit Striemlein nach der länge durchzogen / so viel breiter und länger dann am St. Johanskraut: die Blumen sind Dottergelb: Der Saamen klein und schwarzlecht am Geruch wie Hartz / welcher zwischen den Fingern zerrieben / dieselbige färben / als wann sie mit Blut angestrichen wären.	IV. <sup>54</sup> [Das Hartheu besitzt eine helle, weißliche Wurzel, die sich fasrig verästelt und nicht tief in die Erde reicht; aus ihr sprießen zahlreiche Stengel, braunrot gefärbt und höher aufragend als die des Sankt Johanniskrauts; die Blätter sind dünn, der Länge nach von Nerven durchzogen, im übrigen breiter und länger als beim Sankt Johanniskraut; die Blüten erscheinen dottergelb. Die kleinen, schwärzlichen Samen riechen nach (Koniferen-)Harz und färben, wenn sie zerrieben werden, die Finger dunkelrot, wie mit Blut bestrichen.
V. Conrads kraut	V. Conradskraut aber ist ein standechtes Kraut / mit schmalen rothen Aestlein / die Blätter sind länger und spitziger dann deß Harthew / allwegen ein par beysamen /	V. Das Konradskraut oder Mannsblut zeigt dagegen einen stabilen, aufrechten Wuchs, besitzt schmale, rot-stenglige Verästelungen; seine Blätter sind länger und spitzer als beim

<sup>49</sup> In der Tat bezeichnet „Hartheu“ üblicherweise das Sankt Johanneskraut, also die erstgenannte Art vgl. MARZELL (2000), II, S. 939-940.

<sup>50</sup> Dies bezieht sich auf „Mannsblut“, *Hypericum androsaemum* L., das von den Botanikern des 16. Jahrhunderts allerdings auch als *Hypericum perforatum* gedeutet wurde; vgl. MARZELL (2000), II, S. 937.

<sup>51</sup> DIOSCURIDES (1610), III, S.243; BERENDES (1902), S. 362f.

<sup>52</sup> DODENS (1664), S. 102a.

<sup>53</sup> Zur Bedeutung „ständlich“ ‚stabilis‘ siehe DWB, X/II/I = 17, Sp. 778.

<sup>54</sup> Abschnitt IV und V sind von der Bauhin Redaktion dem Originaltext beigelegt worden. Siehe Anm. 9 bis 11.

	Originaltext	Moderne Übersetzung
	zwischen jedem par wachsen andere kleine blättlein: am obern theil deß Stengels / bringet es viel Nebenzweige / wie Flügel außgespreitet / umb welche kleine gelbe Blümlein wachsen: Der Saamen ligt in Hülsen / dem schwarzen Magsamen ähnlich. Diese beyde Kräuter wachsen an feuchten Orthen.]	Hartheu, sie wachsen gegenständig, und zwischen jedem Blattpaar sprießen kleine Nebenblätter; der obere Stengel verzweigt sich und breitet seine Seitenstengel wie Flügel aus, auf denen kleine gelbe Blüten wachsen. Die Samen liegen in Hülsen wie der schwarze Samen des Schlafmohns. Diese beiden Kräuter <sup>55</sup> bevorzugen feuchte Standorte.]
	St. Johannskraut wächst allenthalben in den Hecken / an den Reinen und in den Wiesen / blühet im Julio.	Das Sankt Johanniskraut ist verbreitet und wächst in Hecken, auf Rainen und Wiesen; im Juli blüht es.
	<p><b>Von den Namen.</b></p> <p>Sanct Johannskraut heißt Griechisch <i>ὑπέρικον</i>, Lateinisch HYPERICUM, PERFORATA, FUGA DÆMONUM. [I. HYPERICUM VULGARE, C.B. HYPERICOUM, BRUNF. MATT. FUCH. ANG. TUR. LAC. LON. DOD. AD. LOB. CÆS. LUGD. CAST. CAM. GER. EYST. HERBA PERFORATA &amp; HYPERICUM VULGARE, TRAG. ASCYRON. DOD. GAL. CORD. IN DIOSC. ANDROSÆMON MINUS, GER. COL. II. HYPERICUM FOLIO BREVIORE, C.B. SYRIACUM &amp; ALEXANDRINUM, LOB. SYRIACUM, LUGD GER.</p>	<p><b>Von den Namen.</b></p> <p>Sankt Johanniskraut heißt auf Griechisch „hypérikon“, auf Lateinisch „Hypericum“, „(Herba) Perforata“, „Fuga daemonum“<sup>56</sup> [...] <sup>57</sup>. Auf Arabisch „Rejo. fricon.“ Auf Italienisch<sup>58</sup> „Hiperico.“ „Herba rossa“, auf Französisch „Mille pertuis“, auf Englisch „G(reat). Johannes woorte“, auf Tschechisch<sup>59</sup> „Zwoncek cerweny“, [auf Niederländisch „Sint Janscruyt“], auf Spanisch „concillo“<sup>60</sup> - „Hartheu“, auch als „Waldhopfen“ bezeichnet, wird „Ascyron“ genannt und heißt auf Niederländisch „Herthooy“, auf Englisch „St. Peterswoort</p>

<sup>55</sup> Nämlich Hartheu und Konradskraut.

<sup>56</sup> Weil es die ‚bösen Geister‘ in die Flucht schlägt; vgl. HWdAgl. (1927-1942), III, 1486f., und IV, 743; RGA (1973-2008), XVI, S. 68ab.

<sup>57</sup> Der terminologische Einschub der Bauhin Redaktion wird in der Übersetzung ausgelassen.

<sup>58</sup> „Welsch“ hier bezogen auf das ‚Italienische‘ (wie in „Welsch Tirol“ oder in „Welsch Bern“ = ‚Verona‘ [im Gegensatz zu „Deutsch Bern“ = ‚Bern‘]).

<sup>59</sup> Im Sinne der Bohemistik ‚das Tschech[oslowak]ische‘.

<sup>60</sup> In der Tabernaemontanus Ausgabe von 1731 auch als „concillo coro“ bezeichnet.

	Originaltext	Moderne Übersetzung
	<p>III. HYPERICUM SUPINUM TOMENTOSUM VEL MONSPELIACUM, G.B. SUPINUM, DOD. TOMENTOSUM LOB. LUGD. GER. ALTERUM TOMENTOSUM, AD. TOMENTOSUM FECUNDUM. CLUS. HIST. ANDROSÆMUM ALBUM DALECH. LUGD. IV. ASCYRUM SIVE HYPERICUM BIFOLIUM GLABRUM NON PERFORATUM, C.B. ANDROSAEMON, MATTH. FUCH. TUR. LAC. CORD. IN DIOSC. CAST. GES. COL. HYPERICUM ALIUD. DOD. GAL. V. ANDROSÆMON ALTERUM FOLIIS HYPERICI, C.B. ANDROSÆMON, LOB. ALTERUM, AD. RUTA SYL. HYPERICOIDES, DOD.]</p> <p>Arabisch <i>Refo. fricon</i>. Welsch <i>Hiperico, herba rossa</i>. Frantzösisch <i>Mille pertuis</i>. Englisch G. Johannes woorte. Böhmisch <i>Zwoncek cerweny</i>. [Niederländisch <i>St. Janscruydt</i>: Spanisch <i>conciillo</i>. Hartheuw aber so auch Waldthoff / wird ASCYRON genannt / Niederländisch <i>Herthooy</i>: Englisch <i>St. Peterswoort square great St. Johanss grasse</i>: Welsch <i>asciro</i>.</p>	<p>square great“ oder „St. Johanss grasse.“ Auf Italienisch heisst er „asciro“.</p>
	<p>Conradsdraut wird gemeiniglich ANDROSÆMUM, und auff Welsch ANDROSÆMON genannt.]</p>	<p>[Das Konradskraut wird üblicherweise Androsaemum genannt oder auf Italienisch Androsaemon.]</p>
	<p><b>Von der Natur / Krafft und Eygenschaftt des St. Johannskrauts.</b></p> <p>AETIUS schreibt / das Kraut sey warm und trucken und einer subtilen Substantz. [Die Geschlecht der Hartheuw / oder St. Johannskräuter / sind warmer und trucknender</p>	<p><b>Von der Natur, Kraft und Wirkung des Sankt Johannskrauts</b></p> <p>Aëtius von Amida schreibt, Sankt Johannskraut sei <b>warm</b> und <b>trocken</b> und zusammengesetzt <b>aus einer feinen, zarten Substanz</b>. [Alle Arten der Hartheu- oder Johannskräuter sind</p>

	Originaltext	Moderne Übersetzung
	Natur im andern / oder wie etliche wöllen im dritten Grad: haben auch gleiche Würckung.]	warmer und trockener Natur <b>im zweiten Grad</b> und werden von manchen Autoren sogar als warm und trocken <b>im dritten Grad</b> eingestuft. Sie alle verfügen über die gleiche (pharmakologische) Wirkung.]
Blut stillen  Wunden	<b>Innerlicher Gebrauch.</b> Wiewol diese Kräuter heylsame Wundkräuter sind / wie die lange und tägliche Erfahruß gnugsam beweißt / wird dieses von den Alten nicht gemeldet / dann sie ihnen nicht weiters zugeben / dann daß sie das Blut in den Wunden stillen / und dieselbigen sonderlich was verbrant ist / heylen. Aber dieser zeit werden sie nicht allein innerlichen zu Wundträncken / sonderen auch eusserlich / Oel und darvon gesottene Brühen / in grossen / tieffen Wunden / Verletzung deß Geäders / nutzlichen gebraucht / solche zu reinigen / und von grund auß zu heylen.]	<b>Innerliche Anwendung</b> [ <sup>61</sup> Obwohl all diese Arten von Johanniskräutern überaus wirksame Heilpflanzen sind, was aus der Langzeiterfahrung bekannt ist und sich durch den täglichen Gebrauch aufs neue erweist, werden die entsprechendem Heilwirkungen von den antiken Autoren nicht erwähnt, insofern als sie den Johanniskräutern lediglich eine <b>blutstillende</b> und <b>wundheilende</b> Wirkung zugestehen, besonders bei <b>Verbrennungen</b> . Heutzutage werden indessen die Johanniskräuter nicht nur innerlich als wundheilende Getränke verwendet, sondern auch äußerlich angewandt als Öl und Absude, die bei <b>großflächigen, tiefen Wunden</b> und <b>Verletzungen von Sehnen, Nerven und Muskeln</b> <sup>62</sup> wirksam sind; solche Präparate haben einen <b>reinigenden Effekt</b> , was eine <b>Heilung vom Wundgrund</b> her ermöglicht.]
Harn treiben	PAULUS ÆGINETA schreibt / daß das gantze Gewächs ein Natur und Krafft habe den Harn fort zu treiben: Darzu	Paulus von Agina schreibt, dass die gesamte Pflanze in ihrer Natur die Heilkraft habe, den <b>Harn zu treiben</b> , wenn man das

<sup>61</sup> Diesen Einschub der Bauhin Redaktion in den Originaltext lässt sich leicht entkräften durch eine Überprüfung des Johanniskraut Kapitels von Dioskurides [wie Anm. 12]; vgl. auch die Vielzahl von mittelalterlichen Indikationen (menstruationsfördernd, diuretisch, gefäßerweiternd, leber-protektiv, antidotisch, traumatologisch, gegen Arthralgien bei Rufinus Bl. 59<sup>rbf.</sup>, THORNDIKE/BENJAMIN (1945), S. 152f.

<sup>62</sup> Zur Bedeutung von frühneuhochdeutsch „Ader“ = ‚strangartiges Gebilde‘ siehe MILDENBERGER (1997), I, S. 38-40, S. 665: Sehnen, Nerven, Muskel(strang), auch Gefäße, Ligamente und Faszien sind inbegriffen.

	Originaltext	Moderne Übersetzung
Gift Weiberzeit	man dann Kraut / Blumen und Saamen in Wein sieden kan und darvon trincken / [welches auch das Gifft außjagt / und der Weiber Blödigkeit treibt.]	Kraut mit Blüten und Früchten <sup>63</sup> in Wein siedet und den Absud davon trinkt. [Die gleiche Abkochung wirkt auch als <b>Antidot</b> , indem sie <b>Gift ausleitet</b> , und den Frauen als <b>menstruationsförderndes Mittel</b> ihr Unwohlsein nimmt <sup>64</sup> .]
Hüftweh	GALENUS schreibt / daß etliche das Kraut oder den Saamen eingeben wider die Schmerzen und Wehethumb der Hüfft. DIOSCORIDES schreibt / man soll den Saamen viertzig Tag langdarzu gebrauchen.	Galen schreibt, dass viele das Kraut oder den Samen bei <b>Hüftweh</b> , also bei <b>Ischialgien</b> <sup>65</sup> und diesbezügliche <b>Schmerzen</b> verordnen, wobei Dioskurides meint, dass der Samen zur <b>Schmerzlinderung</b> 40 Tage lang eingenommen werden sollte.
Harn und Griess treiben. Blasenstein.	PLINIUS schreibt / der Saame [gesotten und getruncken] habe ein Art den Leib zu stopffen / dargegen aber treibe er den Harn und den Grieß. [Ist treffenlich gut dem Blasenstein.	Bei Plinius steht geschrieben, dass der Samen [abgekocht und das Dekokt getrunken] <b>stopfend</b> wirke; im Gegensatz dazu <b>treibe</b> er den <b>Harn</b> und <b>schwemme Grieß</b> aus. [Er hilft auch gegen den <b>Blasenstein</b> .

<sup>63</sup> Hier handelt es sich in der modernen botanischen Terminologie um die sich formenden Früchte, die an einer blühenden Pflanze zusammen mit den Knospen und Blüten vorhanden sein können. Die effektiven Samen bilden sich zu einem späteren Zeitpunkt, wenn keine Blüten mehr vorhanden sind. Brunfels 1532 (Kapitel CCLI) verwendet, genauer als Tabernaemontanus, sowohl den Begriff "Frucht" wie auch als separate Droge "Somen".

<sup>64</sup> „der Weiber Blödigkeit“ bezieht sich auf die Menstruation, siehe FrnhdWb (1986) IV, Sp. 636. Brunfels 1532 (Kapitel CCLI) bestätigt: "...das sye den Frawen ire zeit". Tabernaemontanus scheint hier aber nicht nur von der physiologischen Monatsblutung zu sprechen, wie etwa bei der „Kammille“ (1664, Buch I, Sektion 1, Kapitel 13, S.65) „fürdert die weibliche Monatsblum“, sondern benennt mit dem Begriff „Weiber Blödigkeit“ einen umfassenderen Komplex des Unwohlseins, der auch psychologische Aspekte miteinschließen kann. Heute wird Johanniskraut nach wie vor zur Behandlung von Stimmungsschwankungen und Depression beim prämenstruellen Syndrom, während der Peri-Menopause und im Klimakterium verwendet.

<sup>65</sup> Bock (1577, S.28) erläutert, dass es sich bei Hüftweh um Ischias handelt: "Vertreibt...beschwerlich hüfftwehe, Ischia genant...". 'Ischi-' bedeutet auf Griechisch Hüftgelenk und Hüfte. Sieh auch Rufinus, Bl. 59<sup>a</sup>, THORNDIKE/BENJAMIN (1945), S. 153, Z. 7, wo es vom Johanniskraut heißt: „*Herba sancti Iohannis... femorum dolorem auffert*“. PSCHYREMBEL (1977), S. 572 bestätigt die Synonymität von Hüftweh und Ischias: "Ischias, Ischialgie (...Schmerz): Hüftweh, Neuralgie des *Nervus ischiadicus*, *Neuritis ischiadica*, *Malum Cotuunii*" und erläutert, dass die Kompression des Nerves unter anderem bei latenten Bandscheibenvorfällen, Bandscheibenschäden und Erkrankungen der Wirbelsäule und des Hüftgelenks vorkommt. Siehe auch Psyhyrembel (1993), S. 739. Die empfohlene Anwendung bezieht sich also wahrscheinlich auf Ischialgien und könnte Schmerzen bei Bandscheibenprobleme und Koxarthrosen miteinbeziehen.

	Originaltext	Moderne Übersetzung
Blutspeyen	Der Same zerstoßen mit Wegrichsafft oder Wasser getruncken / dienet wider das Blutspeyen.]	Wenn man <b>Blut speit</b> , sollte Johanniskraut-Samen mit Wegerichsafft oder -wasser getruncken werden.]
Dreytägig Fieber	DIOSCORIDES schreibt / wann man das Kraut mit Wein trincke / so vertreibe es das dreytägige Fieber.	Bei <b>Malaria tertiana</b> solle man laut Dioskurides das Kraut in Wein trinken; dann vertreibt er das <b>Drei-Tage-Fieber</b> .
Gesicht an Füßen	Das Kraut mit dem Saamen gedörrt und gepülveret / mit Wein getruncken / dienet fürs Gesicht an Füßen / [reinigt Nieren und Leber.	Bei <b>rheumatischen Beschwerden</b> <sup>66</sup> <b>an den Füßen</b> hilft Johanniskraut, wenn man das Kraut samt dem Samen trocknet, zerstoßt und das Pulver in Wein trinkt; [das <b>reinigt</b> auch die <b>Nieren</b> und die <b>Leber</b> .
	In Polen pflaget man den jenigen / so jhnen von wegen schwerer Last weh gethan haben / diese Blumen in einem warmen Bier mit Butter und Saltz warm einzugeben.]	In Polen ist es üblich, diejenigen, die sich an <b>schweren Lasten verhoben</b> haben und über <b>Schmerzen</b> klagen, mit Johanniskrautblüten zu heilen: Man legt die Blüten in warmes Bier, fügt Butter und Salz hinzu und gibt das dem Patienten warm zu trinken.]
Wunden und offene Geschwär. Brand	<b>Eusserlicher Gebrauch.</b> Es schreibt AETIUS, wann man das grüne Kraut zerknitsche / und wie ein Pflaster überlege / so heffte es die Wunden und die offene Geschwär widerumb zusammen / und sonderlich was von Brand ist / welches auch GALENUS bezeuget.	<b>Äußerliche Anwendung</b> Für <b>Wunden</b> und <b>offene Geschwüre</b> —insbesondere für solche, die von Verbrennungen stammen – empfiehlt Aëtius von Amida, dass man die Frischpflanze zerdrücke <sup>67</sup> und als Pflaster <sup>68</sup> aufbringe; dann <b>schließe</b> es die <b>Wunden</b> sich <b>heile</b> das <b>offene Geschwür</b> . Galen kann das bezeugen.

<sup>66</sup> „Gesicht“ entspricht mittelhochdeutsch „gesühte“ (‚Krankheit‘), ‚rheumatische Übel‘, LEXER (1872-1878), I, 936; vgl. HÖFLER (1899), S.707a: „*Polyarthritiſ rheumatica*“.

<sup>67</sup> Die Bedeutung von „zerknitschen“ ist ‚zermalmten‘, auch ‚zerstoßen‘ und ‚zerdrücken‘; vgl. MILDENBERGER (1997), V, S.2353.

<sup>68</sup> Ein Pflaster ist ein Kataplasma. Vgl. s.v. den ‚Arzneiformen‘-Artikel von Willem F. Daems im LexMA (1999).

	Originaltext	Moderne Übersetzung
Verstopfte <sup>69</sup> Nerven	FERNELIUS meldet / daß diß Kraut gar nutzlich zu gebrauchen sey zu den zerknitschten und zerstossenen Nerven.	Fernalius meldet, dass dieses Kraut sehr nützlich sei bei <b>zerquetschten</b> und <b>verletzten Nerven</b> .
Zittern.	[Die Glieder mit dem Kraut gerieben / deß Tags zwey mal vor dem Essen / ist gut fürs Zittern und Beben.]	[Wenn man die Extremitäten zweimal täglich mit frischem Johanniskraut einreibt, so wirkt sich dies günstig bei <b>Zittern</b> und <b>Tremor</b> aus.]
Unreine Wunden	PAULUS ÆGINETA saget LIB. 7. DE RE MEDICA; wann man das dürre Pulver in die unreine feuchte Wunden sträuwe / so verzehre es die Feuchtigkeit / und heyle die Wunden / und auch dergleichen Geschwär.	Was <b>unreine</b> und <b>nässende Wunden</b> betrifft, so empfiehlt Paulus von Aegina im siebten Buch seiner ‚De re medica‘, dass man die Trockendroge zerstoßen und das Johanniskraut-Pulver in die <b>Wunden</b> streuen soll, dann höre das Nässen auf und es könne solche <b>Wunden</b> und <b>Geschwüre</b> zur Heilung bringen.
Kindsnöht.	Wenn ein Weib in schweren Kindsnöhten ligt / soll man sie mit dem dürrn Kraut beräuchen. [Etliche beräuchen die sechswöchige Weiber darmit / derohalben nennet man es an etlichen Orten unser Frawenwurtz.]	Wenn eine Frau in schweren <b>Kindsnöten</b> liegt, soll man sie mit getrocknetem Johanniskraut beräuchern <sup>70</sup> . [Manche beräuchern auch die Mütter <b>nach</b> deren <b>Niederkunft</b> in den sechs Wochen <sup>71</sup> ihres Wochenbetts mit getrocknetem Johanniskraut. Derartige (obstetrische) Verwendung hat der Pflanze in einigen Regionen <sup>72</sup> den Namen „Frauenwurz“ eingebracht.]

<sup>69</sup> Reizleitende Nerven, die als Hohlorgan gedeutet wurden, galten als „verstopft“ („oppilati“), wenn sie ihren Dienst verweigerten; EnzMedGesch (2005), II, S. 1039a.

<sup>70</sup> Die Beräucherung erfolgte in der Regel genital. Zu den beim Beräuchern verwendeten Trichtern und Röhren siehe DELVA (1983), S. 172-178; auf S. 176, Z. 14 (= Bl. 7v1) lies „onder eenen stoel“ statt „up eenen stoel“ und vgl. entsprechend KUSCHE (1990), S. 192, Bl. XXIIr4-6: „ende sedt den pot al heet onder hare dat die heete lucht jn haren lichaeme slaen mach van onder op“, ebd. S. 200, XXV<sup>r</sup>2-5: „onder enen stoel met enen gate“, ferner S. 208, XXIX<sup>r</sup>f, und KEIL (2009), S. 174f. mit Abb.1.

<sup>71</sup> Zur Dauer des Wochenbetts siehe RGA (2007), XXXIV, S. 174a-180a.

<sup>72</sup> Allgäu, Bayerisch Schwaben; siehe MARZELL (2000), II, Sp. 951, und vgl. MARZELL (1926), S. 54: „Frauenkraut oder Blutschwitzer“.

	Originaltext	Moderne Übersetzung
Rote Ruhr.	MATTHIOLUS schreibt / wenn jemandts die rote Ruhr hat / dem soll man ein Fußbad auß diesem Kraut machen / und jhn darein setzen / und die Füß waschen / so stopffe es den Durchlauff.	Für Patienten, die an der <b>roten Ruhr</b> <sup>73</sup> erkrankt sind, empfiehlt Matthioli, dass man ihnen aus Johanniskraut ein Fußbad bereite, sie in den Badezuber setze und ihnen die Füße darin wasche. Das wirke <b>stopfend</b> auf den <b>Durchfall</b> .
Gespengst.	Die alte Weiber sagen / daß diß Kraut sey für Gespengst / wann man es bey sich trägt / daher es auch FUGA DÆMONUM soll genennt werden.	Alte Frauen sagen, dass man mit Johanniskraut <b>Gespenster</b> in die Flucht schlagen könne, indem man es als <b>Amulett</b> trage; deswegen würde es auch „Fuga daemonum“ <sup>74</sup> genannt.
	<b>Von dem Safft des Johanneskrauts.</b>  Auß den Blättern und Blumen kan man auch einen Safft außpressen / wie bey dem Wermuhtsafft ist angezeigt worden.	<b>Vom Presssaft des Johanniskrautes</b>  Aus den Blättern und Blumen des frischen Johanniskrauts kann man auch einen Saft auspressen, und zwar auf die gleiche Weise, wie das in bezug auf den Wermut beschrieben wurde <sup>75</sup> .
Durchlauff. Blutspeyen	Dieser Safft mit Wegrich oder Wegtrittwasser getruncken / hilfft wider das Durchlauffen und Bauchflüß / und ist auch gut wider das Blutspeyen.	Wenn dieser Saft mit Wegerichwasser oder Wegetrittwasser <sup>76</sup> gemischt und getruncken wird, wirkt dies gegen (akuten)

<sup>73</sup> Die Ruhr löst blutig-schleimigen Stuhlgang aus.

<sup>74</sup> Erstbeleg in einer Salerner Drogenliste des 13. Jahrhunderts: RGA (2000), XVI, S. 68b. Brunfels schreibt ebenso 1532 (Kapitel CCLI) „...Fuga demonum genennt. Darumb das man meynete, wo solchs kraut behalten würt, da komm der teuffel nicht bey. Möge auch kein gespenst bleiben und darumb berüchet man in etlichen landen die kindtbetterin damit. Lass es aber vorsegen uff unßer frawen offarttag und haben also ire kurzweil damit“. In alten Kräuterbüchern findet man eine Vielzahl von Ausdrücken für Symptome, die man heute auch als depressive Verstimmung und Angstzustände bezeichnen würde, und wo Johanniskraut nicht alleiniglich als Schutzmassnahme eingesetzt wurde, so bei Paracelsus (1525) der Johanniskraut gegen die Geister und tollen Fantasien, die den Menschen in Verzweiflung bringen, verschrieb; bei Carl (1719), der die Heilpflanze als „gute Nervenstärkung und wider die Zauberey“ rühmte; bei Zedler (1732), der Johanniskraut als das heilkräftigste bei Zauberei (= Depression) bezeichnete und bei Krünitz (1784-1836), der es als wirksam beschrieb „bey allen Nervenkrankheiten, bey hypochondrischen, hysterischen und melanchonlischen Zufällen; vgl. TSCHUPP (1998), S. 44-46. Siehe auch Bäumeler (2007), S. 223.

<sup>75</sup> Vgl. Tabernaemontanus (1664), Buch 1, Kapitel, 1, S.10 C bis I.

<sup>76</sup> Es handelt sich hier um wässrige Destillate, vgl. Anm. 39. „Wegerich“ und „Wegtritt“ sind trotz ähnlicher Namen keine Synonyme; während „Wegerich“ für ‚*Plantago major* L‘, ‚*Plantago media* L.‘ und ‚*Plantago lanceolata* L.‘ steht, bezeichnet „Weg(e)tritt“ bzw. „Weggras“ den ‚Vogelknöterich‘, ‚*Polygonum aviculare* L.‘; sieh DAEMS

	Originaltext	Moderne Übersetzung
		<b>Durchfall</b> und (chronische) <b>Diarrhöe</b> und hilft auch bei <b>Blutspucken</b> <sup>77</sup> .
Wunden. Brand.	Der Safft eusserlich in Wunden gethan / reiniget dieselbige und heylet sie: Ist auch gar gut zum Brand eusserlich auffgestrichen.	Wenn man den Saft äußerlich in <b>Wunden</b> träufelt, <b>reinigt</b> er sie und lässt sie <b>heilen</b> . Er wirkt auch ausgezeichnet bei <b>Verbrennungen</b> , wenn man ihn äußerlich aufstreicht.
Würm der Ross	[Diesen Safft gibt man mit Odermenig den Rossen ein für die Würm.]	[Diesen Saft verabreicht man den Pferden zusammen mit Odermennigkraut gegen <b>Wurmbefall</b> .]
	<b>Von Johanneskrautwasser.</b>	<b>Vom Johanniskrautwasser</b> <sup>78</sup>

(1993), Nr. 358, 166 u.ö. WILL (2009), Nr. 49 -51, 257, 287; WELKER (1988), S. 233: „Weggras wasser jst gütt für den rotten durchgang“; SCHILD (2007), S. 13: Weggras Wasser ... ist gut für dy Rurre“.

<sup>77</sup> Hamoptoë und auch Hämoptyse, welche bei verschiedenen Krankheiten, so der Lungentuberkulose und Lungeninfarkt aber auch bei Tumoren, Abszess, Bronchitis, Pilzkrankungen und Gefäßveränderungen wie Aneurysmen vorkommen kann.

<sup>78</sup> Der Begriff „Pflanzenwasser“ ist im Unterschied zu anderen Zubereitungen wie Sirupen oder Weinabsuden keine genaue Angabe, um welche Art der Arzneimittelverarbeitung es sich handeln soll. Heute beschreibt ein „gebranntes Wasser“ eindeutig ein alkoholisches Destillat (siehe auch Anm. 40). In der frühen Neuzeit konnte sich der Begriff „Pflanzenwasser“ jedoch sowohl auf ein wässriges wie auch (selten) auf ein alkoholisches Destillat beziehen oder auch auf eine Art wässrigen Dekokt. Eine Aussage über die Herstellungsweise und dem verwendeten Menstruum war in der frühen Neuzeit autoren- und rezeptspezifisch; siehe MÜLLER-GRZENDA (1996), S. 95. Tabernaemontanus erläutert an dieser Stelle nicht die Zubereitungsart des Johanniskrautwassers. Eine Überprüfung der Zubereitungsart anderer Pflanzenwässer in seiner *materia medica*, zum Beispiel beim „Gedestilliert Grasswasser“ offenbart jedoch, dass Tabernaemontanus unter „Pflanzenwasser“ - wenn er keine weiteren Angaben macht – einen Auszug des frischen und zerkleinerten Pflanzenguts über einem *Balneo Mariae* (Doppeltopf-Methode) meint; vgl TABERNAEMONTANUS (1664) Buch I, Sektion 6, Kapitel 1, S. 524. Dies ist also eine Art Trockendestillation der gewaschenen Pflanzen, die er „ohn allen Zusatz“ ausziehen lässt: ebenda S. 106, G. Eine Variante dieses Auszugs über dem *Balneo Mariae*, bei der eine Weiterverarbeitung mittels Sonnendestillation erfolgt, ist unter „Chamillenwasser. *Aqua Chamaemeli stillatitia*“ zu finden: ...soll man Kraut und Blumen miteinander hacken/ und säfftiglich in *Balena Mariae* abziehen, folgendes ein Zeitlang wol vermacht zu rectificieren in die Sonne setzen / und zum Gebrauch verwahren.“ Eine andere Destillationsvariante, gezielt eingesetzt zum Auszug pflanzenspezifischer Wirkstoffe, beschreibt er im Dillkrautwasser Kapitel. Hier setzt der Autor erst den „blinden Helm“ (*Alembicu coecum*) auf das *Balneo Mariae*, den er nach 24 Stunden mit einem „Helm mit Schnabel“ ersetzt, der die Flüssigkeit nach abgeschlossener Destillation abfließen lässt: ebenda, Buch I, Sektion 2, Kapitel 16, S. 169, D-E. Bezüglich der verwendeten Gerätschaften findet sich beim Erdrauch Kapitel ein Hinweis, dass das frische, gewaschene und zerkleinerte Pflanzengut in ein Gefäß, dem *Cucurbit*, eingeschlossen, und so im *Balneo Mariae* ausgezogen werden soll, also eine Art Vakuumdestillation: ebenda, Buch I, Sektion 1, Kapitel 21, S. 89. Der *Cucurbit* scheint jedoch keine obligatorische Gerätschaft zum Destillieren mittels *Balneo Mariae* zu sein, da er nicht überall erwähnt wird – oder war so selbstverständlich, dass dessen Beschreibung weggelassen wurde. Die Pflanzenwasser beziehen sich bei Tabernaemontanus also in der Regel auf eine Destillation mittels Doppeltopf-Methode ohne Wasser- oder Alkoholmenstruum. Diese Zubereitungsweise deckt sich mit den Anweisungen seines zeitgenössischen Berufskollegen Adam Lonitzer (1528-1586), der ebenfalls solcherartige wässrige Pflanzenwasser

	Originaltext	Moderne Übersetzung
	Im Ende deß Brachmonats soll man das Kraut und Blumen von den Stengeln abstreiffen und ein Wasser darauß brennen.	Ende Juli soll man Blüten und Blätter von den Stengeln abstreifen und einen wässrigen Auszug herstellen <sup>79</sup> .

herstellte. Im Gegensatz zu Tabernaemontanus besprengte dieser die Medizinalpflanzen vor dem Ausziehen manchmal mit einer kleinen Menge Wein oder Essig: LONICERUS (1679), S.11-27; vgl. auch Will (2009) zu den Destillationsvorschriften des Straßburger Chirurgen und Wundarztes Hieronymus Braunschwig. Zusätzlich zu den Trockendestillationen, beschreibt Tabernaemontanus auch Destillationen mit Zusatz von Wasser, die letztlich nichts Anderes als Spielarten von Dekokten sind. Im Kapitel „Wegwarten gedistillirt Wasser“, beschreibt er eine wässrige Destillation, welche er spezifisch für alle kühlenden Pflanzenwasser empfiehlt: „Die beste Zeit das Wegwartenwasser zu distilliren ist mitten in dem Mayen / Kraut und Wurzeln mit einander klein gehackt / und darvon genommen zwölf Krämerpfund / darüber geschüttet 5 oder 6 Maß frisch und kalt Brunnenwasser / solches mit einander in ein *Vesicam* gethan / und davon abgezogen 2 maß / so halten ein sehr kräftiges Wasser...“: ebenda, Buch 1, Sektion 5, Kapitel 22 S. 474 I. Beim „gesottenen Fenchelwasser“ geht er folgendermassen vor: „Man nimbt schönes ausserlesen gesäuberten Fenchel / 3 Loth, guten feinen Zucker / 4 Loth / frisch Brunnenwasser / 2 Mass. Die Stück thut man zusammen in eine grosse glatte Flaesch, die oben ein breite Schraube hat / und verschraubt sie gar geheh zu / stellt die in ein Kessel mit sidendem Wasser / und lässt sie 4 Stund in steter Hitz darin sieden / darnach thut manns heraus / und seihets durch ein Claretsack / und setzts darnach in ein kühlen Keller“: ebenda: Buch I, Sektion 2, Kapitel 12, S. 159 D. Der Autor beschreibt auch die Doppeldestillation, so im Frauenmantelkapitel (ebenda, Buch 1, Sektion 3, Kapitel 20, S. 250 K), und eine Wasserdestillation mit getrocknetem, gepulvertem Pflanzenmaterial mittels eines Perkolators (Kolben), so beim „Gedistillirt Engelwurtz oder Angelickwasser (ebenda, Buch 1, Sektion 3, Kapitel 12 S. 235 B).

<sup>79</sup> Im Gegensatz zu der heutigen Verwendung des Begriffs „brennen“ als Synonym für „destillieren“ von alkoholischen Destillaten, untermauern die deutsch-lateinischen Wörterbücher des 15./16. Jahrhunderts, dass sich der Begriff „brennen“ in erster Linie darauf bezog, eine Substanz mittels Hitze auszuziehen. Hierbei bezeichnet ‚brennen‘ einen Oberbegriff, der alle Tätigkeiten miteinbezieht, die mit starkem Erhitzen und Aufwallen von Flüssigkeiten zu tun hatten. Dies konnte sieden, kochen, brauen und auch destillieren (mit Wasser oder Alkohol) sein; vgl. MÜLLER-GRZENDA (1996), S. 44-46. Die terminologischen Bezeichnungen verschiedener Extraktionsmethoden wie Destillat, Dekokt, Mazeration und Infusion waren in dieser Zeitperiode noch fließend. Deren Bedeutung müssen deshalb von Autor zu Autor neu ermittelt werden; vgl. ebenda, S. 92-94. Bei einer Analyse verschiedener Tabernaemontanus Rezepturen wird offensichtlich, dass der Autor den Begriff „sieden“ und den Begriff „brennen“ auf zwei verschiedene Zubereitungsarten anwendet. Seine Anleitungen „...Wermuth in Wein und Wasser gesotten/ und darmit die frischen Wunden gewaschen...“ (ebenda, S.10A ) bezieht sich auf ein Dekokt im heutigen Sinne, welches mit Wein oder Wasser als Auszugsflüssigkeit hergestellt wurde. Im Gegensatz dazu beschreibt der Begriff „brennen“ – wenn nicht näher erläutert – eine Art Trockendestillation ohne Zusatz von Wasser oder Alkohol mittels eines *Balneo Mariae*, so auch beim Johanniskrautwasser: „... soll man das Kraut und Blumen von den Stengeln abstreiffen und ein Wasser darauß brennen“, siehe auch Anm. 37. Weiter verwendet Tabernaemontanus in den verschiedenen Pflanzenwasserparagraphen synonym zu „brennen“ auch die Begriffe „abziehen“ und „destillieren“, zum Beispiel: „Fenchelwasser. *Foeniculi aqua stillatitia*. Von dem Fenchel wird auch ein heylsames und köstliches Wasser gedistillirt / zu vielen innerlichen und äusserlichen Leibesgebrechen dienlich. Die beste Zeit seiner Distillirung ist im Brachmonat/ Kraut und die Gipffel der Blumen / mit einander klein gehackt / und sänftiglich in *Balneo Mariae* abgezogen / darnach an der Sonne rectificiert.“, S. 157 C. Ein Pflanzenwasser ist bei Tabernaemontanus also nicht eine alkoholische Destillation im heutigen Sinne, sondern entweder ein Dekokt oder eine Art Trockendestillation; vgl. Anm. 39. Absude, Dekokte und wässrige „Destillationen“ waren in der frühen Neuzeit einfache und erschwingliche Arzneiformen, die besonders in der Selbstmedikation des „gemeinen Mannes“ einen zentralen Platz einnahm, da sie jedermann ohne großen apparativen Aufwand durchführen konnte; vgl. MÜLLER-GRZENDA (1996), S.89-92.

	Originaltext	Moderne Übersetzung
Wunden  Fallende Sucht. Schlag.	Diß Wasser ist gut und heylet alle innerliche und eusserliche Wunden / davon [Morgens und Abendts] getruncken / [damit gewaschen] und das Wasser eusserlich auffgeschlagen. Das Wasser mit Päonienwasser getruncken / alle Tag zwey oder drey mal / jedes mahl zwey oder drey loth / ist gut für die Fallendesucht / [und den Schlag.]	Johanniskrautwasser ist hochwirksam und heilt alle <b>innerlichen und äußerlichen Wunden</b> , wenn man davon [morgens und abends] trinkt [bzw. sich damit wäscht] und das Wasser in feuchten Umschlägen auflegt. Johanniskrautwasser mit Pfingstrosenwasser gemischt und täglich zwei oder dreimal eingenommen je in der Menge von 30g-45g ist gut gegen <b>Epilepsie</b> [und <b>Schlaganfall</b> <sup>80</sup> ].
Bauchflüß.	Das Wasser mit rotem Wein vermischet / und davon getruncken / stopffet die Bauchflüß und rohte Ruhr / [wie dann auch mit einem Tuch auff den bauch gelegt.]	Trinkt man Johanniskrautwasser gemischt mit Rotwein, so wirkt dies stopfend bei <b>Diarrhöe</b> und der <b>roten Ruhr</b> . [Es ist auch angezeigt, dieses Mixtur als feuchten Umschlag auf den Bauch aufzulegen.]
	<b>Von Johanneskrautöl.</b>  Die Apothecker und auch die Wundärzte pflegen ein köstlich Oel auß dieses Krauts Blumen zu machen: welches man aber auff ein schlechte weiß also præpariren soll: Nimb der frischen Blumen so viel du wilt / thu sie in ein Glaß / geuß Baumöl darüber / stopffs oben zu / und stelle es an die Sonne etliche Tag darnach seige das Oel ab / truck die Blumen wol auß / und thu andere frische darein / setze es widerumb an die Sonn / darnach trucke	<b>Vom Johanniskrautöl</b>  Sowohl die Apotheker wie auch die Wundärzte <sup>81</sup> sind in der Lage, ein köstliches <sup>82</sup> Öl aus den Blüten des Johanniskrauts herzustellen, das man freilich auch in einem schlichteren Verfahren gewinnen kann: Nimm von den frischen Blüten in beliebiger Menge, tu sie in ein Glas und gieß Olivenöl darüber, verschließ das Glas mit einem Stöpsel und lass es mehrere Tage an der Sonne stehen; dann seihe das Öl ab, drücke den Blütenrückstand gut aus, fülle mit frischen Blüten

<sup>80</sup> Aus humoralpathologischer Sicht waren beide Krankheitsbilder, Epilepsie und Schlaganfall, eng miteinander verwandt; vgl. KEIL (1997), S. 54f. – Die Pfingstrose (*Paeonia officinalis* L. EMEND. WILLD.) galt als eines der wichtigsten Anti-Epileptika; vgl. MILDENBERGER (1997), III, S. 1461f.: „Mittel gegen mehrere, vor allem für unheilbar gehaltene Krankheiten, darunter auch Apoplexie“.

<sup>81</sup> Zur Destillation von Öl durch Chirurgen siehe die Abbildungen von Ölöfen in der ‚Ulmer Wundarznei‘ (um 1485), MARTIN (1991), S. 203, Bl 97<sup>r</sup>, sowie S. 60: „Also mach ainen oelofen / darinn du die oeler brennen wollist... Sant Johans krut oel ofen...“ (mit *Balneum Mariae*) – ; sieh auch CRONE (2002).

<sup>82</sup> „köstlich“ verweist auf die ätherischen bzw. Balsamöle, die durch Destillation gewonnen wurden; das Verfahren schonenden Destillierens (= Brennens) beschreibt die ‚Ulmer Wundarznei‘ [wie Anm. 40], vgl. auch CRONE (2002), S. 24, 35, 40 u.ö.

	Originaltext	Moderne Übersetzung
Wunden  Kalte Gebrechen der Glieder	es auß wie zuvor / solches thue etlich mal nacheinander / zu letzt stoß die Hülsen sampt dem Saamen / und lege sie auch in das Oel / so wird das Oel schön Blutroht: Dieses Oel schreibt MATTHIOLUS, heylet die Wunden gar wol / sonderlich aber die verwundten Sennadern. [Dieses Oel wird viel kräftiger / wann man Myrrhen / Aloe / Mastix und Terpentin darzu thut] Ist auch dienstlich zu allen kalten Gebrechen der Glieder und Gewerben.	nach und stelle es wiederum an die Sonne. Danach presse es ab wie zuvor und wiederhole das ganze etliche Male. Zuletzt nimm auch die Samen in den Schoten, zerstoß sie und fülle sie ihrerseits ins Öl, das (wiederum an die Sonne gestellt und dann abgeseiht) sich wunderschön blutrot färbt: Dieses Öl – so schreibt Matthioli – <b>heilt die Wunden</b> bestens und insbesondere die <b>verletzten Sehnen, Bänder und Nerven</b> <sup>83</sup> . [Wenn man Myrrhe <sup>84</sup> , Aloe <sup>85</sup> , Mastix <sup>86</sup> und Terpentin <sup>87</sup> hinzufügt, lässt sich die Wirkung des Öls noch steigern.] Das Öl hilft (als warm und trocken) auch bei allen kalten <b>Arthrosen der Glieder</b> <sup>88</sup> und <b>Gelenke</b> <sup>89</sup> .
Brand	Ist auch gut zu dem Brand vom Feuer / leget und mildert die Schmerzen der Hüfft.	Das Öl hilft darüber hinaus bei <b>Verbrennungen</b> und <b>heilt</b> oder <b>mildert die Schmerzen</b> und <b>Ischialgien der Hüfte</b> <sup>90</sup> .

<sup>83</sup> Zur weitgespannten Begrifflichkeit von frühneuhochdeutsch „Sehnader“ siehe DWB, X/I = 16, Sp. 148: ‚Flehsen‘ = ‚Faszien‘ und ‚Gefäße‘ waren mit inbegriffen. Siehe auch Anm. 23 bezüglich Geäder.

<sup>84</sup> ‚Myrrhenharz‘ von *Commiphora myrrha* (NEES) ENGL. und andern *Commiphora spec.*, vgl. MILDENBERGER (1997), III, S. 1231-1233.

<sup>85</sup> Eingedickter Saft unterschiedlicher Aloë-Arten wie *Aloe succotrina* LAM. (der Natal-Aloe), *Aloe ferox* MILL. (der Kapland-Aloe) oder *Aloe perryi* BAK., Liliaceae; vgl. MILDENBERGER (1997), I, S. 72-75.

<sup>86</sup> Gummiharz des Mastixstrauches *Pistacia lentiscus* L.

<sup>87</sup> Rohbalsam oder Harz unterschiedlicher Kiefernarten, insbesondere *Pinus palustris* MILL., *Pinus pinaster* Soland, *Pinus halepensis* MILL., *Pinus nigra* aber auch *Pinus sylvestris* L., *Pinus cembra* L. und andere; vgl. (TEUSCHER, MELZIG & LINDEQUIST 2004), S. 401-402. Nach MILDENBERGER (1997), IV, S. 1951-1953 wurde Terpentin auch aus anderen Holzarten gewonnen: ‚Lärchenharz‘, ‚Venetianisches Terpentint‘ von *Larix decidua* MILL. = *Larix europaea* L., Harz der Terpentinpistazie *Pistacia terebinthus* L., ‚Zyprisches Terpentint‘, ‚Straßburger Terpentint‘ und ‚Tannblatterpech‘, was sich auf Flüssigharz aus Harzkammern unter der Weißtannennrinde bezieht.

<sup>88</sup> Zu ‚Glieder‘ als beweglichem Teil einer Extremität vgl. MILDENBERGER (1997), II, S. 679f.

<sup>89</sup> Zur Gleichung ‚Gewerbe‘ = ‚Articulatio‘ = ‚Gelenk‘ siehe DWB, IV/I/III = 6, Sp. 5489.

<sup>90</sup> Siehe Anm. 26.

	Originaltext	Moderne Übersetzung
Rote Ruhr	Es ist dieses Oel auch gut wider die rote Ruhr / so man den Bauch warm damit schmieret / dann es leget den Schmerzen und stopffet das Durchlauffen.	Johanniskrautöl ist des weiteren wirksam bei der <b>roten Ruhr</b> , wenn es warm auf den Bauch aufgetragen wird: es wirkt <b>schmerzlindernd</b> und <b>stopft</b> den <b>Durchfall</b> .
	[Wider gemeldte rohte Ruhr ein Experiment: Nimb ein Stück Netze von einem Schaff / zerschneid es / und röste es in das Oel / legs also warm auff den Bauch / es lindert die Schmerzen / und verstillt die Stulgäng.]	[Experimentell lässt sich die Wirkung gegen die <b>rote Ruhr</b> wie folgt bestätigen: Nimm das Bauchnetz <sup>91</sup> eines Schafes, schneide es in Stücke und röste es in Johanniskrautöl, lege es warm auf den Bauch, so lindert es die <b>Schmerzen</b> und <b>beseitigt den Durchfall</b> .]
Krimmen <sup>92</sup> .	Es wird auch gebraucht wider die COLICAM, wenn man sich umb den Nabel damit schmieret / welches aber kräftiger wird /wann man Dillöl darzu thut / und mit Wachs zu einem Sälblein machet.	Eine zusätzliche Heilanzeigen fürs Johanniskrautöl ergibt sich gegen die <b>Kolik</b> , wenn man sich den Nabel damit salbt. Das Oel wirkt noch stärker, wenn man dem Johanniskrautöl zusätzlich Dillöl <sup>93</sup> beimengt und das Gemisch mit Wachs zu einer Salbe <sup>94</sup> verarbeitet.
	[In Welschland pflaget mans den Kindern / die Grimmen haben / über den Nabel zu legen / daher es viel HERBAM UMBILICAREM nennen.	[In Italien pflegt man den Nabel <sup>95</sup> der Kinder, die an <b>Bauchgrimmen</b> leiden, mit einer solchen Salbe einzureiben; deshalb wird Johanniskraut auch oft auch <i>Herbam umbilicarem</i> oder ‚Nabelkraut‘ genannt <sup>96</sup> .

<sup>91</sup> Das Netz bezeichnet das Bauchnetz oder *Omentum* von *Ovis ammon f. aries* L.; zum Terminus siehe PSCHYREMBEL (2007).

<sup>92</sup> HÖFLER (1899), S. 202<sup>a</sup>: Krimmen ist synonym zu „Darmgrimmen“. Die Lokalität der Schmerzen bezieht sich auf den Kolon, den ‚Grimmdarm‘: ebd. S. 91<sup>ab</sup>.

<sup>93</sup> Öliger Auszug von Dill (*Anetum graveolens* L.) auf Olivenöl-Basis oder auf Keimöl-Grundlage, *Oleum anetinum germinale*, vgl. CRONE (2002), S.7, 13, 16, 20; Dill galt als warm und trocken im zweiten Grade und wurde gezielt gegen die Bildung von Darmgasen eingesetzt, e.g. gegen „*lienae conflatae*“, so bereits im ‚Herbar‘ des Rufinus, Bl. 23<sup>bf.</sup>, THORNDIKE/BENJAMIN [1945], S. 26f. und gegen „*venae inflatae*“ in WÖLFEL (1939), S. 18.

<sup>94</sup> *Unguentum leniens*, entsprechend Galens Konzept; vgl. FEHLMANN (1983).

<sup>95</sup> Der Nabel galt als eine Ein- bzw. Austrittspforte in Bezug auf die Bauchorgane, insbesondere die Därme; sieh KEIL (1961), S. 251; und vgl. auch HWdAgl (1927-1942), IX, S. 855: Nabelwurm, sowie zum Konzept BARGHEER (1931).

<sup>96</sup> *Herbarum umbilicarem* ist eine Bezeichnung, die MARZELL (2000), II, Sp 954ff. fürs Johanniskraut nicht notiert. Wohl aber belegt er in Bezug auf die hier besprochene Indikation „Leibwehblume“, „Kolikgekräutlich“, Abweichgekräut“.

	Originaltext	Moderne Übersetzung
	Dieses wird für das allerbest und nützlichst gehalten. Nimb unzeitig Baumöl zwölf loth / Mastix zwey loth / Terpentinöl anderthalb loth / Rosenöl / lauter Terpentinöl jedes vier loth / Mastix und Weyrauchkörnle jedes ein halb loth / frischer Mirrhen / Aloes / jedes iii. Quintlein / Gummi Elemnij / Griechisch Bech / jedes dritthalb Quintlein / Tausentgüldenkrautsafft / S. Johannskrautsafft / breiten oder spitzigen Wegrichsafft / Katzenwadelsafft / jedes ij. loth / Schaaffgarben j. halb loth /	Diese Johanniskrautöl-Variante wird für die <b>wirksamste</b> und <b>nützlichste Zubereitung</b> gehalten: Nimm 180g <sup>97</sup> grünes, von unreifen Oliven gepresstes Baumöl, 30 g Mastix(-Öl) <sup>98</sup> , 22,5 g Terpentinöl <sup>99</sup> , je 60g Rosenöl <sup>100</sup> und geläutertes Terpentinöl <sup>101</sup> , je 7,5g Mastix-Gummiharz und Weihrauchharz-Körner <sup>102</sup> , je 11,25g frisches Myrrhen-Harz und eingedickten Aloë-Saft, je 9,4g <sup>103</sup> Elemi-Harz <sup>104</sup> und Griechisches Pech <sup>105</sup> , je 30g Saft vom Tausendgüldenkraut <sup>106</sup> ,

<sup>97</sup> Zur Umrechnung siehe MILDENBERGER (1997), II, S. 1104, der bei der Gleichung 1 Lot(h) = (etwa) 15g das in der Oberrheinebene gängige Basler Apothekergewicht zugrunde legt. Ein Lot(h) ist die Gewichtsheit einer halben Unze, was 14.9075g entspricht.

<sup>98</sup> „*Oleum masticinum*“ ist bei CRONE (2002), S. 42, erfasst und wurde als Auszug auf Baumölbasis hergestellt.

<sup>99</sup> Terpentinöl wird aus dem Kiefernrohobalsam verschiedener Kiefer-Arten (*Pinus*-Arten, Pinaceae) gewonnen (siehe Anm. 48).

<sup>100</sup> Der Rosenblütenblätter-Auszug wurde auf Olivenölbasis hergestellt und bezieht sich nicht auf das heute gebräuchlichere ätherische Rosenöl. Tabernaemontanus (1664), Buch 3, Sektion 2, Kapitel 100, S. 1500E beschreibt zwei verschiedene Auszugsarten für die Herstellung des Rosenöls. Die erste schreibt vor, einen Auszug aus frischen, noch geschlossenen roten Rosenköpfen herzustellen, die geschnitten und in Olivenöl während 14 Tagen an der Sonne ausgezogen werden. Die zweite schreibt einen Absud derselben über Hitze vor. Eine Variante davon ist, dass nach einem solchen Absud das Gemisch in einem Glasbehälter während 50 Tagen zusätzlich an der Sonne ausgezogen wird. Siehe auch die zeitlich vorangegangenen, mittelalterlichen Olivenöl Vorschrift des *Circa instans*, WÖLFEL (1939), S. 100 und diejenige des *Breslauer Arzneibuch* (1270/80), Bl. 147<sup>v</sup>, welche ebenfalls die Sonnen-Digestion beschreibt: KÜLZ & KÜLZ-TROSSE (1908), S. 182f.

<sup>101</sup> Lauteres oder Gereinigtes Terpentinöl ist eine durch Wasserdampf gewonnenen klare, flüchtige Flüssigkeit. Dieses ätherische Öl wird aus dem Rohbalsam (Terpentin) verschiedener Kiefer-Arten (*Pinus*-Arten, Pinaceae) gewonnen (siehe Anm. 46). Die bei 155 bis 170 Grad übergehende Fraktion ist farblos und wurde entsprechend als „lauter“ bezeichnet. Gereinigtes Terpentinöl wird auch heute noch äußerlich zur Behandlung rheumatischer und neuralgischer Beschwerden sowie von Bronchitiden eingesetzt; vgl. TEUSCHER, MELZIG & LINDEQUIST (2004), S. 401-402; CRONE (2002), S. 44, Z.2f. Zeitgenössische Untersuchungen bestätigen die antimikrobische Wirkung von *Pinus spp.*. *Pinus elliottii*, zum Beispiel ist wirksam gegen Antibiotika resistente Bakterien wie *Staphylococcus epidermidis*: LEANDRO, CARDOSO, SILVA, SOUZA, VENEZIANI, ABMROSIO, MARTINS (2014).

<sup>102</sup> Erstarrte Harztropfen des Weihrauchbaums *Boswellia carteri* Birdw., synonym zu *Boswellia sacra* FLUECKIGER und anderer harzausscheidender Gehölze der Balsambaum-Gewächse *Boswellia spec.*; MILDENBERGER (1997) V, S. 2292ff; MARTINEZ, LOHS & JANTZEN (1989), S. 81, Abb. 6.8.

<sup>103</sup> „dritthalb“ = ‚zweieinhalb‘; ein Quentchen ist ein Viertellot und wiegt 3,75g.

<sup>104</sup> „*Resina elemi*“ von *Boswellia spec.*, Burseraceae; DRESSENDÖRFER (1978), S. 229; STAHNKE (1983), S. 573: „Elemi (Ölbaum-)Harz“.

<sup>105</sup> Destillationsrückstand nach Abdampfen des Terpentins: Kolophonium, Geigenharz, von *Pinus sylvestris* L., der Gemeinen Kiefer oder Föhre; vgl. MILDENBERGER (1997), II, S. 1000.

<sup>106</sup> *Centaurium erythraea* RAFN., vgl. DAEMS (1993), Nr 111.

	Originaltext	Moderne Übersetzung
Schmerz der Wunden. Frantzosen. Krampff.	Tormentillwurtzel / weissen Diptamwurtzel / Cardenbenedicten / jedes ein Quint. Ferberröte / Scharlachfarbsaamen / jedes ein halb loth /und ein halb quintlein /Saffran ein halb Quint. frischer Regenwürmer gewaschen und bereit iiij. loth / Eschenbaumlaub und Rinden von der Wurtzel / jedes ein halbe Handvoll / guten weissen Wein zwey Pfund. Von obgemelten Stücken / stoß groblecht was sich stossen laßt / seuds dann mit dem Wein und Saffran / biß sich die Feuchte verzehre: dann trucke das uberblieben Oel wol darauß durch ein hänffen Tuch / thu es in ein Glaß / und thu darzu die frischen Blumen von St. Johannskraut / Roßmarinblumen / jedes ein wenig / laß es fünffzehen	vom Sankt Johanniskraut, vom Breit- oder Spitzwegerich <sup>107</sup> und vom Ackerschachtelhalm <sup>108</sup> , 7,5g Schafgarbe <sup>109</sup> , je 3,75 g Blutwurz <sup>110</sup> , Diptamwurtzel <sup>111</sup> und Kardobenedikten(wurzel) <sup>112</sup> , je 7.5g Färberröte <sup>113</sup> und Muskatellersalbeisamen <sup>114</sup> , 1.9 g Safran <sup>115</sup> , 60g frische Regenwürmer <sup>116</sup> , gewaschen und zubereitet <sup>117</sup> , je eine halbe Handvoll Eschenlaub und Wurzelrinde von der Esche <sup>118</sup> sowie 715,5g <sup>119</sup> guten Weißwein. Was sich von dem genannten Ingredienzien zerstoßen lässt, stoß im Mörser leicht an, sied es dann mit Wein und Safran, bis der wässrige Anteil verdampft ist; presse das zurückgebliebene Öl sorgfältig aus, filtriere durch ein Sehtuch aus Hanf, fülle es in ein Glas, füge je ein wenig frische Johanniskraut- und Rosmarin- Blüten

<sup>107</sup> *Plantago major* L., *Plantago lanceolata* L.; vgl. oben Anm. 35.

<sup>108</sup> „Katzewadel“ ist im Alemannischen die Bezeichnung für *Equisetum arvense* L.; MARZELL (2000), II, Sp. 247.

<sup>109</sup> *Achillea millefolium* L., DAEMS (1993), Nr. 316, 637.

<sup>110</sup> Rhizom von *Potentilla erecta* (L.) RAEUSCH. Synonyme sind *Potentilla tormentilla*, *Tormentilla erecta* und *Potentilla laeta*. Blutwurz wird auch „Rotwurz“ oder „Braunwurz“ genannt.

<sup>111</sup> Das Rhizom von *Dictamnus albus* L., dem Brennenden Busch; vgl. MARZELL (2000), II, Sp. 124.

<sup>112</sup> Das Rhizom von *Cnicus benedictus* L.; MARZELL (2000), I, Sp. 1062f.; VL (2002), XI, Sp. 826-829.

<sup>113</sup> *Rubia tinctorum* L.; MARZELL (2000), III, Sp. 1447: Krapp.

<sup>114</sup> Samen von *Salvia sclarea* L., dem Muskateller-Salbei; vgl. MARZELL (2000), IV, Sp. 53-55: „Die Oberlippe der Blütenkrone ist helllila bis rosa“, „Gartenscharlach“.

<sup>115</sup> ‚Gewürzsafran‘, ‚Griffel von *Crocus sativus* L.‘ bzw. ‚das aus den getrockneten Blütennarben von *Crocus sativus* L. (= *Crocus orientalis*) gewonnene Pulver‘; MILDENBERGER (1997), III, S. 1636f.

<sup>116</sup> Rötliche Vertreter der *Lumbricus*-Gruppe, die Carl von Linné unter der Sammelbezeichnung *Lumbricus terrestris* L. zusammenfasste und die bis Ende des 18. Jahrhunderts offizinell waren; SCHNEIDER (1968/75), I, S. 48.

<sup>117</sup> „zubereitet“ bzw. „präpariert“ bezieht sich auf die Droge „*Lumbrici praeparati*“: Lebende Regenwürmer wurden gewaschen, in Weißwein mazeriert und dann getrocknet; SCHNEIDER, I, S. 49.

<sup>118</sup> *Fraxinus excelsior* L., Gewöhnliche Esche.

<sup>119</sup> Zur Umrechnung siehe MILDENBERGER (1997), III, S. 1453, der bei der Gleichung 1 Pfund = (etwa) 358g das in der Oberrheinebene gängige Basler Apothekergewicht zugrunde legt. Das alte Medizinal-Pfund des Apothekergewichts entsprach 357.78g; vgl. Meyer (1851), S. 425.

	Originaltext	Moderne Übersetzung
	<p>Tag an der Sonnen erbeitzen / dann ändere einmal solche nach gethane Blumen / laß widerumb so lang an der Sonnen erbeitzen / so hast ein kostbarlich Oel an statt deß gerechten Balsams zu gebrauchen / in alle Wunden / außgenommen so von harter Zerknitschung verursacht / oder sonst vom Lufft zerstört weren: lindert allen Schmerzen der Wunden / deßgleichen der Glieder / sonderlich nach den bösen Frantzosen: erweicht das Geäder in erlamdben Gliedern: wehret dem Krampff / so von Wunden / und offnen Schäden verursacht worden.</p>	<p>hinzu, lass das ganze zwei Wochen an der Sonne digerieren, verwirf die eingelegten Blüten und fülle neue nach und lass den Ansatz noch einmal vierzehn Tage<sup>120</sup> an der Sonne mazerieren<sup>121</sup>, so hast Du ein kostbares Öl, das dem echten Balsam<sup>122</sup> in den Heilanzeigen entspricht und ihm an Wirkkraft gleichkommt. Es ist indiziert bei allen <b>Wunden</b>, ausgenommen bei solchen, die durch eine schwere Zermalmung<sup>123</sup> verursacht worden sind oder wo Gasbrand<sup>124</sup> die Ursache der Gewerbszerstörung ist. Es lindert bei allen übrigen <b>Wunden</b> die <b>Schmerzen</b>, sowie auch <b>Schmerzen</b> der <b>Gelenken</b>, insbesondere solche Gelenkschmerzen, die sich nach Infektion mit der <b>Frambösie</b><sup>125</sup> einzustellen pflegen: hier lindert es die <b>Kontrakturen</b> und darüber hinaus schützt es vor den <b>Krämpfen</b>, die sich infolge der <b>Wunden</b><sup>126</sup> und <b>offenen Geschwüre</b><sup>127</sup> ergeben.</p>

<sup>120</sup> Der Text spricht von „fünfzehn“ Tagen, wobei sich die Differenz dadurch ergibt, dass (wie bei der *Malaria tertiana* und *quartana*) sowohl der erste wie auch der letzte Tag mitgezählt wurde; vgl. französisch „une quinzaine“ = ‚zwei Wochen‘, ‚Zeit von vierzehn Tagen‘, SACHS/VILLATTE (1907), I, S. 670<sup>e</sup>.

<sup>121</sup> „erbeitzen“ bezieht sich auf ‚digerieren‘ respektive ‚mazerieren‘; vgl. DWB III = 3, Sp. 715, mit Beleg aus Tabernaemontanus. Vgl. zur Sache DAEMS (1983).

<sup>122</sup> Der „echte Balsam“ – ein Commiphoren-Harz namens *Opo balsamum* – galt im 16. Jahrhundert als nicht verfügbar. Valerius Cordus empfahl 1646 entsprechend, ihn durch destillierte Öle zu ersetzen. Ein solches „opobalsamum“-Ersatzöl wird durch Tabernaemontanus in Gestalt seines „köstlich Öls“ bereitgestellt. Andere „opobalsamum“-Surrogate verzeichnet CRONE (2002), S. 43-46. Vgl. zur Sache SCHNEIDER (1968/75), V/1, S. 355ff.; MILDENBERGER (1997), I, S. 174f.: Schlangen-Öl als Balsam-Ersatz.

<sup>123</sup> Zur „harten Zerknitschung“ siehe oben Anm. 28.

<sup>124</sup> Folge der „harten Zerknitschung“ ist die Ablederung (Exkoriation) bzw. Gewebszerstörung mit sich anschließendem Gasbrand, bei dem die „Luft“ – dokumentiert durch die Gasblasen – Ursache der Zersetzung zu sein schien.

<sup>125</sup> „böse Frantzosen“ korrespondieren mit der „größen“ oder „bösen bläter“ der Frambösie-Infektion, dem ulzerierenden Primäraffekt einer Spirochaetose, die den Namen „Franzosen“ trug und den Formenkreis der Syphilis nach Europa (bzw. zum Exazerbieren) brachte. Charakteristisch für sie sind die nächtlichen Schmerz-Sensationen, die Arthralgien, Kontrakturen und Ankylosen. Vgl. KEIL/DAEMS (1977), S. 112f. und 118f.

<sup>126</sup> Wundstarrkrampf einschließlich Narbentetanus.

<sup>127</sup> Schaden bezieht sich generell auf eine Verletzung und ein äusserlicher Körperschaden spezifisch auf ‚Geschwür‘, ‚Ulcus cruris‘, ‚Nekrose‘, ‚Phlegmone‘, ‚Frostbeule‘:

	Originaltext	Moderne Übersetzung
	<p>Auff viel andere weiß wird diß Oel gemacht / also daß schier ein jedweder Wundartzet sein eigen Wundöl hat von diesem Kraut. Under andern ist nachfolgendes sehr nutzlich: Nimm alt Baumöl iiij. Pfundt: weissen guten Wein j. Pf. frische St. Johansblumen und Saamen vier Handvoll / laß durch einander in einem wolvermachten Geschirr zwen Taglang stehen / siede es in BALNEO MARIÆ, trucks wol auß / zu dem außgetruckten thee andere frische Blumen / und das zum drittenmal: seihe es dann durch / und thu darzu ein Terpentin xij. Loth / Wermuthöl vj. Loth / Diptam / Entzian / Cardenbenedicten / Tormentill / Eberwurtz / Kalmuß / jedes ein halb loth / Regenwürm zum offtern in Wein gewaschen iiij. loth / zerstoß alles undereinander / stells</p>	<p>Es gibt noch zahlreiche andere Verfahren, Johanniskrautöl herzustellen, und es sieht so aus, als ob nahezu jeder Wundarzt über seine eigene Johanniskrautöl-Spezialität verfüge<sup>128</sup>. Neben anderen Zubereitungen ist folgende Wundöl-Spezialität überaus hilfreich: Nimm 1432g altes Baumöl<sup>129</sup>, 358g guten Weißwein, vier Handvoll frische Sankt Johanniskrautblüten und Johanniskrautsamen, vermische das und lass es in einem dicht verschlossenen<sup>130</sup> Gefäß zwei Tage lang stehn, dann siede es im <i>Balneum Mariae</i><sup>131</sup>, drücke es aus; zum ausgepressten Ansatz gib erneut frische Johanniskrautblüten hinzu, koche abermals schonend im Wasserbad, und tu das zu drei Malen; seihe es dann ab und füge hinzu: 180g Terpentin, 90g Wermutöl<sup>132</sup>, je 7,5 g,</p>

MILDENBERGER (1997), I, S. 1687f.

<sup>128</sup> Die früheste bisher nachgewiesene magistrale Formel für eine derartige wundheilende Johanniskrautöl-Spezialität chirurgischer Provenienz findet sich im Kapitel 107 der ‚Ulmer Wundarzney‘, für die um 1485 der Wundarzt Magnus Bengger zeichnete; vgl. MARTIN (1991), S. 59. Die Formel steht auf den Blättern 95<sup>r</sup>-96<sup>r</sup>, vgl. VL IX (1995), Sp. 343, und 1238f.

<sup>129</sup> Während das frische Baumöl – insbesondere das grüne, aus unreifen Oliven gepresste – als besonders geeignet für gesunde Menschen galt, wurde das gealterte bevorzugt für die Arzneimittelherstellung herangezogen, so erläutert in der Renaissance Übersetzung des Dioskurides: „so ælter und frischer es ist, so nuerz vnnd bequemer es wirdt zu den Kranckheiten in der Artzney zu gebrauchen“, DIOSKURIDES (1610), S. 19; Siehe auch MILDENBERGER (1997), I, S. 250f. s.v. ‚boum-öle‘; BERENDES (1902), S. 56, I, 29f. Für einen mittelalterlichen Beleg siehe Rufinus, Bl. 75<sup>va</sup> in THORNKIKE/BENJAMIN (1945), S. 210: „*Oleum de olivis* [d.i. ‚Baumöl‘], *si multo magis inveteraverit, ut saporis fiat asperioris ac horribilioris, inconueniens erit esui, medicine tamen utile*“.

<sup>130</sup> „vol... vermachen“ ‚dicht verschließen‘; MILDENBERGER (1997), IV, S. 2127f.

<sup>131</sup> ‚*Balneum Mariae*‘, ist die technische Bezeichnung für Wasserbad, ein Verfahren, das zum schonenden Sieden einer Flüssigkeit bei einer gleichmäßigen Temperatur von 100°C über einem kleinen (Holzkohlen)feuer eingesetzt wurde; vgl. auch den „Sant Johans krut æl ofen“, MARTIN (1991), S. 60 und 303 (mit Abbildung).

<sup>132</sup> Ölauszug von *Artemisia absinthium* L. Zur Herstellung siehe das Wermutkapitel, TABERNAEMONTANUS (1664), Buch 1, Sektion 1, Kap 1, S.15, D-G, welches in Anm. 59 näher beschrieben wird. Vgl. auch das ‚Olmützer ‚Öl-Salben-, Pulver- und Pflasterbuch‘ (15. Jh., Bl. 131‘), publiziert in Mähren: „Oleum absinthei ist von wermut gemacht: Nu nym wermut saf... und gist ol daron und seczit is an dy sonne...“; CRONE (2002), S. 19f., vgl. ebd. S. 13 das „Oleum Absinthii“ süddeutscher Arzneitaxen des 15. Jahrhunderts und sieh auch VAŇKOVÁ (2004), S.59.

	Originaltext	Moderne Übersetzung
	an die Sonn dreissig oder vierzig Tag: setz es dann wol verdeckt an einen sauberen Ort.]	Diptam <sup>133</sup> , Enzian <sup>134</sup> , Kardobendikten(wurzel) <sup>135</sup> , Blutwurz <sup>136</sup> , Eberwurz <sup>137</sup> und Kalmus-Wurzel <sup>138</sup> , 60 g (frische) Regenwürmer, mehrfach in Wein gewaschen und präpariert <sup>139</sup> ; vermenge diese Zutaten alle miteinander, zerstoß sie im Mörser und stell das ganze dreißig bis vierzig Tage an die Sonne; (nach dem Digerieren seihe es ab und) verwahre es dann gut zugedeckt an einem sauberen, geeigneten Platz.]
	<b>Von Johannkrautsaltz SAL HYPERICI</b> genennt.  Von dem Johannskraut kan man auch ein Saltz præpariren, wie aber dasselbige zu machen / darvon kan man lesen bey dem Wermuth saltz.	<b>Vom Johanniskraut-Salz</b> , dem „Sal hyperici“  Mit Johanniskraut läßt sich auch eine mineralische Asche herstellen, deren Herstellungsweise im Wermut-Kapitel <sup>140</sup> mit Bezug auf das Wermut-Salz <sup>141</sup> beschrieben ist <sup>142</sup> .
	Was aber dieses Saltzes besondere Tugende seyn ist noch nicht offenbar / allein sagt man für gewiß / daß dieses	Welche Wirkungen es im Einzelnen hat, ist noch nicht festgestellt worden; als sicher kann indessen gelten, dass es

<sup>133</sup> Vgl. Anm. 70.

<sup>134</sup> Offizinell war *Gentiana lutea* L.; vgl. DRESSENDÖRFER (1978), S. 226; MILDENBERGER (1997), II, S. 552f. und 688f.

<sup>135</sup> Vgl. Anm. 73.

<sup>136</sup> Vgl. Anm. 74.

<sup>137</sup> Eberwurz, *Carlina acaulis* L., MARZELL (2000), I, Sp. 840-844; SCHÜTZEICHEL (2004), II, S. 352<sup>b</sup>-354<sup>b</sup>; EIS (1966).

<sup>138</sup> Das aromatische Rhizom von *Calamus aromaticus* oder synonym *Acorus calamus* L., dem Gewürzkalmus. DRESSENDÖRFER (1978), S. 198; MILDENBERGER (1997), I, S. 33f., 289f., II, S. 945f.; STOLL (1992). Zu historischen Indikationen von Kalamus siehe MADAUS (1932).

<sup>139</sup> Vgl. zum Verfahren oben Anm. 77 und 78.

<sup>140</sup> TABERNAEMONTANUS (1664), Buch 1, Sektion 1, Kap 1, S. 14K-15B.

<sup>141</sup> Von Tabernaemontanus werden zwei Herstellungsverfahren beschrieben, die beide auf das thermische Extrahieren der mineralischen Bestandteile hinauslaufen, die nach Verdunstungs-, Lösungs- und Filtrationsvorgängen als „weißes Saltz“ beim letzten Verdampfen in Gestalt eines kalzinierten (nicht kristallinen) Bodensatzes zurückbleiben. Ein solches Verfahren ist eine Veraschung und wird auch heute noch in der Spagyrik eingesetzt.

<sup>142</sup> Das Verfahren wird im Wermutsalz-Abschnitt als allgemeingültig ausgewiesen und als grundsätzlich für alle Heilkräuter anwendbar deklariert: „Und auf solche Weiß kan man nicht allein auss dem Wermuth / sonder auss einem jeden Kraut das Saltz extrahiren“, S. 14K, Buch 1, Sektion 1, Kapitel 1.

	Originaltext	Moderne Übersetzung
Seitenkräncke	Saltz wider die Seitenkräncke / PLEURITIS genennt / ein sehr köstliche Artzney sey / wie zu lesen ist IN TRACTATU DE RE- MED. SECRET. CONRADI GESNERI.	als vorzügliches Arzneimittel gegen das <b>Seitenstechen</b> bei <b>Rippenfellentzündungen</b> <sup>143</sup> , die man <b>Pleuritis</b> nennt, eingesetzt werden kann; Konrad Geßner berichtet darüber in seinem <i>Tractatu de remediis secretis</i> .
Harn und Sand treiben	Es hat auch ohn zweiffel diß Saltz ein Krafft den Harn und den Sand zu treiben / sonderlich da man es im Hauwechelwasser einnimpt.	Zweifellos ist das Salz auch in der Lage, den <b>Harnfluss</b> anzuregen und <b>Harn-Grieß</b> auszuschwemmen, und diese (lithotriptische) Wirkung wird noch gesteigert, wenn man es mit Hauhechel-Wasser <sup>144</sup> einnimmt.
Brandt. Blutstillen.	<b>[Von der Natur / Krafft / und Wirckung deß Harthew oder Cunrads.</b> Das Kraut zerstossen und wie ein Pflaster ubergelegt heylet den Brandt und gebrandte Schäden: stopfft das Blut der Wunden.	<b>[Von der Natur, Kraft und Wirkungen des Hartheus bzw. des Konradskrauts</b> Das (frische) Kraut von Hartheu wie auch Mannsblut heilt <b>Verbrennungen</b> und <b>deren Geschwüre</b> , und <b>stillt Blutungen</b> , wenn man es zerstöbt und als Kataplasma auflegt.
Gall austreiben Hufftweh.	Der Samen ein halb loth / in einem warmen trunck Meth früh eingenommen / treibt die überflüssige Gallen durch den Stulgang: und so man diß Trancks viel Tag nach	Nimmt man den Samen des Hartheus bzw. Konradskrauts allmorgens je 7,5g in einem Trunk warmen Mets <sup>145</sup> ein, dann <b>treibt</b> das die <b>überschüssige (schwarze) Galle</b> mit dem Stuhlgang aus und beseitigt somit die <b>Melancholie</b> <sup>146</sup> .

<sup>143</sup> „Seitenkräncke“ von HÖFLER (1899), S. 322<sup>b</sup>, in der angegebenen Bedeutung ab dem 18. Jahrhundert gebucht; das DWB, XI/1 = 16, Sp. 395, hat die vorliegende Referenz als einzigen erfasst.

<sup>144</sup> Wässriges Destillat von *Ononis spinosa* L., eine Medizinalpflanze, die rezent „zur Durchspülung... der ableitenden Harnwege und zur Vorbeugung gegen Nierengrieß“ verordnet wird; die moderne Indikation schließt „entzündliche“ Harnwegserkrankungen mit ein; HILLER/MELZIG (2003), II, S. 109<sup>b</sup>; bereits bei Dioskurides beschrieben: „treibt den Harn, zertrümmert den Stein“; vgl. BERENDES (1902), S. 273f.

<sup>145</sup> Ältestes gegorenes Getränk Mittel- und Südeuropas, nach unterschiedlichen Verfahren aus Honig und Wasser hergestellt, bis zu 15% alkoholhaltig, verabreicht mit mehreren Zusätzen; RGA (1973-2008), XIX, 618<sup>a</sup>-622<sup>a</sup>; GOETTLER (1958), S. 310<sup>ab</sup>: „auf einen Teil Honig dürfen nicht mehr als zwei Teile Wasser kommen“.

<sup>146</sup> Galle bezieht sich hier auf eine der vier humoralen Säfte, wie ein Vergleich mit Textstellen aus medizinischen Büchern derselben Zeitperiode zu belegen ist. Der Arzt und Universitätsprofessor Leonhart Fuchs schreibt 1543 (unter Harthaw, Kapitel XXIII): „...treib auß die choleriche überflüssigkeit. Man muss aber solchs offft und so lang tun biß die krankckheit genesen. Der Englische Arzt Willhelm Turner, ein Freund von Tabernaemontanus, schreibt 1551: „... it purgeth largely choleric humours. But it must be

	Originaltext	Moderne Übersetzung
	einander gebraucht dienet es wider das Wehthumb der Hüfft.]	Außerdem, wenn man diesen Trank über viele Tage nacheinander einnimmt, dann hilft das gegen die <b>Schmerzen</b> und <b>Ischialgien</b> der <b>Hüfte</b> <sup>147</sup> .

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taken continually, till the patient be whole.”; vgl. CHAPMAN & TWEDDLE (1989), S. 245. Sein Lehrmeister Bock, schreibt 1577 (S. 28): “...füret auß Choleram”. In der Humoralpathologie bezieht sich die schwarze (mela) Galle (chole) auf den melancholischen Gemüsstypus. In dieser Art der medizinischen Diagnostik führt ein Überschuss an schwarzer Galle zu psychischen Krankheiten und mentalen Zuständen wie der Melancholie, unter der wir heute Depression verstehen; vgl. Francia & Stobart 2014, P.301.

<sup>147</sup> Siehe Anm. 26.

**APPENDIX 13: APPROXIMATION TO THE PHARMACEUTICAL AND PHARMACOLOGICAL  
PROFILE OF *HYPERICUM PERFORATUM*, TABERNAEMONTANUS 1664**

Label	Contemporary English	Contemporary German	Original Text	Use-categories
<b>Contemporary name</b>	St. John's Wort	Johanniskraut		
<b>Botanical name</b>	<i>Hypericum perforatum</i>	<i>Hypericum perforatum</i>	<i>Hypericum, (Herba) Perforata, Fuga daemonum</i>	
<b>Historical names</b>	St. Peterswoort square great / St. Johannis grasse	Sankt Johanniskraut	Sanct Johannskraut heißt Griechisch <i>ὀπέρικον</i> , Leteinisch HYPERICUM, PERFORATA, FUGA DÆMONUM. [I. HYPERICUM VULGARE, C.B. HYPERICOUM, BRUNF. MATT. FUCH. ANG. TUR. LAC. LON. DOD. AD. LOB. CÆS. LUGD. CAST. CAM. GER. EYST. HERBA PERFORATA & HYPERICUM VULGARE, TRAG. ASCYRON. DOD. GAL. CORD. IN DIOSC. ANDROSÆMON MINUS, GER. COL. II. HYPERICUM FOLIO BREVIORE, C.B. SYRIACUM & ALEXANDRINUM, LOB. SYRIACUM, LUGD GER. III. HYPERICUM SUPINUM TOMETOSUM VEL MONSPELIACUM, G.B. SUPINUM, DOD. TOMETOSUM LOB. LUGD. GER. ALTERUM TOMETOSUM, AD. TOMETOSUM FECUNDUM. CLUS. HIST. ANDROSÆMUM ALBUM DALECH. LUGD. IV. ASCYRUM SIVE HYPERICUM BIFOLIUM GLABRUM NON PERFORATUM, C.B. ANDROSAEMON, MATTH. FUCH. TUR. LAC. CORD. IN DIOSC. CAST. GES. COL. HYPERICUM ALIUD. DOD. GAL. V. ANDROSÆMON ALTERUM FOLIIS HYPERICI, C.B.	

Label	Contemporary English	Contemporary German	Original Text	Use-categories
			ANDROSÆMON, LOB. ALTERUM, AD. RUTA SYL. HYPERICOIDES, DOD.] Arabisch <i>Refo. fricon.</i> Welsch <i>Hiperico, herba rossa.</i> Frantzösisch <i>Mille pertuis.</i> Englisch G. Johannes woorte. Böhmisch <i>Zwoncek cerweny.</i> [Niederländisch St. Janscruydt: Spanisch <i>conçillo.</i> Hartheuw aber so auch Waldthoff / wird ASCYRON genannt / Niederländisch Herthooy: Englisch St. Peterswoort square great, St. Johannis grasse: Welsch <i>asciro.</i>	
<b>Constitutional effect</b>	warm and dry in the second or third degree	warm und trocken im zweiten oder dritten Grad	sei warm und trucken und einer subtilen Substantz; sind warmer und trucknender Natur im anderen oder wie etliche wöllen im dritten Grad	
<b>Organoleptics</b>	n.a.	n.a.	n.a.	
<b>Plant part used</b>	aerial parts with flowers and fruits during flowering period; seeds	Kraut mit Blüten und Früchten; Samen	das gantze Gewächs; Kraut, Blumen und Saamen <sup>148</sup> ; Saamen;	
<b>Preparations Internal use</b>	<p><b>Decoction:</b> hot water decoction of herb</p> <p>hot water decoction of seeds</p> <p>wine decoction with fresh, flowering parts, incl. fruits</p>	<p><b>Absud</b> Wasserabsud des Krauts</p> <p>Wasserabsud der Samen</p> <p>Weinabsud des (frischen<sup>149</sup>) blühenden Krauts, inkl. Früchte</p>	<p><b>Absud</b> Wässriger Absud; davon gesottene Brühen [Kraut]</p> <p>der Saame gesotten und getruncken</p> <p>Kraut, Blumen und Saamen in Wein sieden</p>	

<sup>148</sup> In contemporary botany, this refers to forming fruits which can appear together with buds and flowers on a flowering plant. The true seeds form after the flowering stage.

<sup>149</sup> It is likely, that this refers to a preparation made with fresh plants, as in other passages the author specifically refers to “gedörnt” (dry) when he discusses a preparation made with dry plant material (Tabernaemontanus, 1664, p. 1251C).

Label	Contemporary English	Contemporary German	Original Text	Use-categories
	warm beer extraction of flowerheads with salt and butter	warmer Bierauszug der Blütenständen, mit Salz und Butter	Blumen in einem warmen Bier mit Butter und Saltz warm einzugeben	
	<b>Juice:</b> fresh plant juice of leaves and flowerheads	<b>Saft</b> frischer Pflanzensaft aus den Blättern und Blütenständen	<b>Safft</b> aus den Blättern und Blumen kann man auch einen Safft außpressen	
	<b>Hydrosol:</b> St. John's Wort water (hydrosol of fresh flowers, leaves)	<b>Hydrolat</b> Johanniskrautwasser (Hydrolat aus frischen Blüten und Blätter)	<b>Wasser brennen</b> Kraut und Blumen von den Stengeln abstreifen und ein Wasser darauß brennen <sup>150</sup> ; davon getrunken	
	mixture of St. John's Wort hydrosol with red wine	Mixtur aus Johanniskrauthydrolat mit Rotwein	das Wasser mit rotem Wein vermischt	
	<b>Fresh herb</b> flowering plant with fruits	<b>Frisches Kraut</b> blühendes Kraut mit Früchten	<b>Kraut</b> das gantze Gewächs - Kraut / Blumen / Früchte	
	herb taken with wine	Kraut mit Wein einnehmen	Kraut mit Wein trinke	

150 The term "Wasser brennen" (burning water) (Tabernaemontanus, 1664, p. 1251G) refers today to an alcohol distillation. However, during the early modern period this term was not conclusively defined and could, depending on author and book, refer to an extraction with water or more rarely with alcohol. Encyclopaedias of the 15<sup>th</sup> and 16<sup>th</sup> century define the term "brennen" (burning) as the extraction of a substance with heat without specifying the medium (Müller-Grzenda, 1996, pp. 44-46). Based on Tabernaemontanus' descriptions of "Wasser brennen" in various plant monographs (e.g. St. John's Wort, Fennel, Dill, Wormwood, Chamomile and others), the author appears to reference a type of steam distillation where the medicinal plants were first decocted for 24 hours via a *Balneo Mariae* (water bath) that was covered with an *Alembicu coecum* (blind helmet), before the saturated fluid was drained off with a helmet with beak (Tabernaemontanus, 1664, p. 169). The sizable dosage of 30-45g of this 'burnt water' of St. John's Wort to be taken 2-3x per day adds to the plausibility that Tabernaemontanus references a water steam distillate and not an alcohol distillate (Tabernaemontanus, 1664, p. 1251G). For more on the technology of distillation see Pfeiffer (1986) and Will (2009).

Label	Contemporary English	Contemporary German	Original Text	Use-categories
	<p><b>Crude drug</b> powder of dried herb and fruit taken with wine</p> <p>seed; pounded seed</p> <p>sees taken with warm mead</p> <p><b>Combustion of plant</b> ash (salt)</p>	<p><b>Droge</b> Pulver aus getrocknetem Kraut mit Früchten mit Wein einnehmen</p> <p>Samen; zerstoßener Saamen</p> <p>Samen einnehmen mit warmer Met</p> <p><b>Veraschung</b> Asche (Salz)</p>	<p><b>Kraut mit dem Saamen gedörst</b> das Kraut mit dem Saamen gedörst und gepülveret mit Wein getruncken</p> <p>Saamen eingeben; Saamen gebrauchen; der Samen zerstoßen mit Wegerichsafft<sup>151</sup> oder Wasser getruncken</p> <p>der samen ... in einem warmen trunck Meth ... eingenommen</p> <p><b>Saltz</b> von dem Johanskraut kan man auch ein Saltz praeparieren</p>	
<p><b>Preparations</b> <b>External use</b></p>	<p><b>Decoction:</b> hot water decoction of flowering plant</p> <p><b>Oil:</b> olive oil extract of fresh flowerheads</p>	<p><b>Absud:</b> Wasserabsud des blühenden Krauts</p> <p><b>Öl:</b> Olivenölauszug aus frischen Blüten(kronen)</p>	<p><b>Absud</b> wässriger Absud (blühende) Kräuter</p> <p><b>Oel:</b> frische Blumen... geuß Baumöl darüber</p>	

<sup>151</sup> Some recipes in this monograph consist of complex formulations. This hinders a direct correlation of St. John's Wort with an indication. Nonetheless, its use in complex formulation points to an indication where St. John's Wort is considered to contribute to the pharmacological action.

Label	Contemporary English	Contemporary German	Original Text	Use-categories
	<p><b>Fresh plant preparations:</b> poultice (cataplasm) of fresh herb</p> <p>rub with fresh herb</p> <p>fresh juice of leaves and flowerheads</p> <p><b>Hydrosol:</b> St. John's Wort water (hydrosol of fresh herb and flowerheads)</p> <p><b>Specialties:</b> gauze compress with a mixture of St. John's Wort hydrosol and wine</p> <p>plaster from peritoneum of sheep roasted in St. John's Wort oil</p> <p>ointment with St. John's Wort oil and wax</p> <p>wound powder of dry herb</p>	<p><b>Frischpflanzen Anwendung:</b> Breiumschlag (Kataplasma) aus dem frischen Kraut</p> <p>Frischpflanzeneinreibung</p> <p>frischer Pflanzensaft aus den Blättern und Blütenständen</p> <p><b>Hydrolat:</b> Johanniskrautwasser (Hydrolat aus frischem Kraut und Blütenständen)</p> <p><b>Spezielle Präparate:</b> Umschlag aus einer Mixtur aus Johanniskrauthydrolat und Wein</p> <p>Pflaster aus dem Bauchnetz eines Schafes geröstet in Johanniskrautöl</p> <p>Salbe aus Johanniskrautöl und Wachs</p> <p>Wundpulver aus getrocknetem Kraut</p>	<p><b>Grünes<sup>152</sup> Kraut</b> grünes Kraut zerknitsche und wie ein Pflaster überlege</p> <p>Glieder mit dem (grünen) Kraut gerieben</p> <p>Aus den Blättern und Blumen kann man auch einen Safft außpressen</p> <p><b>Wasser brennen</b> Kraut und Blumen von den Stengeln abstreifen und ein Wasser darauß brennen</p> <p>das Wasser mit rotem Wein vermischt...mit einem Tuch auff den bauch gelegt</p> <p>ein Stück Netze von einem Schaff, zerschneide es und röste es in Öl, legs also warm auff den Bauch</p> <p>Oel ...und mit Wachs zu einem Sälblein machtet</p> <p>dürre Pulver [von Kraut] in die unreine feuchte Wunden sträuwe</p>	

<sup>152</sup> „Grünes Kraut“ (green herb) refers to a medicinal plant in its fresh state.

Label	Contemporary English	Contemporary German	Original Text	Use-categories
	fumigation with dry herb	Beräucherung mit getrocknetem Kraut	mit dürrem Kraut beräuchen	
	talisman made with herb	Talisman aus Kraut	Kraut sey für Gespengst wann man es bey sich trägt	
	foot bath with herb	Fußbad mit Kraut	Fussbad auß diesem Kraut	
	a wash with St. John's Wort water of herb and flowerheads (hydrosol)	Waschung mit Johanniskrautwasser destilliert aus Kraut und Blütenständen	Kraut und Blumen von den Stengeln abstreifen und ein Wasser darauß brennen; damit gewaschen	
	wet compress with St. John's Wort hydrosol	Feuchter Umschlag mit Johanniskrautwasser (Hydrosol)	das Wasser eusserlich aufgeschlagen	
<b>Actions internally</b>	analgesic (hips, musculo-skeletal system)	schmerzlindernd (Hüfte, Bewegungsapparat)	wider die Schmerzen und Wehethumb der Hüfft; so ihnen von wegen schwerer Last weh gethan haben; mildert die Schmerzen der Hüfft; wider das Wehthumb der Hüfft	nerve
	chases excess (black) bile (anti-depressive)	überflüssige (schwarze) Galle treiben (anti-depressiv)	treibt die überflüssige Gallen <sup>153</sup>	somatoform
	anti-diarrheal	stopfend	habe ein Art den Leib zu stopffen; hilfft wider das Durchlauffen und Bauchflüß; stopffet die Bauchflüß und rothe Ruhr; stopffet das Durchlauffen; verstillt die Stulgäng	gastro-intest
	anti-epileptic	anti-epileptisch	ist gut für die Fallendesucht	head
	anti-haemorrhagic	blutstillend	dienet wider das Blutstpeyen <sup>154</sup>	respiratory

<sup>153</sup> See Francia & Stobart (2014, p. 301). To 'chase excess (black) bile' references a humoral concept and relates to the elimination of melancholy. *Melas* is Greek for black and *kholē* is bile. In humoralism, fear, sadness, gloom and fright were seen as typical symptoms of melancholic illnesses (Zimmermann, 1975, pp. 91-96). Such mental and emotional afflictions are today commonly referenced as depression (Tschupp, 1998, pp. 44-47).

<sup>154</sup> „Blutspeyen“ or “Blutspeyen” references coughing or vomiting of blood, or a pulmonary haemorrhage (DWB, 1854-1960, pp. Band 2, Sp. 192). It may also relate to

Label	Contemporary English	Contemporary German	Original Text	Use-categories
	anthelmintic	entwurmend	diesen Saft gibt man mit Odermenig den Rossen ein für die Würm	gastro-intest
	anti-malaria	anti-malaria	so vertreibe es das dreytägige Fieber ( <i>Malaria tertiana</i> )	infection
	anti-rheumatic	anti-rheumatisch	dienet fürs Gesicht <sup>155</sup> an Füßen	musc-skel
	anti-stroke	anti-apoplexisch	ist gut für ... den Schlag	head
	detoxifying	entgiftend	welches auch das Gifft außjagt	liver-spleen
	diuretic	diuretisch	ein Natur und Krafft habe den Harn fort zu treiben; treibe er den Harn; ein Krafft ... den Harn zu treiben	uro
	kidney cleansing	nierenreinigend	reiniget Nieren	uro
	lithotriptic	lithotriptisch	treibe ... den Grieß; ist treffenlich gut dem Blasenstein; ein Krafft ... den Sand zu treiben sonderlich da man es im Hauwhechelwasser...	uro
	liver cleansing	leberreinigend	reiniget ... Leber	liver-spleen
	menstruation promoting	menstruationsfördernd	der Weiber Blödigkeit treibt <sup>156</sup>	gyn

symptoms of tuberculosis, an illness known and described by 16<sup>th</sup> century authors (Ackerknecht, 1967, p. 89).

<sup>155</sup> „Gesicht“ relates to the Middle High German word „gesülte“ which references „rheumatisches Übel“ (rheumatic complaint) (Lexer, 1872-1878, pp. I, 936). See also reference „*Polyarthrititis rheumatica*“ in Höfler (1899, p. 707a).

<sup>156</sup> „der Weiber Blödigkeit“ broadly refers to menstruation (FrnhdWb, 1986-, pp. IV, Sp. 636). However, in the St. John's Wort monograph of Tabernaemontanus this term seems to cover more than the physiological process of bleeding since the author uses elsewhere a different term for this: „...fürdert die weibliche Monatsblum“ (Tabernaemontanus, 1664, p. 65). Thus, the term „Weiber Blödigkeit“ may refer to broader physical and psychological aspects of menstruation. Today, St. John's Wort is used for the treatment of pre-menstrual syndrome (PMT), mood changes and dysphoria in connection with the menstrual cycle. It is assumed here, that the term „Weiber Blödigkeit“ references these broader complaints.

Label	Contemporary English	Contemporary German	Original Text	Use-categories
	pre-menstruation discomfort relieving	pre-menstruelles und mensturuelles Unwohlsein erleichternd	der Weiber Blödigkeit treibt	somatoform
	styptic	blutstillend	daß sie das Blut in den Wunden stillen	skin-mucous
	tissue healing (in burns) vulnerary (in wounds and ulcers)	gewebeheilend (in Verbrennungen) wundheilend (in Wunden und Geschwüren)	was verbrannt ist heylen; so hefte es wiederum zusammen ... sonderlich was von Brand ist innerlich zu Wundtränken; heylet alle innerliche und eusserliche Wunden; so hefte es die Wunden und offene Geschwär wiederum zusammen	skin-mucous skin-mucous
	wound cleansing (antiseptic)	wundreinigend	in grossen, tieffen Wunden, Verletzungen deß Geäders nutzlichen gebraucht solche zu reinigen	skin-mucous
<b>Actions externally</b>	analgesic (joints, belly, colic, wounds, nerves)	schmerzlindernd (Gelenke, Bauchweh, Kolik, Wunden, Nerven)	mildert die Schmerzten der Hüfft ; legs also warm auff den Bauch es lindert die Schmerzten; gut wider die rote Ruhr so man den Bauch warm damit schmieret dann es leget den Schmerzten; legs also warm auff den Bauch es lindert die Schmerzten; wider die COLICAM; lindert allen Schmerzten der Wunden deßgleichen der Glieder ... sonderlich nach den bösen Frantzosen <sup>157</sup>	nerve
	antidiarrheal	stopfend	legs also warm auff den Bauch es ... verstillet die Stulgäng; stopffet die Bauchflüß und rothe Ruhr ...wie dann auch mit einem Tuch auff den bauch	gastro-intest

<sup>157</sup> The term „böse Frantzosen“ corresponds with „grôzen“ or „bösen bläter“, a sexually transmitted infection which presented with chancres, sores and neurological symptoms (Keil & Daems, 1977, pp. 112-113, 118-119). It is presumed that this illness references the spectrum disorder of syphilis. This infection was named after the French who were thought to have brought the illness to Europe (or had exacerbated the spreading of it).

Label	Contemporary English	Contemporary German	Original Text	Use-categories
			gelegt; wenn jemandts die rote Ruhr hat ... so stopffe es den Durchlauff	
	anti-trembling	gegen Tremor	Die Glieder mit dem Kraut gerieben / ist gut fürs Zittern und Beben...	nerve
	apotropaic	apotropäisch	sey für Gespengst / wann man es bey sich trägt / FUGA DAEMONUM soll genennt werden <sup>158</sup>	apotrop
	birthing support	geburtserleichternd	wenn ein Weib in schweren Kindsnöthen ligt	gyn
	nerve healing	Nerven heilend	zu den zerknitschten und zerstossenen Nerven	nerve
	spasmolytic	Krampf lösend	wehret dem Krampff so von Wunden und offnen Schäden verursacht; gebraucht ... die COLICAM; den Kindern die Grimmen haben über den Nabel zu legen; erweicht das Geäder in erlamnden Gliedern;	musc-skel
	styptic	blutstillend	stofft das Blut der Wunden	skin-mucous
	tissue healing	Gewebe heilend	heylet ... sonderlich aber die verwundeten Sennadern <sup>159</sup>	musc-skel
	tissue healing (in burns)	wundheilend bei Verbrennungen	so heffte es die Wunden und die offene Geschwär widerumb zusammen ... sonderlich was von Brand ist; gar gut zum Brand eusserlich aufgestichen; gut zu dem Brand vom Fewer; wie ein Pflaster ubergelegt	skin-mucous

<sup>158</sup> This term has been first noted in the 13th century in a catalogue of drugs from Salerno (Italy) (Reallexikon der Germanischen Altertumskunde, 1973-2008, pp. XVI, 68b). In herbals of the early modern period there are a number of expressions for symptoms which would be referenced today as states of anxiety or depressive mood disorders (Tschupp, 1998, pp. 44-46).

<sup>159</sup> The term „Ader“, references here “strangförmiges Gebilde” (strand-like formation) (Mildenberger, 1997, p. 38). „Ader“, „Sehnader“, „Sennader“ or „Geäder“ may include ligaments, tendons, facia, nerves and muscles (DWB, 1854-1960, pp. Band 16, Sp. 148; Mildenberger, 1997, pp. 38-40, 665).

Label	Contemporary English	Contemporary German	Original Text	Use-categories
	tissue healing (in ulcers)	(offene) Geschwür heilend	heylet den Brandt und gebrandte Schäden  so heffte es ... die offene Geschwär widerumb zusammen; Pulver in die unreine feuchte Wunden sträuwe so verzeher es die Feuchtigkeit und heyle ... auch dergleichen Geschwär;	skin-mucous
	tissue healing (in wounds)	wundheilend	heylet alle ...eusserliche Wunden; der Wunden deßglichen der Glieder; zu Wundtränken ... auch eusserlich; in grossen, tieffen Wunden, Verletzungen deß Geäders nutzlichen gebraucht...von grund auß zu heylen; so heffte es die Wunden ... widerumb zusammen; eusserlich in Wunden gethan ... heylet sie; eusserliche Wunde ... damit gewaschen und das Wasser eusserlich auffgeschlagen; Pulver in die unreine feuchte Wunden sträuwe so verzeher es die Feuchtigkeit und heyle die Wunden; heylet die Wunden gar wol in allen Wunden außgenommen so von harter Zerknitschung verursacht oder sonst von Lufft zerstört;	skin-mucous
	warming (stiff limbs and joints)	wärmend (steife Glieder und Gelenke)	ist auch dienstlich zu allen kalten <sup>160</sup> Gebrechen der Glieder und Gewerben	musc-skel
	wound cleansing (antiseptic)	wundreinigend	in grossen, tieffen Wunden, Verletzungen deß Geäders nutzlichen gebraucht solche zu reinigen; eusserlich in Wunden gethan reiniget dieselbigen	skin-mucous

<sup>160</sup> In humoralism, St. John's Wort was classified as warm and dry in the second or third degree. The plant was therefore applied to warm up cold or stiff areas as experienced in various types of arthritis.

Label	Contemporary English	Contemporary German	Original Text	Use-categories
<b>Medicinal uses: Internally</b>	bladder stone	Blasenstein	trefflich gut dem Blasenstein	uro
	bleeding wounds	Blutungen aus Wunden	das Blut in den Wunden stillen	skin-mucous
	blood spitting	Blutspucken	wider das Blutspeyen	respiratory
	burns	Verbrennungen	was verbrant ist heylen	skin-mucous
	diarrhea	Durchfall	stopffet die Bauchflüße und rohte Ruhr; ein Art den Leib zu stopffen; wider das Durchlauffen und Bauch Fluß	gastro-intest
	epilepsy	Epilepsie	ist gut für die Fallendesucht	head
	gravel (in urinary tract)	Gries (im Harntrakt)	treibe... den Griebß; den Sand zu treiben... sonderlich da man es im Hauwhechelwasser einnimpt	uro
	hip pain, sciatica	Hüftweh; Ischialgien	Wehethumb der Hüfft <sup>161</sup>	musc-skel,
	kidney detoxification	Nierenentgiftung	reinigt Nieren; Gifft außjag	uro
	liver detoxification	Leberentgiftung	reinigt ... Leber; Gifft außjag	liver-spleen
	<i>Malaria tertiana</i>	<i>Malaria tertiana</i>	vertreibe das dreytägige Fieber	infection
	melancholy	Melancholie	treibt die überflüssige [schwarze] Galle	somatoform
	menstruation	Menstruation	der Weiber Blödigkeit treibt	gyn

<sup>161</sup> Bock (1577, S.28) explains, that „Hüftweh“ (hip pain) refers to „Ischias“ (sciatica): “Vertreibt...beschwerlich hüftwehe, Ischia genant...”. “Ischi-“ is Greek for hip, hip joint, hip bone. See also Rufinus, Bl. 59<sup>a</sup>, where it says: „*Herba sancti Iohannis... femorum dolorem auffert.*“ (Thorndike, 1945, pp. 153, Z.157).

Label	Contemporary English	Contemporary German	Original Text	Use-categories
	menstruation: discomfort around menstruation	Beschwerden im Zusammenhang mit Menstruation	der Weiber Blödigkeit treibt	gyn
	musculo-skeletal injuries (ligaments, tendons, fascia, nerves and muscles)	Verletzungen von Gewebe des Bewegungsapparats (Bänder, Faszie, Nerven, Muskeln)	Verletzungen des Geäders; heylet ... sonderlich aber die verwundeten Sennadern	musc-skel
	pain (in the musculo-skeletal system) from heavy lifting	Schmerzen (im Stütz- und Bewegungsapparat) durch schweres Heben	von wegen schwerer Last weh gethan haben	nerve
	rheumatism	Rheuma	Gesicht an Füßen	musc-skel; nerve
	pleurisy	Rippenfellentzündung	wider die Seitenkränke PLEURITIS genennt	respiratory
	stiff limbs and joints	steife Glieder und Gelenke	dienstlich zu allen kalten Gebrechen der Glieder <sup>162</sup> und Gewerben <sup>163</sup>	musc-skel
	stroke	Schlaganfall	ist gut für den Schlag	head
	toxic exposure	Vergiftungen	Gifft außjagt	liver-spleen
	urine voiding (in urine retention)	Urin befördernd (bei Harnverhalten)	Harn .. zu treiben ... sonderlich da man es im Hauwechelwasser einnimpt	uro
	worms (horses)	Wurmbefall (Pferde)	mit Odermenig den Rossen ein für die Würm	gastro-intest

<sup>162</sup> The term „Glieder“ refers here to the mobile part of an extremity or a limb (Mildenberger, 1997, pp. II, 679-680).

<sup>163</sup> The term „Gewerbe“ refers to “*articulatio*” or joint (DWB, 1854-1960, pp. IV/I/III = 6, Sp. 5489).

Label	Contemporary English	Contemporary German	Original Text	Use-categories
	wounds (deep, infected, large)	Wunden (großflächige, infizierte, tiefe)	innerlich zu Wundtränken .. grossen, tieffen Wunden... solche zu reinigen und von grund auß zu heylen; heylsame Wundkräuter; heylet alle innerliche und eusserliche Wunden .. davon getruncken	skin-mucous
<b>Medicinal uses: Externally</b>	abdominal pain	Bauchweh	So man den Bauch warm damit schmieret dann es leget den Schmetzen; legs also warm auff den Bauch es lindert die Schmetzen	gastro-intest
	birth complications	Geburtskomplikationen	in schweren Kindsnöhten	gyn
	bleeding in wounds	Blutungen in Wunden	Stopfft das Blut der Wunden	skin-mucous
	burns	Verbrennungen	was vom Brand ist; gar gut zum Brand; gut zu dem Brand vom Feuer; heylet den Brandt und gebrandte Schäden	skin-mucous
	colic, colic in children	Bauchkolik, Kolic in Kindern	wider die COLICAM; Krimmen; den Kindern die Grimmen haben	gastro-intest
	demons (banish)	Zur Vertreibung von Gespenstern	sey für Gespengst...FUGA DAEMONUM soll genennt werden	apotrop; somatoform
	diarrhea	Durchfall	stopffet die Bauchflüße und rohte Ruhr wie dann auch mit einem Tuch auff den bauch gelegt; rote Ruhr ... so stopffe es den Durchlauff; wider die rote Ruhr; verstillt die Stulgäng	gastro-intest
	hip pain, sciatica	Hüftweh; Ischialgien	leget und miltert die Schmetzen der Hüfft	nerve, musc-kele
	lame joints - soften	lahme Glieder erweichen	erweicht das Geäder in erlamnden Gliedern	musc-skel

Label	Contemporary English	Contemporary German	Original Text	Use-categories
	musculo-skeletal injuries (ligaments, tendons, muscles, fascia, nerves and muscles)	Verletzungen vom Gewebe des Bewegungsapparats (Bänder, Muskeln, Faszie, Nerven, Muskeln)	Verletzungen des Geäders; die verwundten Sennadern	musc-skel,
	nerve injuries	Nervenverletzungen	zerknitschten und zerestossenen Nerven; verstopfte Nerven	nerve
	nerve pain	(Nerven) Schmerzen nach Syphilis	Schmerzen...nach den bösen Frantzosen	nerve
	pain (abdomen, limbs, musculo-skeletal, rheumatism, womb, wounds)	Schmerzen (Abdomen, Glieder, Bewegungsapparat, weiblicher Unterleib, Wunden)	alle Schmerzen der Wunden, deßgleichen der Glieder; Krimmen; der Weiber Blödigkeit; in schweren Kindsnöhten	nerve
	puerperium (confinement)	Wochenbett	sechswöchige Weiber <sup>164</sup>	gyn
	spasms in wounds	Wundkrämpfe	Krampf so von Wunden und offnen Schäden verursacht <sup>165</sup>	musc-skel
	stiff limbs and joints	bei steifen Gliedern und Gelenken	dienstlich zu allen kalten Gebrechen der Glieder und Gewerben	musc-skel
	talisman	Talisman	sey für Gespengst / wann man es bey sich trägt Die Glieder mit dem Kraut gerieben / deß Tags zwey mal vor dem Essen / ist gut fürs Zittern und Beben...	apotrop
	trembling, tremor	Zittern, Tremor		nerve

<sup>164</sup> For the period of post-birth confinement see Reallexikon der Germanischen Altertumskunde (1973-2008, pp. XXXIV, 174a-180a).

<sup>165</sup> It is not certain if this could relate to tetanus or more generally to wound pain.

Label	Contemporary English	Contemporary German	Original Text	Use-categories
	ulcer	Geschwür	die offene Geschwür widerumb zusammen; unreine, feuchte...Geschwär	skin-mucous
	wounds (deep, large, infected)	Wunden (blutende, großflächige, tiefe infizierte)	grossen tieffen Wunden; so heffte es die Wunden; in Wunden gethan reiniget dieselbigen und heylet sie; unreine Wunden; heylet all ... eusserliche Wunden ... damit gewaschen und das Wasser eusserlich aufgeschlagen; heylet die Wunden gar wol; stopft das Blut der Wunden; in allen Wunden aussgenommen so von harter Zerknitschung verursacht oder sonst vom Lufft zerstört weren; Wundöl hat von diesem Kraut	skin-mucous
<b>Dosage internal use</b>	<b>Decoction:</b> dose unknown  <b>Fresh juice:</b> dose unknown  <b>Hydrosol:</b> 30-45ml; 2-3x per day  <b>Ash (salt):</b> dose unknown	<b>Absude:</b> Dosis unbekannt  <b>Presssaft:</b> Dosis unbekannt  <b>Johanniskrautwasser (Hydrolat):</b> 30-45ml; 2-3x pro Tag  <b>Asche (Salz):</b> Dosis unbekannt	<b>Absud</b>  <b>Safft auspressen</b>  <b>Wasser brennen</b>  <b>Saltz</b>	
<b>Dosage external use</b>	<b>Decoction:</b> <b>for washes, compresses, foot baths:</b> dose unknown <b>Fresh juice:</b> drip into wound	<b>Absud:</b> <b>für Waschungen, Umschläge, Fußbad:</b> Dosis unbekannt <b>Presssaft:</b> in Wunde träufeln	<b>Absud</b>  <b>Safft auspressen</b> Safft eusserlich in Wunden gethan	

Label	Contemporary English	Contemporary German	Original Text	Use-categories
	<p><b>Hydrosol for wet compresses:</b> dose unknown</p> <p><b>Cataplasm:</b> covering surface with fresh, pounded plant</p> <p><b>Oil:</b> sufficient for massage</p> <p><b>Ointment:</b> covering of navel</p> <p><b>Fumigation</b> dose unknown</p>	<p><b>Johanniskrautwasser (Hydrolat) für feuchte Umschläge:</b> Dosis unbekannt</p> <p><b>Pflaster:</b> flächendeckend mit zerdrückten Pflanze</p> <p><b>Öl:</b> genügend für Massage</p> <p><b>Salbe:</b> Nabel deckend</p> <p><b>Beräucherung</b> Dosis unbekannt</p>	<p><b>Wasser brennen</b></p> <p><b>Pflaster</b> grünes Kraut zerknitsche und wie ein Pflaster überlege</p> <p><b>Johanniskrautöl</b></p> <p><b>Sälblein</b></p> <p><b>Beräucherung</b></p>	
<b>Contraindications</b>	None mentioned	Keine genannt		
<b>Warnings and Precautions</b>	None mentioned	Keine genannt		
<b>Pregnancy and Lactation</b>	<p>No contraindication mentioned for use during pregnancy or breastfeeding</p> <p>Fumigations for six weeks after birth (coincides with breastfeeding)</p>	<p>Keine Kontraindikation genannt für Gebrauch während Schwangerschaft oder Stillzeit</p> <p>Beräucherung während sechs Wochen nach Geburt (fällt zusammen mit Stillzeit)</p>	<p>[Etliche beräuchen die sechswöchige Weiber darmit / derothalben nennet man es an etlichen Orten unser Frawenwurtz.]</p>	
<b>Side effects</b>	None mentioned	Keine genannt		

## APPENDIX 14: INDICATIONS FOR *HYPERICUM PERFORATUM* IN MEDICAL TEXTBOOKS

Use-categories	Tabernaemontanus 1664	Löseke 1790 / Plenck 1794	Richter 1827	Strumpf 1855	Hager 1878	Schulz 1919	Madaus 1938	Kroeber 1948	Weiss 1974	Saller et al 1995	Bäumler 2007
<b>apotrop</b>	✓	0	0	(✓)	(✓)	0	0	0	0	0	(✓)
	talisman against ghosts and demons			<i>talisman</i>	<i>talisman</i>						<i>talisman against ghosts and demons</i>  <i>against lightning</i>
<b>card-vasc</b>	0	0	0	0	0	✓	✓	✓	✓	✓	✓
						circulatory insufficiency  congestive states		circulatory insufficiency  congestive states	varicose veins	varicose veins	varicose veins
							haemorrhoids	Haemorrhoids	haemorrhoids	proctitis	
							cardiac neurosis				<i>heart strengthening</i>
								anaemia			
<b>gastro-intest</b>	✓	✓	(✓)	✓	(✓)	(✓)	✓	✓	✓	✓	✓
	abdominal pain, colic					<i>catarrh of mucus membranes of stomach</i>	stomach colic stomach ulcer	stomach catarrh <i>abdominal pain</i>	stomach catarrh stomach ulcers inflammation of the colon	gastritis stomach ulcer proctitis	gastritis gastroenteritis, proctitis,
	diarrhoea	<i>dysentery</i>	<i>dysentery bloody diarrhoea</i>	dysentery	<i>dysentery</i>		bloody diarrhoea	diarrhoea, dysentery		<i>diarrhoea</i>	<i>diarrhoea</i>

Use-categories	Tabernaemontanus 1664	Löseke 1790 / Plenck 1794	Richter 1827	Strumpf 1855	Hager 1878	Schulz 1919	Madaus 1938	Kroeber 1948	Weiss 1974	Saller et al 1995	Bäumler 2007
								dyspepsia, reflux and gas lack of appetite		dyspeptic complaints	dyspeptic complaints
	worms (horses)	worms	worms	worms				worms			worms
<b>gyn</b>	✓	0	0	✓	0	(✓)	✓	✓	0	✓	✓
	birth complications										to accelerate birth
	menstruation-unease before and during menstruation			breast complaints			pre-menstrual syndrome	pre-menstrual syndrome (headaches, migraines)			pre-menstrual dysphoria high prolactin levels
				menstruation (emmenagogue) dysmenorrhoea menorrhagia		menstruation (emmenagogue)	menstruation			menopausal complaints	dysmenorrhoea; menopause induced nervous tension
	puerperium (childbirth confinement)										puerperium (birth nervous tension)
				white discharge			endometriosis uterine spasms				
						uterine spasms					fertility
<b>head</b>	✓	0	0	0	0	0	✓	✓	0	✓	✓

Use-categories	Tabernaemontanus 1664	Löseke 1790 / Plenck 1794	Richter 1827	Strumpf 1855	Hager 1878	Schulz 1919	Madaus 1938	Kroeber 1948	Weiss 1974	Saller et al 1995	Bäumler 2007
	epilepsy						epilepsy (from trauma) cyanosis in newborns from brain bleeds	<i>epilepsy</i> convulsions (from trauma to the head)			
	stroke										<i>stroke</i>
							cerebral concussion	cerebral concussion, brain bleeds			
							migraine	headaches		migraines meteoropathy	tension headaches
											increase of cognitive function
											<i>toothache</i>
<b>hormonal</b>	0	0	0	0	0	0	0	✓	0	0	0
								metabolic disorders			
<b>infection</b>	✓	0	0	✓	0	0	0	(✓)	0	0	✓
	Malaria tertiana			Malaria tertiana Malaria quartana							
				chronic infections							
								<i>fever</i>			<i>fever</i>

Use-categories	Tabernaemontanus 1664	Löseke 1790 / Plenck 1794	Richter 1827	Strumpf 1855	Hager 1878	Schulz 1919	Madaus 1938	Kroeber 1948	Weiss 1974	Saller et al 1995	Bäumler 2007
											viral infection (Herpes zoster); bacterial infections
<b>liver-spleen</b>	✓	0	0	✓	0	0	✓	✓	0	(✓)	(✓)
	liver detoxification							<i>liver diseases</i>		<i>liver diseases</i>	<i>liver tonic</i>
	poison			poison ( <i>snake bite</i> ) catalepsy							<i>detoxification of poison</i>
				bile stagnancy			liver and gallbladder stones	jaundice, biliary excretion disorders		<i>biliary disorders, biliary excretion disorders, inflammation</i>	<i>biliary disorders</i>
<b>musc-skel</b>	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	hip pain / sciatica	spinal injuries		hip pain / sciatica			sciatica	hip pain / sciatica			
	musculo-skeletal injuries (ligaments, tendons, fascia, nerves, muscles)	musculo-skeletal injuries	musculo-skeletal injuries			musculo-skeletal injuries	musculo-skeletal injuries	musculo-skeletal injuries		musculo-skeletal injuries (sharp and blunt)	musculo-skeletal injuries (sharp and blunt); sprains; trauma <i>strain</i>
	rheumatism		rheumatism	rheumatism	rheumatism		rheumatism, gout	rheumatism, gout		rheumatic disorders; <i>gout</i>	<i>rheumatism and gout</i>
	stiff limbs and joints; relaxing lame joints										

Use-categories	Tabernaemontanus 1664	Löseke 1790 / Plenck 1794	Richter 1827	Strumpf 1855	Hager 1878	Schulz 1919	Madaus 1938	Kroeber 1948	Weiss 1974	Saller et al 1995	Bäumler 2007
	spasms in wounds						spasms from tetanus	spasms in wounds; convulsions			
						<i>spasms (uterus)</i> spasms (bladder)	spasms (uterus, bladder)	spasms (bladder, gastro-intestinal tract)			
				haematoma		bruises	haematoma	bruises, contusions, swelling		effects of sharp and blunt injuries	haematoma, contusions
										myalgia	myalgia
									bone infection		<i>bone infection</i>
<b>nerve</b>	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	hip pain / sciatica	spinal injuries		hip pain / sciatica			sciatica	hip pain / sciatica			
	nerve injuries						nerve injuries, trauma after surgery	nerve injuries			
	nerve pain					<i>neuralgias in the face</i>	neuralgias (coccyx, heart, migraine, sciatica, trigeminus)	neuralgias in the face		myalgias migraines meteoropathy	tension headaches
	pain (abdomen, limbs, musculo-skeletal, rheumatism, womb, wounds)	pain (musculo-skeletal)	pain (musculo-skeletal, rheumatism)	pain (musculo-skeletal, rheumatism, womb)	pain (rheumatism)	pain (musculo-skeletal, womb)	pain (gout, musculo-skeletal, nerve rheumatism, scars, womb, wounds)	pain (gastro-intestinal, musculo-skeletal, rheumatism, scars, womb, wounds)		pain (musculo-skeletal, rheumatic disorders)	pain (musculo-skeletal, <i>teeth</i> , womb)
	trembling										

Use-categories	Tabernaemontanus 1664	Löseke 1790 / Plenck 1794	Richter 1827	Strumpf 1855	Hager 1878	Schulz 1919	Madaus 1938	Kroeber 1948	Weiss 1974	Saller et al 1995	Bäumler 2007
							exhaustion - neurasthenia from overtaxing the nervous system or from anaemia		vegetative nervous system dysfunction	exhaustion vegetative nervous system dysfunction	
							neurofibromatosis				
	lame joints						paralysis (from brain and spinal cord)	paralysis			
<b>respiratory</b>	✓	✓	(✓)	✓	(✓)	(✓)	✓	✓	0	✓	(✓)
	pleurisy							<i>pleurisy</i>			
	spitting of blood	tuberculosis  ulcerations in chest	<i>tuberculosis</i>	tuberculosis spitting of blood  passive bleeding	<i>tuberculosis, spitting of blood haemorrhage</i>			<i>tuberculosis</i>  bleeding from chest cavity			
				chest and lung infections		<i>catarrh of mucous membranes of bronchi</i>	chest infections (with phlegm)	<i>bronchitis</i>  <i>cough</i>  <i>asthma</i>		respiratory tract infections  cough	<i>bronchitis</i>  <i>cough</i>
<b>skin-mucous</b>	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	bleeding (wounds: styptic action)			bleeding (wounds: styptic action)				bleeding (wounds)			<i>bleeding (wounds styptic action)</i>
	burns			burns	<i>burns</i>		burns	burns	burns	<i>burns; burns</i>  sunburn	<i>burns, burns</i>  sunburn

Use-categories	Tabernaemontanus 1664	Löseke 1790 / Plenck 1794	Richter 1827	Strumpf 1855	Hager 1878	Schulz 1919	Madaus 1938	Kroeber 1948	Weiss 1974	Saller et al 1995	Bäumler 2007
	ulcers	ulcers (internal, external)	ulcers (internal, external; infected)	ulcers (internal, external; infected)			ulcer Ulcer cruris	ulcers malignant ulcers	ulcers Ulcer cruris		<i>ulcers</i> protect skin against Ulcer cruris and decubitus
	wounds (deep, large, infected, inner, outer)		wounds	wounds	wounds	wounds	wounds (after surgery, from stabs and cuts, badly healing, itchy)	wounds (infected, inflamed, painful)	wounds (infected)	<i>wounds, wounds</i>	<i>wounds; wounds (infected)</i>
				<i>mouth and throat issues (astringent for gargling)</i>						stomatitis gingivitis <i>gargle, gargle</i>	
										inflammation	inflammation
										<i>skin care</i>	
<b>somato-form</b>	✓	0	✓	✓	(✓)	(✓)	✓	✓	✓	✓	✓
	demons (banish)			<i>against bedevilment</i>	<i>against bedevilment</i>		<i>against bedevilment</i>				<i>against phantasies, ghosts, demons</i>
								anxiety	anxiety	anxiety and / or nervous unrest <i>anxiety neuroses</i>	anxiety

Use-categories	Tabernaemontanus 1664	Löseke 1790 / Plenck 1794	Richter 1827	Strumpf 1855	Hager 1878	Schulz 1919	Madaus 1938	Kroeber 1948	Weiss 1974	Saller et al 1995	Bäumler 2007
	menstruation: unease before and during menstruation						pre-menstrual syndrome	pre-menstrual syndrome		menopausal unease	premenstrual dysphoria  menopause induced anxiety
	melancholy		<i>melancholy</i>	melancholy			<i>melancholy</i>	depression (functional; after head injuries)  mood disorders	depression	depressive moods	depression
			<i>mania</i>	mania			<i>mania</i>				
						<i>enuresis in children</i>	enuresis	enuresis in children	enuresis		
							exhaustion neurasthenia)	exhaustion (neurasthenia)  nervous breakdown	dystonia		
							hysteria	hysteria  somnambulism	neurotic behaviour		
							insomnia	insomnia		insomnia, <i>insomnia</i>	insomnia
							nervous tension	nervous tension, hysteria  headaches from nervous tension	nervous tension	nervous tension	nervous tension  headaches

Use-categories	Tabernaemontanus 1664	Löseke 1790 / Plenck 1794	Richter 1827	Strumpf 1855	Hager 1878	Schulz 1919	Madaus 1938	Kroeber 1948	Weiss 1974	Saller et al 1995	Bäumler 2007
				mental afflictions			somatoform disorders	somatoform disorders traumatic neurosis and neuritis	somatoform disorders	psychovegetative disturbances	somatoform disorders addiction (alcohol withdrawal)
<b>tonic</b>	0	0	0	✓	0	0	✓	0	✓	✓	✓
				for tonification			mental exhaustion neurasthenia		for tonification	exhaustion	dysphoria
									dystonia		
<b>uro</b>	✓	0	0	✓	0	✓	✓	✓	✓	(✓)	✓
	bladder stone, gravel							<i>bladder stone; gravel</i>			<i>bladder stone</i>
	kidney detoxification, poison										<i>kidney detoxification</i>
	urine voiding (diuretic agent)			urine voiding (diuretic agent)				<i>oedema</i>		<i>urine voiding (diuretic agent)</i>	<i>diuretic agent</i>
		kidney ulceration		kidney stones				<i>kidney stones</i>			
						bladder spasms	bladder spasms	<i>bladder spasms</i>			
						<i>enuresis in children</i>	enuresis	enuresis in children	enuresis	<i>enuresis bedwetting</i>	enuresis
				blood in urine			bladder catarrh	bladder catarrh			irritable bladder

Dark green rows refer to continued use  
Light green rows refer to intermittent but present-day-use  
Grey rows refer to present-day discontinuation  
Indications in italics and brackets (✓) reference historical uses or folk medicine uses

**APPENDIX 15: *HYPERICUM PERFORATUM* DATABASE  
RESEARCH EXCEL SPREADSHEET**

This spreadsheet is attached separately.

# **APPENDIX 16: DEFINITION AND SPECIAL CHARACTERISTICS OF TRADITIONAL PLANT MEDICINES**

## **1. Definition of a traditional plant medicine**

A traditional plant medicine is a health product that is intended for a therapeutic application rather than for nutritional support as intended for a dietary supplement. It contains extracts of plants (as opposed to individual phytochemicals, vitamins, or other active compounds) as the only claimed active ingredient(s).

A traditional plant medicine contains:

- herbs, seeds, berries, roots, leaves, bark, flowers, algae, lichens, certain exudates, fossilised remains of marine phytoplankton, and macroscopic fungi.

A traditional plant medicine does not contain:

- pharmaceutical drug material
- individual synthetic or isolated chemical compounds
- isolated plant constituents (e.g. menthol, thymol etc.)
- animal products (except propolis and honey)
- added amino acids
- added minerals or vitamins, or other non-plant ingredients, unless these are excipients only
- organisms listed in Schedule 1 of the Convention on the International Trade in Endangered Species (CITES) or locally endangered plants.

Representative traditional preparations are:

- fresh or dry plant tinctures
- fresh-plant and its juice
- alcohol extracts (traditional extraction ratio up to 2:1)
- dried extracts
- comminuted dried herbs and powders
- decoctions, infusions

- oil, vinegar, glycerine, wine or spirit extracts
- essential oils and hydrosols
- mels, and oxymels.

Traditional plant medicines are applied orally, externally, or through inhalation. The main meaning of external use relates to topical applications to the skin. However, if the traditional use of a herbal medicinal product relates to oral, nasal, rectal, vaginal mucosae, ocular, or auricular delivery, such delivery is also accepted if no safety concerns exist.

Delivery formats include:

- oral liquid, spray, syrup, pressed powder, tablet, capsule, lozenge, cream, liniment, gel, oil, compress, poultice, pessary, suppository, enema, eye drop, inhalation, gargle.

Long-standing effectiveness of traditional plant medicines relates to unadulterated, traditional preparations only. The potential inhibitory effects of modern additives on absorption and bioavailability of therapeutic plant compounds is poorly understood. It is therefore recommended that the classification of a ‘traditional plant medicine’ pertains to a product that has a natural composition and does not contain modern artificial colours, flavours, synthetic sweeteners, monosaccharides, and GMO ingredients or substances derived from GMO manufacturing processes.

## **2. Quality standards**

The safety and effectiveness of a traditional plant medicine directly relate to the quality of the raw herbal drug(s) and the manufacturing process of the remedy. It is therefore recommended that quality standards for traditional plant medicines are developed to ensure their quality, safety and effectiveness, thus protecting consumer health. The most common risks with herbal drugs are due to a lack of stringent quality control measures rather than to the pharmacological activity of traditionally known and used herbal ingredients themselves (Bowen et al., 2012). Risks can be minimised with proper quality control measures during harvesting and manufacturing. The most common quality risks of traditional plant medicines relate to misidentification or mislabelling of herbal ingredients with an incorrect species, adulterations, substitutions, and contamination with heavy metals, pesticides,

herbicides and toxic microbes (Ekar & Kreft, 2019; He, Ung, Hu, & Wang, 2015; Keane, Munn, Vivier, Higgins, & Taylor, 1999). In turn, lack of efficacy may be linked to incorrect harvesting times of the medicinal plant (when active constituents are not at their prime), the collection of the wrong plant part or species, and incorrect processing.

This makes it imperative that the quality control process for traditional plant medicines starts in the field. Protocols should require full supply chain traceability, including authentication details for the raw plant, plant part used, location and time of harvest, growing conditions (wild, cultivated), vegetation stage, as well as processing techniques applied (i.e. drying method, extraction ratio, solvent used in extraction), and storage. Medicinal plants should be harvested according to WHO Good Agricultural Practice (GAP) or similar guidelines to yield a defined raw material of high quality. Medicinal plants should not be exposed to pesticides, herbicides, heavy metals, and toxic microbes.

### **3. Special characteristics of traditional plant medicines**

There are special characteristics of traditional plant medicines that should be considered for their regulation. They relate to their compounding and scope of claims.

#### **3.1 Multi-component formulations**

Traditional plant medicines either contain a single ingredient, or more commonly a combination of ingredients. To enable traditional prescribing that is based on empirical knowledge of effectiveness and safety, it is recommended that a daily therapeutic dose may be made up with several plant ingredients. If regulations specify that the dosage for *each* individual ingredient is to be in line with the dosage used in a clinical trial where a medicinal plant was investigated in isolation, then a traditional multi-component formulation may not be able to be registered. This is because in a multi-component formulation the total dose is made up of several ingredients. Each single component might therefore fall below the mono dosage applied in a clinical trial or suggested in monographs that discuss mono preparations.

### **3.2.Traditional health claims**

Permitted health claims for traditional medicines sold over the counter should be appropriate for use without supervision. Consistent with documented traditional use it is recommended that approved indications relate to health supporting claims, structure-function claims, risk-reduction claims, treatment claims, and to the complementary use of traditional medicines in the management of symptoms of chronic, non-life-threatening illnesses, including the easing of treatment side-effects.

It is recommended that communication of health claims relating to traditional plant medicines is consumer friendly. Permitting claims solely in relation to modern biomedical nosologies as indexed in the International Disease Classification (IDC) is unsuitable and too narrow for the communication of traditional indications. Moreover, terms described in the IDC are often too technical to be understood by consumers not trained in medical sciences, and therefore it is recommended that equivalent vernacular terms for such indications also be permitted. In addition, it seems appropriate to approve traditional health claims based on traditional evaluations with their typical descriptions of signs and symptoms.

## APPENDIX 17: HISTORICAL ASSESSMENT TOOL: A DATA COLLECTION FRAMEWORK

Use-categories	Foundational historical textbook of a written medical tradition	Author 1	Author 2	Author 3
apotrop				
cancer				
card-vasc				
gastro-intest				
hormonal				
gyn				
head				
infection				
liver-spleen				
musc-skel				
nerve				
respiratory				
sex				
skin-mucous				
somatoform				
tonic				

For the independent verification of data, it is recommended that the following information from the selected sources is recorded:

Data	Record
conclusive identification of data source: author, title of source, year of publication, reference pages	
conclusive identification of botanical and vernacular name(s)	
plant part(s) used	
indication(s)	
use-category: function, organ and/or body system addressed	
preparation	
posology (if noted): dosage, frequency, duration	
external / internal application	
safety considerations: cautions, warnings, contra-indications (if noted)	
age range (if noted)	
traditional guidelines on harvesting and processing (if noted)*	

\*A purely analytical approach towards characterisation of medicinal plants does not necessarily capture quality requirements because it is often not known which components or combinations of components are responsible for the therapeutic effects.