DOTTORATO DI RICERCA IN NEUROSCIENZE

Ciclo XXIX

Herbal drugs in European tradition
-
A phylogenetic, chemosensory and neuropharmacological approach

Settore scientifico

BIO/14 - Farmacologia

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Esame finale anno accademico 2015 – 2016

Tesi discussa nella sessione d'esame marzo – aprile 2017

Abstract

Historical texts have emerged as valuable tools to study the therapeutic knowledge of past cultures. Dioscorides' *De Materia Medica* (*DMM)* written in the 1st century CE is one of the most influential historical texts on use of herbal drugs in the Euro-Mediterranean area and inventories over 1000 plant, animal and mineral drugs. Despite the impact of *DMM* on modern (herbal) medicine the content of this work has never been systematically assessed.

This thesis studied the herbal drugs described in *DMM* (*ex* Matthioli, 1568) using a multi-disciplinary approach. The aims were I) to analyze the use of botanical drugs in the ancient Mediterranean world; II) to provide historical background data to better contextualize modern herbal medicine; III) to characterize the influence of chemosensory properties of herbal drugs on their therapeutic usage; and IV) to systematically screen herbal drugs in European tradition for cannabinomimetic effects.

A quantitative survey of the plant knowledge described in *DMM* (*ex* Matthioli, 1568) resulted in a database comprising 5314 unique therapeutic uses of 536 plant taxa and 924 herbal drugs. Salient patterns in the data, such as the frequent mention of Apiaceae exudates for the treatment of neurological and mental disorders, are discussed. It is suggested that drugs that lost importance over time, remedies for diseases now controlled by industrially produced drugs and preventive medicine might be interesting starting points for research on herbal medicine and drug discovery.

A diachronic analysis estimated the causal effect of the ancient works by Dioscorides and Galen on contemporary herbal medicine in three Italian provinces. The analysis of 87 commonly used medicinal plant taxa suggests that ancient scripts have exerted strong influence on the usage of herbal medicine until today. It is concluded that the repeated empirical testing and scientific study of therapeutic claims guides the selection of efficacious remedies and evidence-based herbal medicine.

Methodological problems associated with the classification of pathologies in pre- and non-scientific knowledge systems are addressed. Three different classification systems are proposed and critically discussed in terms of their potential application in ethnobotany and ethnomedicine.

Based on the plant descriptions in *DMM*, botanical fieldwork in the Euro-Mediterranean area (2014 - 2016) resulted in the collection of a botanical library comprising 697 herbal drugs derived from 404 species. Extracts of 436 herbal drugs were bioassayed for inhibitory activity on fatty acid amide hydrolase (FAAH), a major target of the endocannabinoid system. Among the 34 (8%) hits that reduced FAAH activity to 40% or less, were the extracts of *Glycyrrhiza glabra* root (licorice; 2.6%), *Medicago arborea* leaves (12.1%), *Zingiber officinale* rhizome (ginger; 12.4%) and *Anacyclus pyrethrum* root (26.6%). The phytochemistry and ethnopharmacology of these plants are discussed in relation to observed ECS modulation. A comparison of cannbinomimetic activity and traditional uses of herbal drugs showed that specific categories of use were at best only weak predictors of the measured FAAH inhibitory effects.

To test how taste and smell properties correlate with the therapeutic use of medicinal plants, chemosensory profiles of 697 herbal drugs were experimentally assessed in 4026 sensory trials. Both specific flavor properties and overall flavor bouquet complexity resulted as predictors of plant use. The results support previous claims that the compilation of *De Materia Medica* was guided partly by plant taste and smell. It is suggested that chemosensory cues are important criteria for the selection of food and herbal drugs, supporting and expanding specific flavor use-links reported in the literature.

Overall, the results of this thesis perpetuate the view that ancient texts have potential for 1) natural products research; 2) contextualizing contemporary phytopharmacy; 3) theory building in medical anthropology.

Acknowledgements

I would like to express my deepest thanks to:

My supervisor Prof. Marco Leonti for giving me the amazing opportunity of doing this PhD and for his support and advice.

Dr. Laura Casu, Prof. Micaela Morelli, Dr. Stefano Cabras for their invaluable scientific support.

Dr. Caroline Weckerle for countless valuable discussions and scientific support,

My parents Olgi and Osi; Patricia, my son Jaro and his mother Larissa for their encouragement, infinite patience and love.

Dr. Julie Hawkins for hosting me during a three month research stay at the University of Reading (UK).

Prof. Theophanis Constantinidis, the Greek Ministry of Environment and Energy and the Ethics Committee of the University Hospital of Cagliari for their help with permits.

The sensory panelists for their endurance and voluntary help.

Dr. Paolo Mura for making the sensory analysis possible.

The colleagues, friends and collaborators of the MedPlant Training Network for the great scientific exchange and the amazing time we had together.

Moreover I would like to thank the following institutions and persons for providing botanical material: The Chios Mastiha Growers Association, the Botanical Gardens and Herbaria of the Universities of Cagliari (CAG), Zurich (Z+ZT) and Jerusalem (HUJ), Phytax GmbH, Padma GmbH, Mansour Ahmadi, Lea Bona, Matthias Geck, Rina Štrajn, Pouya Faridi, Marc el Beyrouty, Karen Martinez, Irene Teixidor, Bettina Stäubli, Lisa Destri, Carmen Romero Contreras, Karl Geck, Norhayati Binti Ngah, Dr. Dhafer Ahmed Al-Zahrani, Thuraiya Al Jabri, Lyna Medjedline Hani, Omaima Ben Salem, Lucifero Collu.

This project has received funding from the European Union’s Seventh Framework Programme for research, technological development and demonstration under grant agreement no. 606895.

Publications from this research

Leonti, M., Staub, P.O., Cabras, S., Castellanos, M.E., Casu, L., 2015. From cumulative cultural transmission to evidence-based medicine: evolution of medicinal plant knowledge in southern Italy. Frontiers in Pharmacology 6, 207.

Staub, P.O., Geck, M.S., Weckerle, C.S., Casu, L., Leonti, M., 2015. Classifying diseases and remedies in ethnomedicine and ethnopharmacology. Journal of Ethnopharmacology 174, 514–519.

Staub, P.O., Casu, L., Leonti, M, 2016. Back to the roots: A quantitative survey of herbal drugs in Dioscorides' De Materia Medica (ex Matthioli, 1568). Phytomedicine 23, 1043-1052.

Conference contributions

Staub, P.O., Casu, L., Leonti, M., 2015. Shaping of medicinal plant use: A phylogenetic and organoleptic approach. The 15th International Congress of the International Society of Ethnopharmacology. Petra, Jordan. Oral Presentation.

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Chapter 1 General Introduction

The Mediterranean basin is known as a cradle of human civilization, having witnessed the birth of ancient Egyptian, Greek and Roman civilizations (King et al., 1997). As part of cultural evolution, Mediterranean societies have developed elaborate systems of diet, agriculture and medicine (Flint-Hamilton, 1999), passing down their heritage orally and in written form (Hardy and Totelin, 2016:33-62). Ethnopharmacology, which is devoted to the pharmacological study of culturally important drugs (Gertsch, 2009), has increasingly focused on historical texts to access past knowledge on medicinal plants (Lardos 2015).

In the ancient Mediterranean, the Hippocratic Corpus (ca. 5th century BCE - 2nd century CE); Dioscorides' (1st century CE) *De Materia Medica* and Galen's (2nd century CE) *De Simplicium Medicamentorum Temperamentis et Facultatibus* formed the chief reference for herbal medicine of later ages (Touwaide, 2005). While Hippocrates established medicine as a profession, Dioscorides compiled an amazing pharmacological inventory comprising about 1000 botanical, zoological and mineral drugs known at his time.

This thesis studied the herbal drugs described in *DMM* (*ex* Matthioli, 1568) by using approaches from different scientific disciplines:

A phylogenetic approach was embraced to quantitatively analyze medicinal plants in an evolutionary framework. As part of a broader trend towards the use of evolutionary tools in drug discovery (e.g. Rønsted et al., 2012; Smith and Wheeler, 2006), the phylogenetic exploration of medicinal plants was also the overarching goal of the MedPlant International Training Network, through which this project was funded.

A chemosensory approach was chosen to systematically test the role of taste and smell in medicinal plant selection. Hereto, methods from sensory analysis were applied to obtain standardized inter-subjective chemosensory profiles of plants. This is important, as quantitative hypothesis testing may help to better separate different aspects of medicinal plant selection.

Lastly, a neuropharmacological approach was selected to explore the interface between historical ethnopharmacology and drug discovery as well as to meet the requirements of the Ph.D. program in Neuroscience at the University of Cagliari.

Ethnopharmacology of historical medico-botanical texts

Historical texts on medico-botanical knowledge have become an established resource in ethnopharmacology and ethnomedicine (Lardos, 2015). Historical scripts are regarded as unique gateways to access past medicinal knowledge systems, and thus, their careful analysis was suggested to help contextualizing contemporary medicinal systems (Heinrich, 2005). For example, it was argued that written historical information may help documenting the tradition of use, which can be a legal requirement for the regulatory approval of new commercial herbal products (Helmstädter and Staiger 2014). Moreover, historical texts may also inspire natural products research by highlighting candidate species that merit further examination (Adams, 2011; Buenz, 2004; Holland, 1994; Helmstädter, 2016). This can be illustrated using Gerard's *Herball*, as, since its publication in 1597, 18 different pharmaceuticals were developed from plants described therein, of which 16 became approved drugs (Cox, 1998).

Studies that used a historical ethnopharmacological approach can be grouped into three more or less distinct categories (Lardos, 2015): 1) Surveys of yet undocumented past knowledge on therapeutic substances; 2) diachronic or spatial comparisons of different bodies of knowledge to assess the development of pharmacopoeias; and 3) approaches to identify candidate species for drug discovery attempts.

The first type was followed, for example by Lardos (2006) who documented medicinal plant knowledge contained in the *iatrosophikon*, a collection of prescriptions from a Cypriotic monastery written down during the Ottoman period. Lev and Amar (2006) attempted to reconstruct the natural substances used by Jews of medieval Cairo by analyzing prescriptions found in a storeroom (*genizah*) of the *Ben Ezra* Synagogue in Old Cairo. Other authors focused on more recent medico-botanical texts, such as correspondences and manuscripts of European 19th century naturalists (Helmstädter, 2015, Fagg et al., 2015).

Approaches of the second type were adopted, for instance, by dal Cero et al. (2014), who traced the therapeutic use of the Swiss local flora from antiquity to the present. Similarly, De Vos (2010) attempted to reconstruct the historical development of European herbal medicine by comparing plant mentions in texts from different epochs. Touwaide and Appetiti (2013) assessed the historical introduction of Eastern *materia medica* and associated therapeutic knowledge into pre-modern Mediterranean medical traditions. In contrast, a more quantitative approach was pursued by Leonti et al. (2010), who estimated the causal effect of the plant knowledge in a Renaissance herbal by Matthioli (1568) on present day Campanian (Italy) medicinal plant use.

The third approach was pursued by a series of papers by Adams et al. (2007, 2009, 2011a, 2011b, 2012), who searched different 16th and 17th century European herbals for herbal drugs with specific uses, such as against age-related brain disorders, epilepsy, rheumatic disorders and malaria. Likewise, Giorgetti et al. (2007) screened Brazilian 16th – 19th century texts for herbal drugs with potential effects on the central nervous system. Another study cross-validated plant uses described in the 17th Herbarium Amboinense - a modern flora of the Island of Amboina (Indonesia) containing local medicinal plant knowledge - with modern ethnomedical, biochemical data from the Natural Products Alert database (NAPRALERT^{TM}; Buenz et al., 2005). Further, Lardos and colleagues (2011) evaluated Byzantine *iatrosophia* texts and compared selected remedies with modern bioactivity and ethnomedicinal data. Lastly, Valiakos et al. (2015) cross-checked the medicinal plant knowledge described in the Byzantine codex of *Dynameron* with contemporary therapeutic indications as recorded by the European Medicines Agency (EMA).

Despite the evident opportunities offered by historical ethnopharmacology, the analysis of historical scripts also poses several methodological challenges, such as the legibility of original manuscripts, difficult plant identifications as well as the interpretation of historical terms for symptoms and diseases (see Lardos, 2015 and Touwaide, 2010 for a more detailed discussion). Several studies have proposed standard methodologies to tackle these issues: Touwaide (2010) introduced standards from a historical perspective, in particular concerning the contextualization of primary sources and the treatment and interpretation of primary data. Buenz et al. (2004) and Lardos et al. (2011) proposed flowchart protocols for the extraction of historical plant use data and their comparison against modern phytochemical, pharmacological and ethnomedicinal information. Buenz (2006) suggested the automation of the aforementioned steps into a high throughput pipeline, however unfortunately remaining vague regarding feasibility and effectiveness. Lastly, Evergetis and Haroutainen (2015) developed a workflow for the standardized identification of historical plant descriptions, including visual representations and textual data.

European herbal medicine and Dioscorides' *De Materia Medica*

Mediterranean cultures have a long tradition of medicinal plant use, which can be traced back through an extensive body of literature (e.g. dal Cero et al., 2014; Lardos et al., 2013; Leonti et al., 2010;

Heinrich et al., 2006; Touwaide and Appetiti, 2013). Among the earliest extant medico-botanical documents are Sumerian clay tablets from around the early second millennium BCE, describing over 250 medicinal plants, 120 minerals and 180 other drugs (Spiegel and Springer, 1997) and the Ebers Papyrus, which dates to ca. 1550 BCE and includes some 800 prescriptions combining minerals, plants and essential oils (Mann, 1984; Comrie, 1909). The earliest and most important sources from the ancient Greco-Roman world were the Hippocratic Corpus (ca. 5th century BCE - 2nd century CE); Dioscorides' (1st century CE) *De Materia Medica* and Galen's (2nd century CE) *De Simplicium Medicamentorum Temperamentis et Facultatibus* (Touwaide, 2005).

This thesis is concerned with the knowledge on herbal drugs described in *De Materia Medica* (Old Greek*: Περὶ ὕλης ἰατρικῆς*), a medico-botanical script written 50 – 70 CE by the Greek pharmacologist Pedanios Dioscorides. In brief, Dioscorides was born in the region of Anazarba (Cilicia, Asia Minor), and according to his own mention, has traveled a great deal in the Roman Empire (Scarborough and Nutton, 1982:196). *De Materia Medica* is thought to be one of the most comprehensive pharmacognostic guides from the ancient Mediterranean, containing information on over 1000 drug in about 800 chapters (Riddle, 1980). A typical chapter on plants includes the following information: 1) Plant name and synonyms; 2) botanical information; 3) pharmacological properties and therapeutic uses; 4) potential side effects; 5) posology and formulation; 6) details on collection and storage; 7) adulterants and substitutes; and 8) other uses such as magic or veterinary medicine. Whether *De Materia Medica* also included plant illustrations, like the herbal by the earlier physician Crateuas (1st cent. BCE), is matter of debate (Touwaide, 2005).

The entire treatise consists of five documents, each of which covers certain kinds of drugs (Stannard, 1966):

- Book I includes mainly aromatics, salves, oils, fluids, gums and fruits
- Book II includes animal derived drugs, cereals and plants with acrid and bitter tastes
- Book III lists roots, juices and seeds
- Book IV contains roots and herbs
- Book V is about wines and minerals.

Although this structure suggests an organic division of the contents, it was argued that the separation into five scripts of about equal size could be due to the maximum length of papyrus scrolls, which were the medium of the original version of treatise (Touwaide, 1998). Apart from the macrostructural arrangement into themed books, the work also shows some interesting microstructural patterns. Dioscorides himself, in the preface to *De Materia Medica* states to have ordered the chapters based on drug *dynameis,* i.e. "properties" (preface 4; Scarborough and Nutton, 1982:196). Typically, these qualities are mentioned at the beginning of each chapter before other, more specific therapeutic actions are discussed. Some of these properties are temperature qualities (e.g. warming and cooling), chemosensation-related features (e.g. burning and sharp) and metabolism-affecting properties (e.g. drying, softening, ulcerating and breaking). It was argued that these properties reflect perceived physiological effect of a drug on the body (Riddle, 1985). Thus, knowledge about which property is needed to treat some pathology would have been sufficient to select the right remedy, and vice versa, knowledge of the main properties of a drug would have helped to get an idea of its therapeutic potential.

Apart from this system of 'drug-affinity' (Riddle, 1985), others have suggested a drug classification based on therapeutic, taxonomic and organoleptic similarities (Scarborough, 2013; Touwaide, 1998). Moreover, Touwaide (1998) argued that Dioscorides' classification scheme reflects ancient concepts of the universe, expressing continua between opposing poles (e.g. from perfumed to scentless, from hot to cold, from polychromatic to black and from religion to magic). According to this view, the chapters are grouped into thematic clusters, each of which begins with a prototype chapter that is followed by further chapters progressively adding variation.

Apart from Dioscorides' system of drug classification, which he himself considered superior to those of previous authors (Scarborough and Nutton, 1982), one can also find sporadic references to both the Doctrine of Signatures (DoS) and humoral theory. The DoS posits that plant morphology informs about which ailments a specific plant is best used to treat (Bennet, 2007; Effert and Grethen, 2016) and humoral theory, which was formulated by Hippocrates (ca. 460-370 BCE), states how disequilibrated bodily humors (blood, phlegm, yellow bile and black bile) may affect a person's temperament and health. For example, the influence of the DoS can be exemplified with *Coronilla scorpioides* (L.) Koch (Book 4, Chap. 194; *Scorpioide*), which owes its vernacular (and scientific) name(s) to the scorpion-tail-like pods, whose only therapeutic use is that as an external antidote against scorpion stings. The influence of humoral theory is evident with the recommendation of caper (*Capparis spinosa* L.; Book 2, Chap. 164; *Capparo*) to purge phlegm from the head and that of basil (*Ocimum basilicum* L.; Book 2, Chap 130; *Basilico*) to reduce a patient's excess black bile. A comprehensive analysis of how Dioscorides' system of drug classification relates to humoral theory and the DoS would be very interesting but is beyond the scope of this thesis.

The historical impact of *De Materia Medica* is epitomized by the fact that its content was extensively copyedited and translated for over 1500 years, what resulted in a myriad of complexly interrelated manuscripts that circulated in the Mediterranean and the Near East (Riddle, 1980). The oldest surviving and most famous edition of the treatise is the beautifully illustrated alphabetical Vienna Dioscorides, which dates to 512/513 CE (Figure 1-1; Mazal, 1998: vol. 1, p.4). The bound volume is now in possession of the Austrian National library and is available in facsimile (Mazal, 1998).

Figure 1-1 Illustration from the Vienna Dioscorides (*fol*. 5 *verso*; Mazal, 1998).

Artist (left) painting a mandrake (*Mandragora officinalis* Mill.) held by *Epinoia* (center), the personification of thought, while Dioscorides (right) is studying a book.

Figure 1-2 Facsimile version (1967-1970) of Pier Andrea Matthioli's Renaissance edition of Dioscorides' *De Materia Medica* from 1568 (Book 1; Chap. 84; *Ginepro*).

This project is based on Matthioli's translation of *De Materia Medica* from 1568 in the form of a five-volume facsimile printed by the S*tabilimento Tipografico Julia* in Rome between 1967 and 1970 (Figure 1-2). The 1568 commentary was Matthioli's first Italian edition featuring enlarged woodcuts (Stannard, 1969), which greatly facilitate the identification of the often scantly described Dioscoridean simples. A historical contextualization of this edition and Matthioli's professional life can be found in Chapter 2.

Phylogenetic exploration of medicinal plant diversity

Over the last decade, phylogenies have become increasingly important in drug discovery and ethnomedicine (Saslis-Lagoudakis et al., 2011; Schwikkard and Mulholland, 2014). The phylogenetic approach to drug discovery is based on the assumption that certain plant metabolites tend to be conserved in evolutionary lineages (Wink, 2003; Ramesha et al., 2011) and that, in consequence, phylogenies may predict phytochemicals among evolutionary relatives (Wink, 2003). A canonically cited example (Ramesha et al, 2011) for how the use phylogenetic rationale may facilitate drug discovery concerns the anticancer drug taxol (paclitaxel), which was initially isolated from the bark of the *Taxus brevifolia* Nutt. (Goodman and Walsh, 2001). Since the quantity of taxol in *T. brevifolia* was not sufficient for large-scale extraction, a search of congeneric species led to the identification of *T. baccata* L. leaves as a suitable and up-scalable source of the taxol precursor 10-deacetyl baccatin.

Apart from phytochemical similarities, closely related (plant) species may also share similar biochemical or pharmacological properties. For example, Rønsted et al. (2008), aimed to identify candidate species in the genus *Narcissus* for drug discovery in relation to Alzheimer's disease by finding evolutionary patterns in alkaloid distribution and acetylcholinesterase (AChE) inhibitory activity. Similarly, by phylogenetically correlating alkaloid diversity, serotonin reuptake transporter (SERT) binding and AChE inhibition in Amaryllidoideae, Rønsted et al. (2012) found that evolutionary distance was predictive of chemical diversity and bioactivity. Another study (Zhu et al. 2011) mapped the species origin of approved, clinical and pre-clinical drugs as well as bioactive natural products onto bacteria, Viridiplantae, Fungi and Metazoa phylogenies to determine evolutionary distribution patterns. It turned out that most drug-prolific species are clustered in a limited number of lineages and that the scarcity of drugs outside of these lineages is not necessarily due to an under-exploration or late exploration of these resources.

Driven by the predictive potential of phylogenies in bioprospecting, studies also applied evolutionary tools to analyze ethnomedicinal data. The goals of these studies were, 1) to quantitatively compare medicinal floras of different cultures (Saslis-Lagoudakis et al., 2014); 2) to visualize the phylogenetic distribution of ethnomedicinal plant use (e.g. Alrashedy and Molina, 2016; Xavier and Molina, 2016); 3) to test for phylogenetic structure in ethnomedicinal data (Forest et al., 2007; Halse-Gramkow et al., 2016; Yessoufou et al., 2014); 4) to determine the effect of diseases classification schemes on phylogenetic predictivity (Ernst et al., 2016) and 5) to test how human plant use (e.g. for food or medicine) can be attributed to specific plant traits (Cámara-Leret et al., 2017).

Methodologically, these studies relied on various metrics, some of which are borrowed from community phylogenetics (Webb, 2000). For example, Saslis-Lagoudakis et al. (2014) and Ernst et al. (2016) relied on the mean nearest taxon distance (MNTD) measure to assess overall similarities between sample of medicinal plants, medicinal floras and floristic environments. The MNTD is a phylogenetic distance measure (β-diversity) and indicates the average distance of all taxa in one sample to those in another (Webb, 2008). Similarly, Saslis-Lagoudakis et al. (2012) calculated the relatedness index (NRI), which too measures phylogenetic β-diversity but is standardized by the some null model (Webb 2008). Other studies (Ernst et al., 2016; Halse-Gramkow et al., 2016) used the D statistic (Fritz and Purvis, 2010), which determines the phylogenetic distribution of a trait (i.e. a plant use). Importantly, this statistic does not only test the observed trait pattern against a random sample, but also against a modeled pattern expected under Brownian motion (Fritz and Purvis 2010). Finally, some papers tested for so-called ‘hot nodes’ (Webb, 2008), which are plant lineages (phylogenetic branches) with an overabundance of terminal taxa having certain traits (i.e. ethnomedicinal uses; Ernst et al. 2016; Halse-Gramkow et al., 2016; Saslis-Lagoudakis et al., 2012).

In spite of the growing use of phylo-statistical tools in ethnomedicine and ethnopharmacology, several methodological issues have remained largely unaddressed. For example, it has not been studied how tree shape and sample size (Mazel et al., 2015; Ricotta et al., 2014) affects phylogenetic predictivity in the context of drug discovery. Also, understanding of how the classification of ethnomedicinal use data influences phylogenetic metrics is still not well-explored (Ernst et al. 2016). Further, the reliability of phylogenies to predict functional traits (e.g. ethnomedicinal use data) beyond short evolutionary distances has recently been questioned (Kelly et al., 2014). Lastly, cross-cultural convergence in the therapeutic use of specific plant lineages does not strictly imply independent discovery of bioactivity but may also just reflect effects of the meaning response (i.e. the placebo effect; Moerman and Jonas 2002; cf. Gertsch, 2012).

Neuropharmacological evaluation of *De Materia Medica*

Although little is recorded on neurology before the ancient Greeks, it appears that the term 'brain' was first used in the Edwin Smith papyrus, dating to 1600 BCE (Allen and Mininberg, 2005:40; Rose, 1993). In the pre-Hippocratic Mediterranean world most references to brain disorders were either religious or literary, and starting from Homer, there had been a multi-century debate as to whether the brain or the heart was the seat of the soul (Rose, 1993). Nevertheless, pre-Hippocratic medicine also saw some notable contributions to ancient neurology, such as first anatomical description of optic nerves by Alcmaeon of Croton (5th cent. BCE), the recognition of peripheral nerves by Anaxagorus (6th-5th cent. BCE) and Empedocles’ (5th cent. BCE) first mention of the inner ear (Rose, 1993). However, these contributions seem rather primitive, when contrasted with the seminal achievements attributed to Hippocrates (i.e. the Hippocratic corpus). For example, Hippocrates is credited with having identified the brain as the analyst of the outside world and the seat of the mind, *the hegemonikon* (Breitenfeld et al., 2014). Moreover, the *Corpus Hippocraticum* contributed significantly to neuroanatomy, such as through the first descriptions of the dura and pia mater, and the better understanding of neuropathologies like epilepsy, headache, meningitis, hemiplegia and paraplegia (Breitenfeld et al., 2014; Rose, 1994).

As part of the increasing anatomical and physiological understanding of the nervous system, ancient neurology also saw some major advances in neuropharmacology (Rose, 1993). This is best evidenced by the extraordinary neuropharmacological armamentarium described in *DMM* (*ex* Matthioli, 1568). Out of over 900 herbal drugs described in the treatise, 176 have at least one use relating to neurological disorders mental illnesses, such as pain, epilepsy, paralysis and mood disorders (see Chapter 2). For example, Dioscorides made clear reference to the sedative and analgesic properties of mandrake (*Mandragora officinalis* Mill.) and opium (both of which have already been known earlier; Wink, 1998). Further, the treatise lists the effects of *Sedum roseum* (L.) Scop. (syn. *Rhodiola rosea* L.) against pain, which is noteworthy given the current interest in the effects of this plant on the central nervous system (McClatchey et al., 2009). Another example is the mention of *Anacyclus pyrethrum* (L.) Lag. root against toothache, which may reflect the analgesic potential of *N*-alkylamides (NAAs) found in this plant (Albin and Simons, 2010; Boonen et al., 2012; Gertsch et al., 2008; Rios et al., 2007).

Due to the extensive coverage of neurological and mental illnesses in *DMM*, one main aim of this thesis was to systematically scrutinize the described herbal drugs using modern pharmacological evidence. This is relevant given the global prevalence of neuropsychiatric disorders (WHO, 2001) and given that drug development still heavily depends on plant natural products (Newman and Cragg, 2012). For the systematic evaluation of herbal remedies the endocannabinoid system (ECS), and in particular fatty acide amide hydrolase (FAAH), were selected as molecular target (Figure 1-3). Further, given the emerging role of the ECS, a systematic screening was assumed to identify hitherto unknown phytocannabinoid-producing plant taxa, and to extend knowledge on scaffold diversity of FAAH inhibitors.

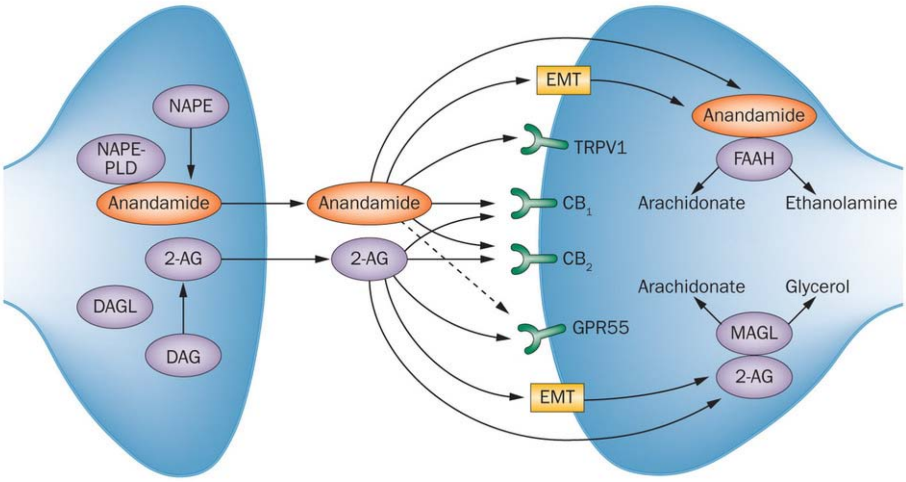

Figure 1-3 Scheme of the endocannabinoid system (from Schicho and Storr, 2014). The endocannabinoids anandamide and 2-AG are synthesized and released on demand in a paracrine fashion. NAPE needs arachidonic acid as a precursor and is cleaved by a phospholipase D (NAPE-PLD) into anandamide. The key enzyme in synthesizing 2-AG from diacylglycerol is diacylglycerol lipase. Anandamide and 2-AG primarily activate cannabinoid receptors (CB_1, CB_2), but anandamide could also act as a ligand for TRPV1 and GPR55. The existence of an endocannabinoid membrane transporter (EMT) is still controversial. The main enzyme in degrading anandamide is FAAH, whereas 2-AG is degraded by MAGL. EMT, GPR55 and TRPV1 are considered part of the endocannabinoid system. Abbreviations: 2-AG, 2-arachidonoylglycerol; CB, cannabinoid receptor; EMT,

endocannabinoid membrane transporter; FAAH, fatty acid amide hydrolase; GPR55, G-protein coupled receptor 55; MAGL, monoacylglycerol lipase; NAPE, *N*-arachidonoyl phosphatidylethanolamine; NAPE-PLD, *N*-arachidonoyl phosphatidylethanolamine phospholipase D; TRPV1, transient receptor potential cation channel subfamily V member 1.

Chemosensory selection of medicinal plants

A major question of research on traditional medicine is to understand how processes of experimentation, discovery and knowledge transmission shape botanical pharmacopoeias over time. Since Moerman's (1979) seminal paper, which demonstrated significant taxonomic selectivity in the Native American medicinal flora, subsequent studies have largely confirmed that traditional people rely on non-random taxonomic subsets of the botanical environment (Bennett and Husby, 2008; Saslis-Lagoudakis et al., 2011; Weckerle et al., 2012). The fact that many phytomedicinals are derived from rather few taxa has inspired studies on the processes that guide the selection of herbal drugs. For example, it was shown that the composition of medicinal floras depends on factors like the botanical environment (Moerman et al., 1999), cultural migration patterns (van Andel et al., 2014), the trade of *materia medica* (Lardos and Heinrich, 2013; Touwaide and Appetiti, 2013) and locally prevalent diseases (Cohen and Armelago, 1984). Also, chemosensory properties (i.e. taste and smell features) were found to be important selection criteria, first, for providing clues to the phytochemical properties of plants, and second, for driving medical belief (Bennet, 2007; Brett, 1998; Casagrande, 2000; Etkin, 1988; Leonti, 2011; Leonti et al., 2002; Shepard, 2004). Due to the complex role of chemosensory perception in medicinal plant selection, a further aim of this thesis was to quantitatively analyze the relation of uses and flavors of herbal drugs. Since previous studies used only small datasets and relied on rather limited methodologies, this was approached by using *DMM* (*ex* Matthioli, 1568) as a model pharmacopoeia and by experimentally profiling a large number of plants described in this work. The overarching aim of this was to disentangle different aspects of medicinal plant selection and to enhance understanding of the development of pharmacopoeias at large.

Outline

This chapter provided a brief introduction into Dioscorides' *De Materia Medica* and formulated the aims and approaches of this thesis.

The **second** chapter surveys the herbal drugs described in Dioscorides' *De Materia Medica*, (*ex* Matthioli, 1568) and identifies historical, therapeutic and botanical patterns. This chapter will contextualize the relied upon edition of *De Materia Medica* and provides quantitative data for the subsequent chapters.

The **third** chapter raises and discusses methodological issues in relation to how descriptions of pathologies in non-scientific knowledge systems are classified in ethnomedicine and related research.

The **fourth** chapter statistically explores the historical effect of two ancient Greco-Roman scripts on contemporary folk medicinal plant use in Italy. A diachronic analysis of the therapeutic uses of 87 commonly used plant taxa suggests that historical medico-botanical texts have exerted strong influence on herbal medicine until today.

The **fifth** chapter describes a systematic *in vitro* screening of 436 herbal drugs referred to in *DMM* (*ex* Matthioli, 1568) for inhibition of fatty acid amide hydrolase (FAAH), a chief molecular target of the endocannabinoid system (ECS). The phytochemistry and ethnopharmacology of strong hits are discussed. Specific traditional plant uses are analyzed in terms of their predictivity of cannabinomimetic effects.

The **sixth** chapter uses *DMM* (*ex* Matthioli, 1568) as a botanical model pharmacopoeia to examine how chemosensory properties (i.e. taste and smell) of herbal drugs correlate with their therapeutic uses. Specific links between flavor features and therapeutic uses are identified and interpreted from semantic, historical and chemical-ecological perspectives.

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Chapter 2 Back to the roots: A quantitative survey of herbal drugs in Dioscorides' *De Materia Medica* (*ex* Matthioli, 1568)

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Abstract

Background: *De Materia Medica* written by Pedanios Dioscorides (1 century CE) has shaped European and Mediterranean herbal medicine to a large extent. Despite its fundamental importance for modern medico-botanical traditions the content of this work has never been systematically assessed.

Purpose: We present a quantitative survey of the botanical drugs described in *De Materia Medica* (*ex* Matthioli, 1568) and identify overall therapeutic, diachronic and botanical patterns. The extracted data may serve as a baseline and help to better contextualize research on herbal drugs and phytotherapy.

Methods: Therapeutic uses of herbal drugs were extracted through line-by-line reading of a digitized version of the treatise. For each plant usage mentioned in the text we recorded (I) the chapter number, (II) the putative botanical identity, (III) the plant part, (IV) the symptoms or disease, (V) the mode of administration, (VI) our biomedical interpretation of the ancient ailment or disease description as well as (VII) the organ- and symptom-defined category under which the use was filed.

Sections: An introduction to Dioscorides' *De Materia Medica* and Matthioli's Renaissance commentary is followed by a description of the employed methodology. The results and discussion section introduces the generated database comprising 5314 unique therapeutic uses of 536 plant taxa and 924 herbal drugs. Separate subsections address salient patterns such as the frequent recommendation of Fabaceae seeds for dermatology, Apiaceae seeds as antidotes and Apiaceae exudates for neurology and psychological disorders as well as the heavy reliance on subterranean parts as drugs.

Conclusions: The therapeutic knowledge described in *De Materia Medica* (*ex* Matthioli, 1568) offers unique insights into classical Mediterranean epidemiology and herbal medicine. Drugs that lost importance over time as well as remedies used for diseases now controlled by preventive medicine and industrially produced drugs may be interesting starting points for research on herbal medicine and drug discovery. Apart from promoting future data mining, the study may also help to prove the tradition of use, which is required for the regulatory approval of certain herbal products.

[1] Published as: Staub, P.O., Casu, L., Leonti, M, 2016. Back to the roots: A quantitative survey of herbal drugs in Dioscorides' De Materia Medica (ex Matthioli, 1568). Phytomedicine, 23 (10), pp. 1043-1052.

Introduction

Over the past decade, research on medicinal plants has increasingly turned to historical medico-botanical texts both to study the development of pharmacopoeias and to identify candidate species for drug discovery (e.g. Adams et al., 2011, Buenz et al., 2005, dal Cero et al., 2014, Lardos and Heinrich, 2013, Leonti et al., 2010 and Touwaide, 2010). There is a broad consensus that ancient herbals such as Dioscorides' *De Materia Medica* and Galen's *De simplicium medicamentorum facultatibus* have influenced and guided the development of Mediterranean and European herbal medicine (Mann, 1984, Riddle, 1985 and Tschirch, 1910). In addition, recent diachronic studies traced back elements of contemporary herbal medicine to Dioscorides' *De Materia Medica* (dal Cero et al., 2014, De Vos, 2010, Lardos et al., 2011, Leonti et al., 2015 and Leonti et al., 2009). Despite the profound influence on western herbal medicine, the content of *De Materia Medica* has hitherto not been quantitatively assessed.

This paper presents a comprehensive survey of the herbal remedies described in the Renaissance translation of *De Materia Medica* by Pier Andrea Matthioli (1568) and analyzes botanical, therapeutic and diachronic patterns. Moreover, we introduce a software-assisted technique allowing for a transparent extraction of textual information. Given Dioscorides' importance, a systematic assessment and reappraisal of *De Materia Medica* may help to better contextualize research in phytotherapy and herbal medicine. In particular, this study may guide research on novel phytotherapeutic agents, inform safety evaluations and help to prove tradition of use in the context of drug regulation (Helmstädter and Staiger, 2014).

Dioscorides' *De Materia Medica*

Dioscorides of Anazarbos (Asia Minor; 1st century CE) is the author of *De Materia Medica*, which is the most detailed pharmacognostic guide from the ancient Mediterranean world passed down (Riddle, 1980). In about 800 chapters Dioscorides monographed over 600 different kinds of plants, 35 animals and 90 minerals, and summarized what was considered to be the consensus on efficacious medicine (Riddle, 1971). To compile the treatise, Dioscorides drew on previous writings, his own experience as a physician as well as on local traditions in the Mediterranean and the Near East (Riddle, 1985:3–4; Scarborough, 2012). Based on geographical references in the text, Dioscorides' compilation is thought to be the fruit of extensive journeys while the predominant but contentious view is that he travelled as a military physician of the Roman army (Riddle 1985:2–4; Scarborough and Nutton, 1982:213–217).

The historical impact of *De Materia Medica* is epitomized by the fact that for over one and a half millennia its content has been extensively copied, edited and translated into different languages (Riddle, 1980). By the end of the 15th century, this development resulted in a myriad of complexly interrelated Greek, Latin, Syriac and Arabic manuscripts that circulated in the Mediterranean and the Near East (Riddle, 1980). Apart from these copyedited texts, Dioscorides also influenced many medieval codices as well as Arab scholars such as Serapion the Elder (9th century), Avicenna (980–1037), and Ibn al-Baitar (1197–1248), whose scripts temporarily eclipsed *De Material Medica* in popularity (Riddle, 1980 and Stannard, 1966). Dioscorides' reception in Europe was restored in the late 15th–16th centuries. During that time Renaissance humanists recovered ancient Latin and Greek botanical manuscripts (Palmer, 1985, Reeds, 1976 and Stannard, 1966), which, thanks to the advent of book printing techniques, were disseminated amongst a wider public, also in different European vernaculars (Reeds, 1976).

Matthioli's renaissance commentary

Arguably the most important Renaissance commentator of Dioscorides, both in terms of popularity and textual output, was Siena (Italy) born Pier Andrea Matthioli (1501–1578) who dedicated large parts of his life to the study of medicine and botany (Kühnel, 1962, Leonti et al., 2010 and Riddle, 1980). Upon receipt of his medical degree from the University of Padua in 1523 and after having collected additional experience as a surgeon in Rome, Matthioli soon became personal physician of Archduke Ferdinand I of Austria and his successor Maximilian II (Kühnel, 1962 and Stannard, 1966). Under their patronage Matthioli worked intensively on his commentary on *De Materia Medica*, which he first published in 1544. This and all his subsequent editions *of De Materia Medica* are based on Jean Ruel's (1474–1537) Latin translation from 1516 of the Greek *editio princeps* (printed by Aldus Manutius in Venice in 1499). One of the reasons for Matthioli's popularity was that his commentary had a high practical value for readers who were concerned with legibility of ancient the text rather than with philological accuracy (Stannard, 1969). Moreover, Matthioli included plant identifications in the form of multilingual vernaculars. Following his initial success he soon started producing further versions of his text in Latin and multiple European vernaculars, making available classical herbal tradition to a wider audience. An extensive network of correspondents provided Matthioli with notes and specimens, which helped to improve his commentary. In addition, from 1554 onwards, Matthioli equipped his work with woodcuts, which further facilitated the identification of the described simples (Riddle, 1980 and Stannard, 1969). Overall, Matthioli's commentary on Dioscorides (It.: *discorsi*, Lat.: *commentarii*) enjoyed wide success among professionals, such as physicians, pharmacists and plant collectors, without sufficient command of Latin. According to Matthioli's dedicatory letter to the Archduchess of Austria, the combined print run of all pre-1568 Italian versions together totaled at least 30,000 copies (Matthioli, 1568). Even long after Matthioli's death his commentary continued to be printed so that by the end of the 17th century about 60 different editions, reprints and translations had been published in Italian, Latin, German, French and Czech (Fabiani, 1872). Consequently, Matthioli was regarded as the dominant interpreter of Dioscorides and his translation and commentary remained the main pharmaceutical reference for Italian pharmacists and physicians until the end of the 17th century (Cosmacini, 1997:264; Ferri, 1998).

Materials and methods

The medico-botanical analysis of historical texts poses several methodological challenges such as the modern interpretation of past pathologies and the identification of pre-Linnaean plant descriptions (Lardos, 2015 and Touwaide, 2010). Data sourced from pre-scientific texts are by their nature interpretations limiting their objective evaluation. Therefore, we consulted previously proposed methods to ensure the reliability of the generated data as far as possible (Buenz et al., 2004; Evergetis and Haroutounian, 2015; Lardos et al., 2011; Touwaide, 2010). In the following we describe the employed methodology and exemplarily point out specific problems and explain how these were addressed.

Text source

This study is based on Matthioli's (1568) translation of *De Materia Medica* in the form of a five-volume facsimile printed by the Stabilimento Tipografico Julia in Rome between 1967 and 1970, henceforth referred to as “*De Materia Medica*”. This was Matthioli's first Italian edition with enlarged woodcuts (Stannard, 1969). We chose Matthioli's translation as a proxy for Dioscorides’ text because (I) unlike the current standard edition (Wellmann, 1906–1914), Matthioli (1568) facilitates the identification of the often scantly described simples; (II) Matthioli's medico-botanical expertise imparts authority resulting in practical yet qualified interpretations; and (III) it is written in Italian and therefore easily accessible to readers without any knowledge of Latin or Ancient Greek. Particularly the 1568 edition was selected because it is available in facsimile and one of Matthioli's later and thus repeatedly revised versions of the text. The content analyzed in this study comprises only Matthioli's translation of Dioscorides’ text printed in roman type. Matthioli's italicized commentaries on Dioscorides’ chapters were not considered as these represent Renaissance knowledge (Figure 2-1). Of all 831 chapters attributed to Dioscorides we only included those 531 that deal with single botanical substances (i.e. plant simples or drugs). Chapters dealing with drugs derived from animal (incl. human), mineral, fungal, algal or other sources, as well as processed plant parts (e.g. distillates, pickles or colophony) and compound drugs (e.g. unguents, incense mixtures or flavored wines) were disregarded. Moreover, we excluded unspecific (e.g. generic woods or resins) and spuriously described botanical drugs.

Data management

Data extraction from *De Materia Medica* was done in ATLAS.ti (version 7.5.4), a proprietary software commonly used in the social sciences to explore and manage large amounts of unstructured primary data. We chose this tool as it allows for rapid extraction of text quotes from written sources and for linking these quotes to interpretative codes, which in our case were therapeutic categories of use. By coding the data this way, we could thus separate the original text (the emic or historical perspective) from our biomedical interpretation (the etic or scientific perspective) and maintain our analysis transparent (Leonti and Weckerle, 2015). Plant uses were extracted and databased through line-by-line reading of a digitized and OCRed (optical character recognition) version of Matthioli (1568). The PDF version of Matthioli (1568; Books 1–6) can be found in the supplementary material.

The basic units of analysis were single uses of herbal drugs, including insect repellents, poisons and foods. For each usage mentioned in the text we recorded (I) the chapter number, (II) the putative botanical identity, (III) the reported plant part, (IV) the described symptom, ailment or specific use (V) the mode of administration, (VI) our modern (*viz*. biomedical) interpretation of the described symptom or ailment as well as (VII) the category of use under which we filed the specific use. Each recorded combination of the variables I-V was counted as one individual (therapeutic) use. Data conversion and plotting were done using R and several add-on libraries (Feinerer and Hornik, 2015; R Core Team, 2016; Thuiller et al., 2014; Wei, 2013 and Wickham, 2015).

Classification of historical uses

The following eleven plant parts or products were differentiated: Ashes (i.e. charred plant matter), barks, exudates (incl. gums, resins and saps), flowers (incl. inflorescences and parts thereof), fruits (incl. parts thereof), herbs (incl. branches and shoots), leaves, oils (e.g. olive oil), seeds (incl. seed-like fruits), subterranean parts (incl. bulbs, rhizomes, roots and tubers) and wood (incl. pith). Seed-like fruits, such as Apiaceae indehiscent schizocarps or *Urtica* spp. achenes, were classified as seeds.

The modes of administration were divided into four groups: Internal (e.g. infusions and pills), external (e.g. baths, mouthwashes, ointments and poultices), fumigations (incl. smokes and steams) and clysters (incl. enema, pessaries and suppositories). Therapeutic uses were classified into organ-, symptom- and ailment- defined categories of use largely following the bioprospecting-oriented classification scheme proposed by Staub et al. (2015). The applied 21 categories of use comprise: Andrology (incl. male fertility), antidotes (internally applied), cardiovascular problems (incl. both suppositories and internal applications against hemorrhoids), dermatology (e.g. abscesses, cosmetics, skin inflammations, tumors, wounds and external applications against hemorrhoids and animal bites/stings), fever (incl. malaria), food (incl. spices), gastroenterology (e.g. carminatives, colics, diarrhea, dysentery, liver and spleen), gynecology (incl. female fertility), libido regulators (i.e. aphrodisiacs and anaphrodisiacs), musculoskeletal ailments (e.g. cramps, fractures, gout, hematoma and spasms), neurology (incl. mental ailments), ophthalmology (i.e. eye problems), oral cavity (e.g. dentistry, gums and tonsils), others (e.g. magic, indefinable pathologies, unspecific inflammations, veterinary medicine and uses related to humoral pathology without any link to specific organs), otology (i.e. ear problems), parasites (e.g. lice, scabies and tapeworms), poisons (e.g. hunting or fish poisons), repellents (e.g. against insects), respiratory system (e.g. asthma, coughs, dyspnea and tuberculosis), rhinology (incl. epistaxis and polyps) and urology (e.g. diuretics, dropsy, kidneys and painful urination). This classification system was chosen particularly to facilitate future comparative and quantitative studies. It is noteworthy, however, that the leveling of historical terms to fit biomedical categories may misrepresent ancient Mediterranean medical concepts and disease delimitations.


632 Discorsi del Matthioli

Dell'Arisaro. Cap. CLVIII.

LO ARISASO è una picciola herba. la cui radice è grande, come una oliua, molto piu acuta, che quella dell'Aro. Et però ferma impiastrata l'ulcere, che mangiano. Fannosi d'essa efficacissimi collirij contra le fistole. Impiastrata la radice à i membri genitali di tutti gli animali quadrupedi, gli corrompe.

NASCE l'Arisaro, per quanto scriue Plinio al XVI. capo del XXIIII. libro, in Egitto simile all'Aro, ma con foglie minori, minore di pianta, & parimente di radice, la quale è grossa come una grande oliua. Mostranne hoggi i semplicisti due spetie: & amendue mi furono prima note per mezo dell'eccellente medico, & mio co.

ARISARO.

Figure 2-1 Sample chapter on *Arisarum vulgare* O.Targ.Tozz (Dell'Arisaro; Book II, Chap. 158).

In the analysis, we only considered information described in Matthioli's translation of *De Materia Medica* (green frame). Matthioli's commentaries in italics were not included. Data on the mentioned plant part (marked in yellow), mode of administration (red) and specific use (blue) were extracted separately.

Difficulties with the translation of historic terms for diseases and symptoms into modern biomedical terminology were resolved by consulting Matthioli's (1568) vocabulary included in volume five as well as the *Vocabolario degli accademici della Crusca* (online, 2015), the first Italian dictionary. In this context, it is important to mention that spleen disorders were treated as gastrointestinal (and not lymphatic) conditions because in Ancient Greek medicine the spleen was variously regarded co-responsible for humoral balance and thus possibly perceived as being related to the proximate digestive system (Paraskevas et al., 2016). This is in line with the finding that textual mentions of spleen afflictions in *De Materia Medica* usually appear along with gastrointestinal problems in the narrower sense. Also, special attention was given to mentions of nerves ("*nervi*"), since due to the ancient confusion between nerves, tendons and ligaments (Haubrich, 2003:156) the addressed organ can, if at all, only be interpreted through the context. Several obscure historical pathologies could not be translated unequivocally into modern terms and were thus included in the category of 'others'. One of these is "*rotti e spasimati*" (including the less frequent variant "*fraccassati e spasimati*")**,** which literally translates into "(the) ruptured and (the) spastic." Based on the fact that textual mentions of *rotti e spasimati* were often preceded by respiratory conditions such as cough and followed by abdominal ailments such as side stitch, we initially hypothesized that this disease may translate into some advanced form of tuberculosis. However, since *rotti and spasimati* also occurred as isolated symptoms (of which the former, "*i rotti*" (i.e. "(the) ruptured"), was left unclassified and the latter, "*i spasimati***"** (i.e. "(the) spastics"), was counted as a musculoskeletal ailment) the compound term was assumed to represent symptoms of unknown pathology.

Plant identification

Plant identifications were established by crosschecking the descriptions in *De Materia Medica* with the Flora Europaea (Tutin et al., 1968–1993) and the pharmacognostic discussions presented in Berendes (1902 and references therein). Berendes (1902) reviews the botanical identifications of the Dioscoridean simples proposed by authorities such as Theophrast (ca. 371–287 BCE), Pliny (23–79 CE), Sibthorp (1758–1796) and Sprengel (1766–1833). In cases where the kind(s) of plant(s) described in a single chapter (e.g. Book IV, Chap. 96: *Dell'Ortica*) was (were) found to correspond to two or more closely related taxa (e.g. *Urtica dioica* L., *U. membranacea* Poir. ex Savigny, *U. pilulifera* L., *U. urens* L.) we limited our interpretation to one inclusive scientific taxon (e.g. *Urtica* spp.) per chapter. In other cases, where clearly distinguishable species were treated in one chapter (e.g. in Book I, Chap. 132: *De tutte le Mele* (on all apples)), these were identified separately (i.e. as *Citrus medica* L., *Cydonia oblonga* Mill., *Malus domestica* Borkh., *Prunus armeniaca* L., *Prunus persica* (L.) Batsch). Species names were checked against The Plant List 1.1 (2013 and references therein) and family names follow the Angiosperm Phylogeny Group 4 (APG IV, 2016).

Results and discussion

General patterns

In total 536 plant taxa including 924 drugs were recorded. Of these, 316 taxa (including 563 drugs) could be identified to the species level, 128 taxa (including 234 drugs) were identified to the genus level and 27 taxa (including 37 drugs) were identified only to the family level. For 65 taxa (including 90 drugs) no identification was possible. *Arbutus unedo* L. (*Arbuto*; Book I, Chap. 139) and *Calystegia sepium* (L.) R. Br. (*Smilace liscia*; Book IV, Chap. 147) are not recommended for any use and were thus not considered. Overall, 5314 medical uses (i.e. unique combinations of a specific taxon, plant part, route of administration and specific use) were recorded for 534 mentioned taxa. Internal applications such as pills or infuses (2655 uses) and external applications such as poultices, sitz baths or eye drops (2350 uses) prevail, while enemas, suppositories and pessaries (235 uses) as well as steams and fumigations (74 uses) are less frequent (Figure 2-2). The categories including most uses are dermatology (1216), gastroenterology (805), gynecology (615), urology (437), respiratory system (374) and neurology (269; Figure 2-2). A condensed dataset of the recorded plant taxa, plant parts and therapeutic uses is presented in the supplementary material (Table 7-1).Most drugs (894 derived from 512 taxa) are derived from Mediterranean floristic elements including those species previously introduced. Central European elements are represented by the aromatic alpine species *Valeriana celtica* L. and *Sedum roseum* (L.) Scop. (syn.: *Rhodiola rosea* L.). A smaller number (30 drugs derived from 24 taxa) are exotics that have been imported from Africa, Arabia, Central Asia, Himalaya or the Indo-Malayan ecozone. This shows that ancient Mediterranean herbal medicine was deliberately enriched with foreign *materia medica* (Miller, 1969 and Touwaide and Appetiti, 2013). Most drugs stem from subterranean organs (212), seeds (190), herbs (165) and leaves (161; Figure 2-3). The drugs derive from members of 109 vascular plant families with Asteraceae (46 species; 74 drugs), Apiaceae (44 taxa; 85 drugs), Lamiaceae (36 taxa; 44 drugs), Fabaceae (27 taxa; 35 drugs) and Rosaceae (20 taxa; 40 drugs) comprising the most taxa.

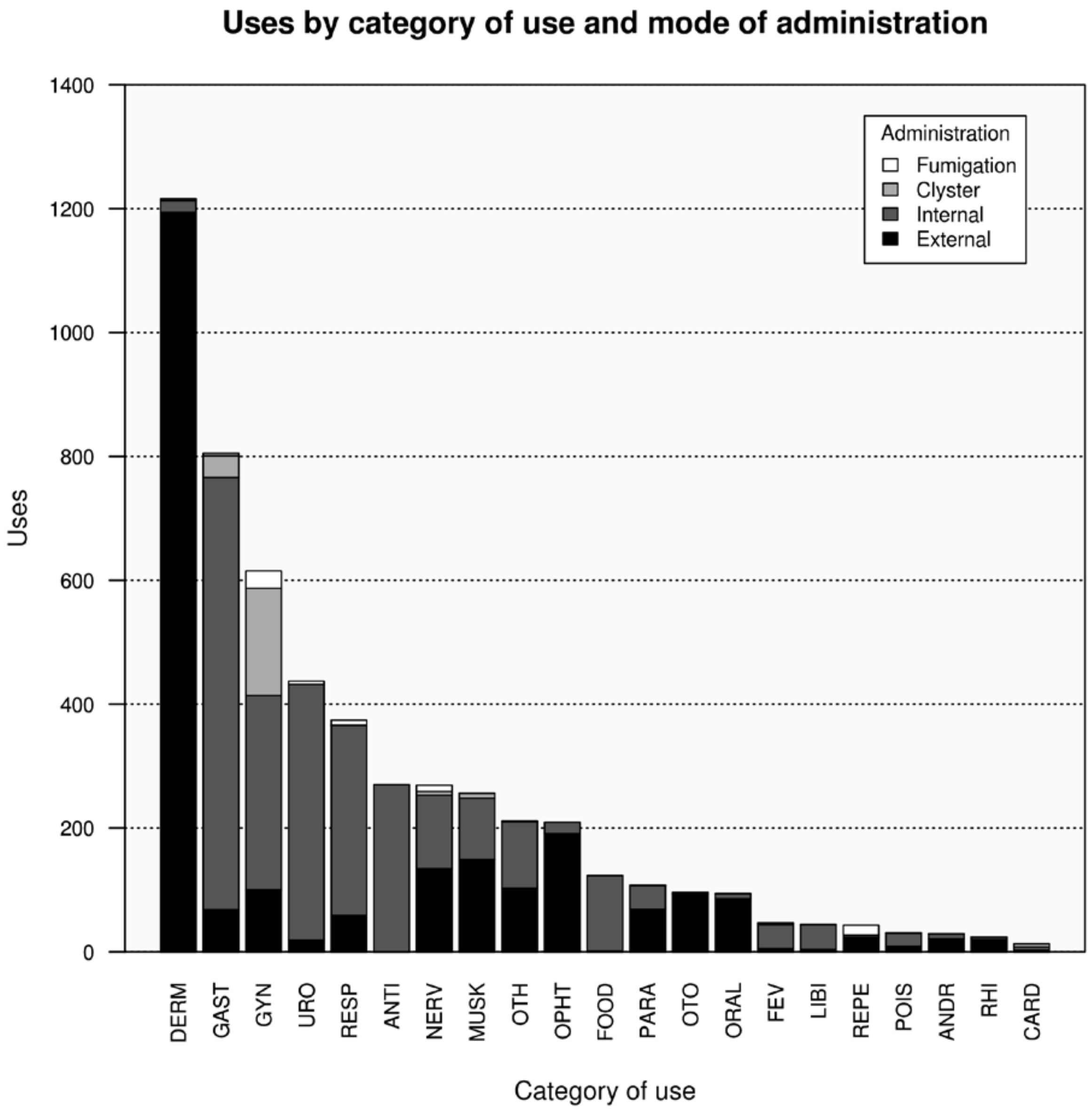

Figure 2-2 Number of recorded uses by category of use and mode of administration (N=5314).

ANDR: Andrology; ANTI: antidotes; CARD: cardiovascular problems; DERM: dermatology; FEV: fever; FOOD: food; GAST: gastroenterology; GYN: gynecology; LIBI: libido regulators; MUSK: musculoskeletal ailments; NERV: neurology; ORAL: oral cavity; OPHT: ophthalmology; OTH: others; OTO: otology; PARA: parasites; POIS: poisons; REPE: repellents; RESP: respiratory system; RHI: rhinology and URO: urology.

Medico-botanical patterns

To characterize therapeutic preferences associations between taxonomy, plant part and category of use were analyzed (Figure 2-4 - Figure 2-7; Supplementary Figs. Figure 7-1, Figure 7-2). Apiaceae are frequently cited for gastroenterology (91), gynecology (90), urology (72) as well as neurology (45). Apiaceae seeds are important as antidotes (20) and their exudates frequently recommended for musculoskeletal ailments (19). Lamiaceae are often mentioned for gastroenterology (66), dermatology (65) and gynecology (62), while specifically Lamiaceae herbs and leaves are dominant for the treatment of the respiratory system (31). Other associations include the use of Fabaceae seeds for dermatology (55), Rosaceae fruits for gastroenterology (20), Araceae subterranean parts for ophthalmology (12) and Amaryllidaceae drugs for rhinology (10). The drugs described in *De Materia Medica* show high taxonomic and therapeutic diversity indicating a comprehensive snapshot of ancient Mediterranean herbal medicine. The symptoms and ailments addressed largely match the therapeutic spectrum of a general practitioner rather than that of a military physician. This was already observed by Riddle (1985:2–4) who noted that the high frequency of gynecological uses combined with the few treatments for battle wounds is unusual for an army doctor.

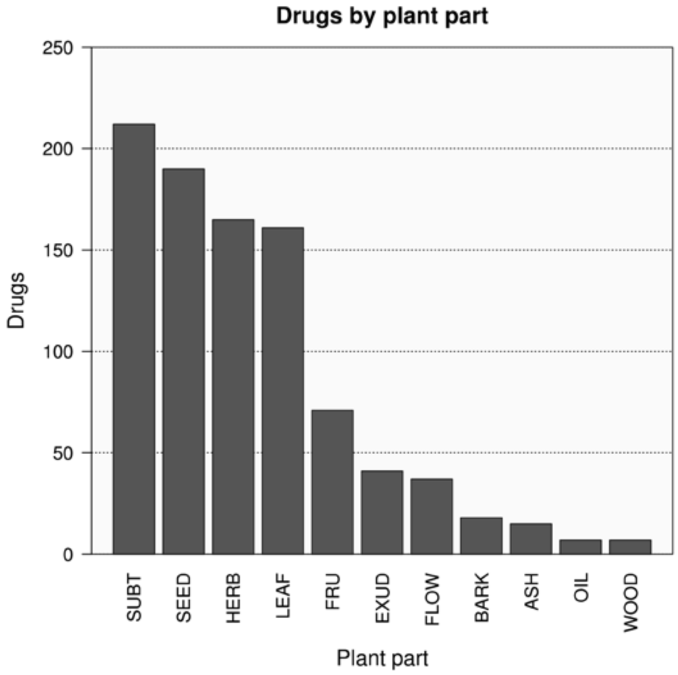

Figure 2-3 Number of drugs by plant part (N=924).

ASH: Ashes; BARK: barks; FLOW: flowers; FRU: fruits; HERB: herbs; LEAF: leaves; OIL: oils; EXUD: exudates; SEED: seeds; SUBT: subterranean parts; WOOD: wood.

Apart from this hint at Dioscorides' professional life, the overall picture of therapeutic uses allows inferences about the epidemiology in the Roman Empire in the 1st century CE. Many uses cover infectious diseases such as abscesses (111), dysentery (82), and ear infections (16) as well as infestations by scabies (59) and tapeworms (37), indicating poor sanitation and hygiene. Moreover, the large number of uses for envenomations (193) and the presence of animal repellents (31) reflect ecologically less controlled environments. The sporadic mention of remedies against tertian and quartan fever (11) testifies to the prevalence of malaria in the Mediterranean.

Important categories of use

Dermatological uses are the most frequent (1216; Figure 2-2) and cover ailments such as ulcers (205), abscesses (107), animal stings and bites (only topical applications; 106), wounds (60), erysipelas (58), burns (42), tumors (31), gangrene (26), fistula (25), skin inflammations (25), indurations (24), carbuncles (21), chilblains (19), pustules (17) and dandruff (16). The remedies for these conditions are taxonomically diverse, including 438 different drugs derived from 319 plant taxa. Fabaceae seeds account for a comparably high number of uses in this category (55; Figure 2-5) and comprise peas (*Pisum sativum* L.), chickpeas (*Cicer arietinum* L.), lentils (*Lens culinaris* Medik.), fenugreek (*Trigonella foenum-graecum* L.), bitter vetch (*Vicia ervilia* (L.) Willd.) and lupine (*Lupinus* spp.). Legume seeds contain significant amounts of protease inhibitors (Birk, 1996) that may beneficially modulate epidermal homeostasis, which is dysregulated in various skin disorders (de Veer et al., 2014).

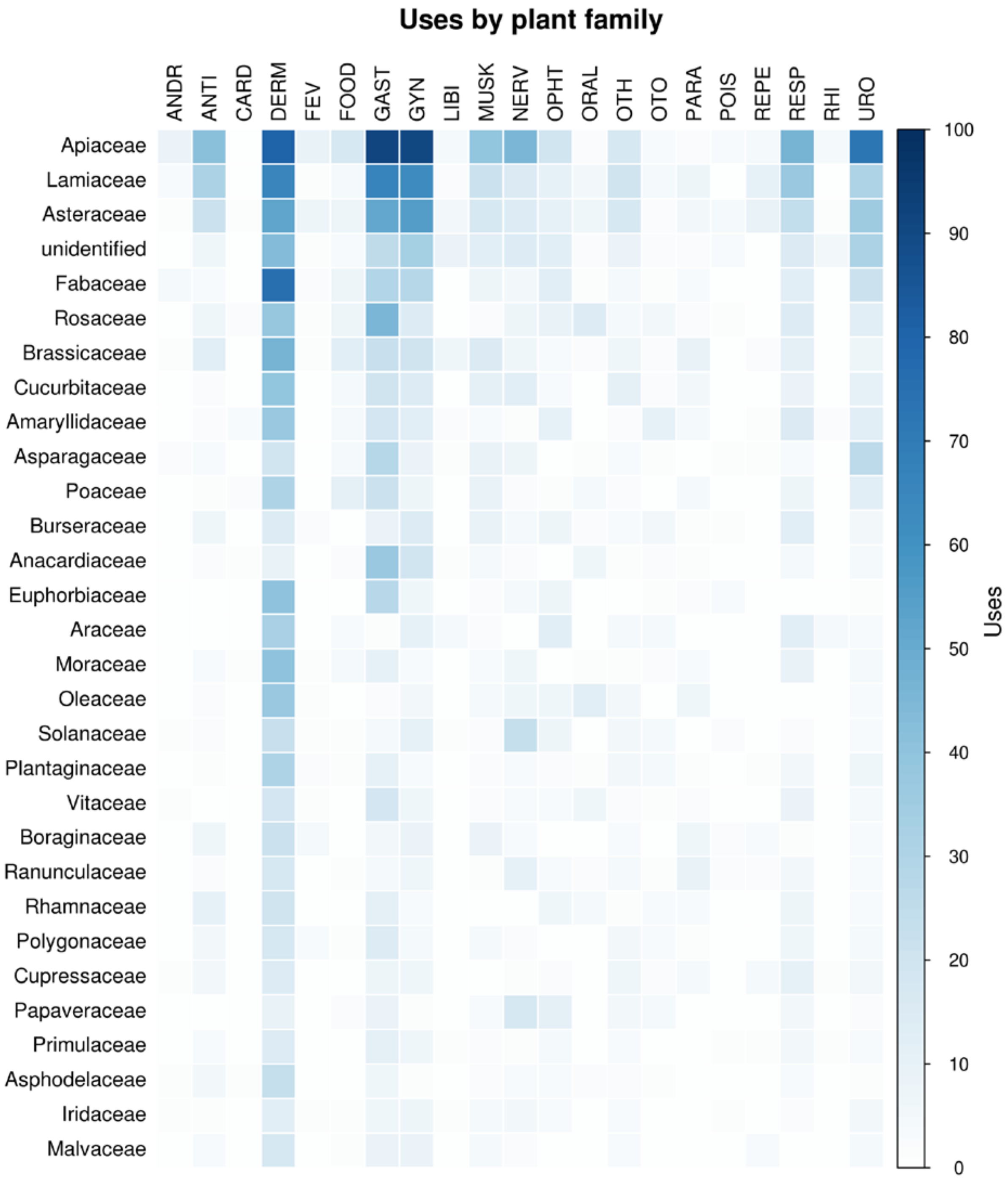

Figure 2-4 Quantification of uses by category of use and the most important botanical families. The categories of use are abbreviated following the legend of Figure 2-2.

Gastrointestinal uses (805; Figure 2-2) comprise diarrhea (138), dysentery (82) spleen afflictions (80), jaundice (60), abdominal pain and stomachache (76), liver problems (38), flatulence (20), hiccup (13), hematemesis (eleven) and vomiting (eleven) as well as uses as purgatives (62) and carminatives (13). Lamiaceae herbs and leaves (62) as well as Apiaceae seeds (38) are the most frequently recommended simples (Figure 2-5) including species like *Mentha* x *piperita* L., *Melissa officinalis* L., *Origanum vulgare* L. and *Carum carvi* L., which are well known stomachics and carminatives containing large amounts of essential oil (Hänsel and Sticher, 2007 and Wichtl, 2002). Amelcorn (*Triticum dicoccon* (Schrank) Schübl.), apart from being cosnidered nutritive ("*abondantemente nutrisce*"), is also praised for its positive (but not further specified) effects on the stomach (Book II, Chap. 87) and exemplifies the blurred boundaries between ancient dietetics and medicine (Totelin, 2015).

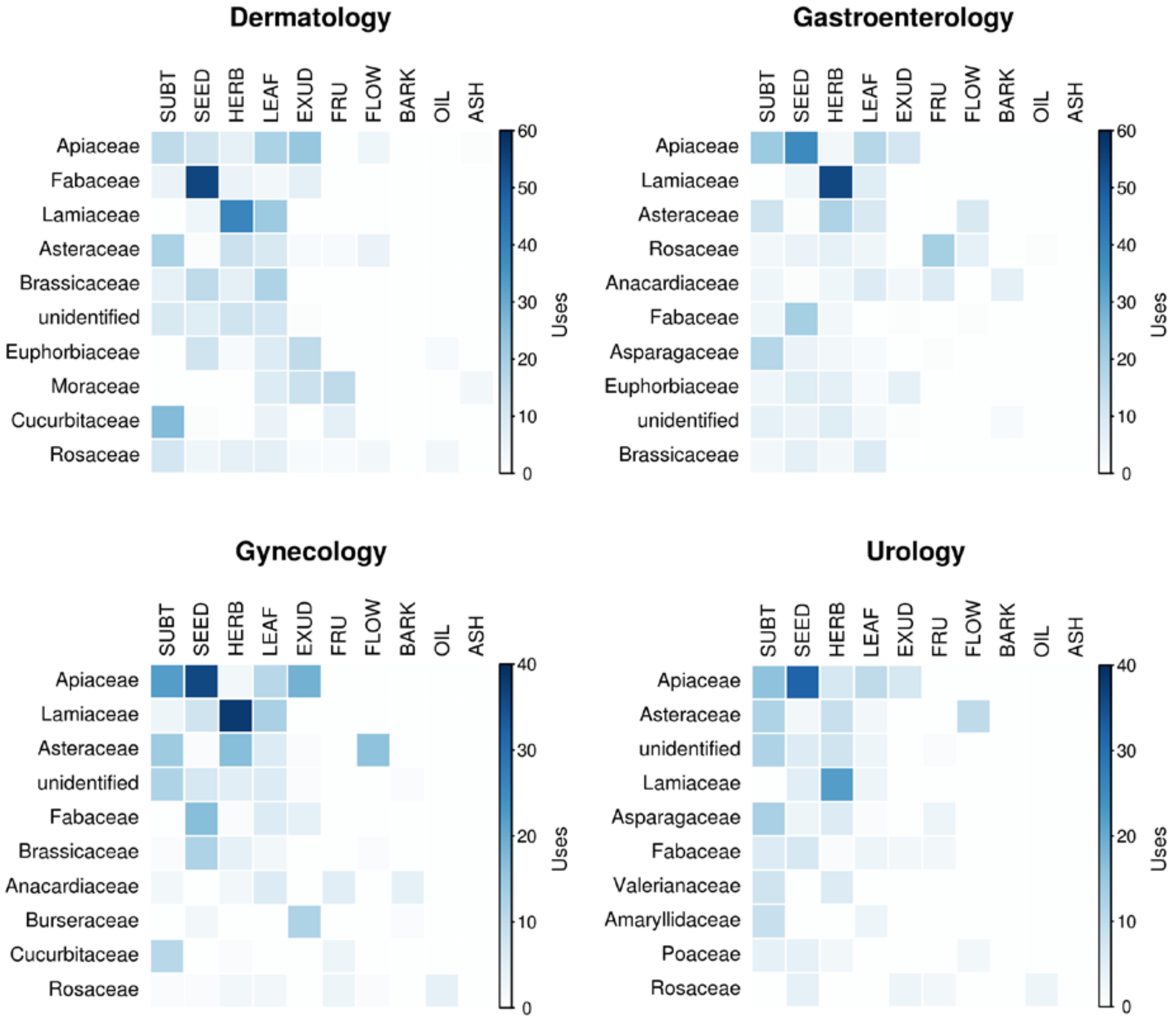

Figure 2-5 Quantification of uses for the categories of dermatology, gastroenterology, gynecology and urology.

Plant part abbreviations follow the legend of Figure 2-3.

Gynecology is the third largest category of use (Figure 2-2) and mainly covers pre- and perinatal uses (204), various uterine and vaginal conditions (131) and applications for controlling the menstrual cycle (71). Explicit abortifacient (17) and contraceptive (four) uses are rare, but as discussed in Riddle (1992:31–32), these may be implied within emmenagogues. Lamiaceae herbs and leaves (51) as well as Apiaceae seeds (36) were the most frequently mentioned drugs in this category (Figure 2-5).

The category of nervous system and mental disorders (269; Figure 2-2) includes general analgesics (72), headache (50), soporifics (31), epilepsy (36), fatigue (16), paralysis (11), lethargy (6), frenzy (6), melancholy (3) and mood enhancers (3). Apart from the expected prevalence of Solanaceae (23) and Papaveraceae (17) drugs many uses are based on Apiaceae (45) such as *Apium graveolens* L., *Heracleum sphondylium* L., *Opopanax* spp., *Peucedanum officinale* L., *Pimpinella anisum* L., *Seseli tortuosum* L., three species of the genus *Ferula* L. as well as the notoriously cryptic *Silphium* (*Laserpitio*; Book III, Chap. 88). This clustering may be due to the presence of coumarins, which are known to have various effects on the central nervous system *in vitro* and *in vivo*, including anticonvulsant, anxiolytic, antidepressive, neuroprotective and procognitive activities (Skalicka-Woźniak et al., 2016). Additionally, phenylpropanoids such as myristicin, present in different Apiaceae (Hall, 1973), may contribute to neurological effects (Hallström and Thuvander, 1997). Three of the six Crassulaceae drugs are recommended for headache (i.e. the subterranean parts of *Sedum roseum* as well as the leaves of *Aeonium arboreum* Webb & Berthel. and *Sedum amplexicaule* DC.).

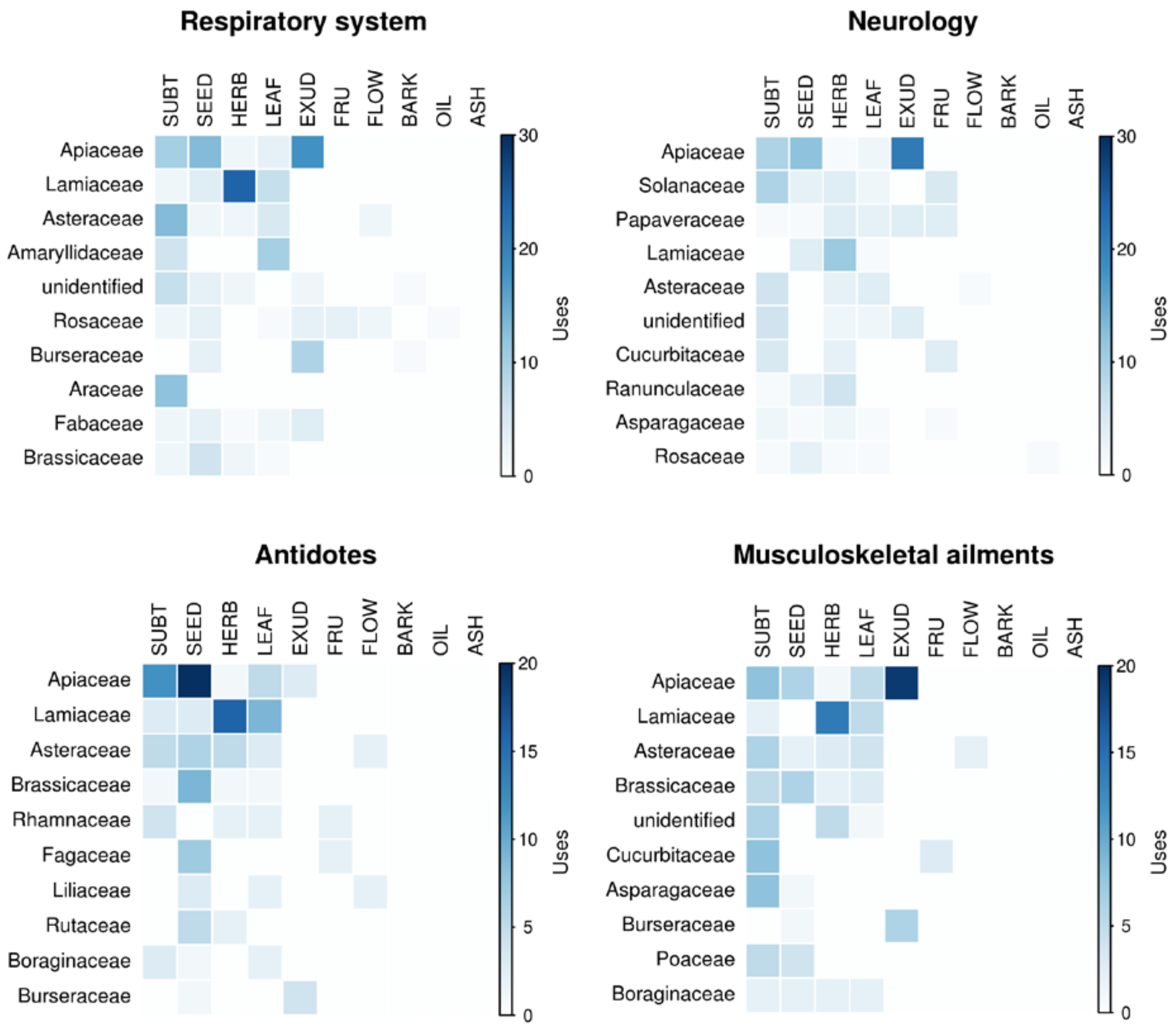

Figure 2-6 Quantification of uses for the categories of respiratory system, neurology, antidotes and musculoskeletal ailments.

Plant part abbreviations follow the legend of Figure 2-3.

Diachronic aspects

While many uses such as those of Lamiaceae drugs for gastroenterology and respiratory problems are still popular today, the applications of drugs with problematic side effects and high risk/benefit ratio (e.g. *Aconitum* spp., *Bryonia* spp., *Chelidonium majus* L., *Convolvulus scammonia* L., *Delphinium staphisagria* L.) have disappeared or are less prominent. For the same reason, drugs from the genus *Euphorbia* (20 derived from nine taxa) are avoided in European herbal medicine today. However, the genus Euphorbia is currently regaining attention in drug discovery (Ernst et al., 2015).

Wetland taxa (e.g. *Alisma* spp., *Cressa cretica* L., *Hippuris vulgaris* L., *Lemna minor* L., *Nuphar lutea* (L.) Sm., *Persicaria hydropiper* (L.) Delarbre, *Sparganium* spp. and *Trapa natans* L.) appear to be overrepresented in *De Materia Medica* as compared to modern herbal pharmacopoeias. Past changes in ecological management regimes resulting in a loss of wetland areas and availability of these drugs are probably the main factor responsible for this shift. Several other drugs, which are less important today, derive from early domesticated crops (e.g. *Citrus medica* L., *Sorbus domestica* L., *Triticum dicoccon* (Schrank.) Schübl. and *Vicia ervilia* (L.) Willd.) and arable weeds (*Agrostemma githago* L., *Bongardia chrysogonum* (L.) Spach and *Leontice leontopetalum* L.). In contrast, several species important in contemporary European phytotherapy as well as for the production of biomedical drugs are apparently not mentioned in *De Materia Medica*. These include *Borago officinalis* L., *Calendula officinalis* L., *Digitalis* spp. and *Humulus lupulus* L.

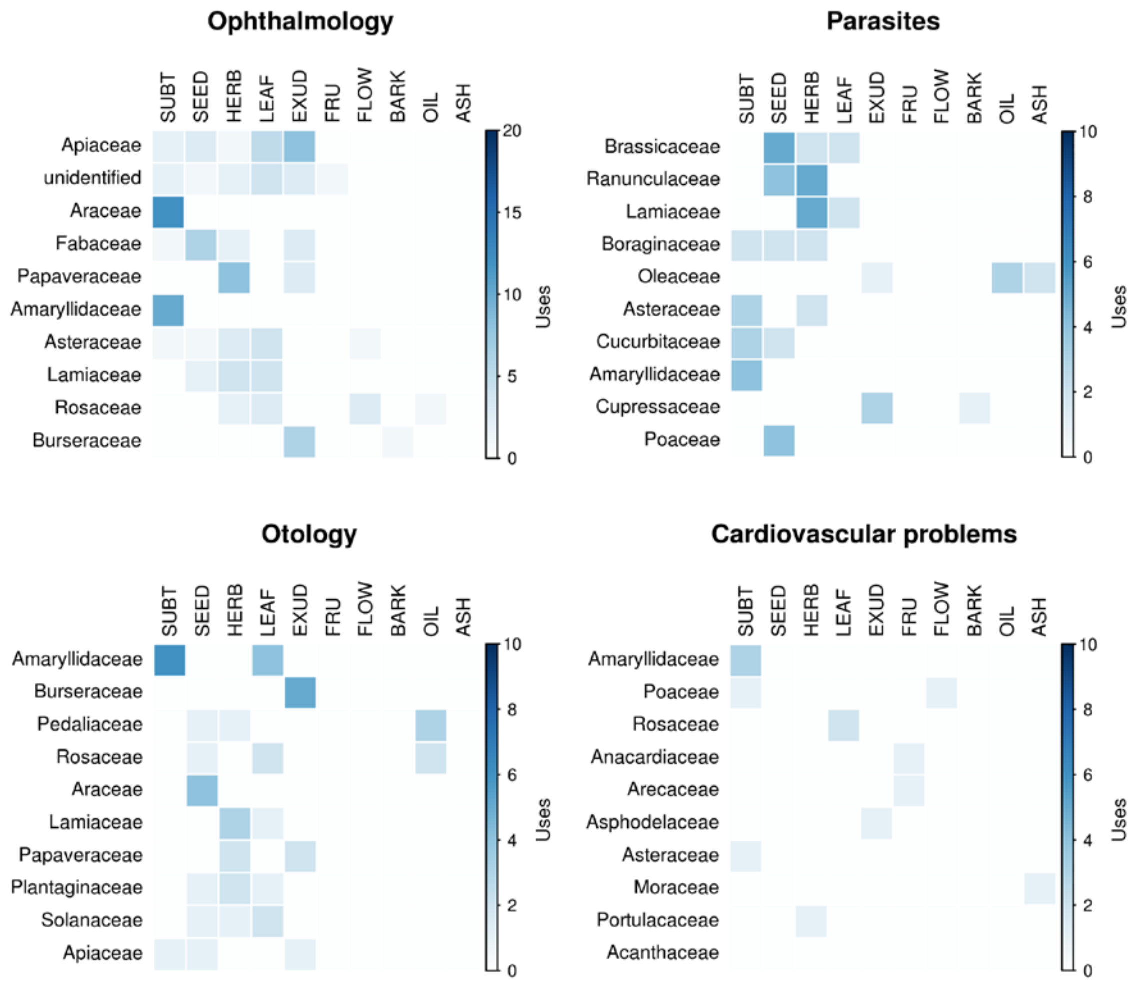

Figure 2-7 Quantification of uses for the categories ophthalmology, parasites, otology and cardiovascular problems.

Plant part abbreviations follow the legend of Figure 2-3.

The few drugs mentioned for cardiovascular problems (13) are mainly remedies for hemorrhoids and varicose veins (8) while two are recommended against cardiac chest pain (i.e. the leaves of raspberry and blackberry), two for vasodilation (flowers and roots of *Cymbopogon schoenanthus* (L.) Spreng.) and the ash of *Ficus carica* L. as a blood liquefier. The low number of drugs and uses in this category contrasts with the importance of phytotherapeutics for cardiovascular diseases today and may reflect epidemiological shifts and differences in nosologies and disease etiologies.

With respect to the specific plant organs, drugs derived from subterranean parts, seeds and exudates appear more frequent in *De Materia Medica* as compared to modern pharmacopeias. Subterranean plant parts may have lost importance as sources for drugs due to their comparably time consuming collection, which is, moreover associated with a negative impact on wild populations. The historical prevalence of these drugs testifies to their past importance and alludes to the so-called *rhizotomoi*, who were specialist collectors and traders of root drugs. Several plant exudates may have been eliminated from modern herbal medicine because of toxicological concerns or their potential for allergic reactions (Lardos et al., 2011). Moreover, the collection of plant exudates is costly and overharvesting might have compromised their supply. In one case (Book III, Chap. 88: *Laserpitio* commonly known as *Silphium*) this might have even led to the extinction of a species (Koerper and Kolls, 1999). Via trade, the use of seeds as medicine very probably contributed to the dispersal of germplasm (Beinart and Middleton, 2004 and Brockway, 1979:36), which at the same time must have had a self-affirming effect on the transmission of the associated pharmaceutical knowledge. However, the removal of antidotes from the European phytotherapeutic heritage is in part responsible for the reduced importance of seed drugs today. Irrespective of the reasons for why subterranean organs, seeds and exudates became partly obsolete such drugs once formed an important but nowadays neglected part of the Euro-Mediterranean dispensatory. This, together with the fact that seeds, resins and gums are considered unconventional natural resources, potentially rich in yet unknown metabolites (Tulp and Bohlin, 2004), calls for further research on their phytochemistry and pharmacology.

Conclusions

This paper presents a data mining approach and a survey of the herbal drugs contained in Dioscorides' *De Materia Medica* (*ex* Matthioli, 1568). Besides human medicine *De Materia Medica* also covers foods, cosmetics, repellents, poisons and plant uses related to animal husbandry and spiritual practice. By using a systematic data extraction technique we elucidated several salient therapeutic patterns. These include the importance of Fabaceae seeds for dermatology, the frequent mention of Apiaceae seeds as antidotes, the use of Amaryllidaceae bulbs for rhinology, the application of Araceae tubers for ophthalmology and the reliance on exudates from Apiaceae for neurology as well as musculoskeletal ailments. The former existence of the *rhizotomoi*, who were specialized root collectors and traders in ancient Greece, is reflected in the large number of drugs derived from subterranean plant parts. Moreover, the past importance of wetland species and the frequent uses against envenomations and intoxications mirrors the closer interaction of past societies with their biological environment and different ecological, epidemiological and hygienic conditions. The systematic analysis of herbal texts offers unique insights into past herbal medicine. We suggest that those drugs with discontinued use might represent interesting starting points for drug discovery and the evaluation of ancient herbal medicine. Comparing such data with contemporary herbal medicine and phytotherapy might widen our understanding of modern practices and help to document the tradition of use, which is required for the regulatory approval of new herbal drugs.

Conflict of interest

The authors declare to have no conflict of interest.

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Chapter 3 From cumulative cultural transmission to evidence-based medicine: evolution of medicinal plant knowledge in Southern Italy

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Abstract

In Mediterranean cultures written records of medicinal plant use have a long tradition. This written record contributed to building a consensus about what was perceived to be an efficacious pharmacopeia. Passed down through millennia, these scripts have transmitted knowledge about plant uses, with high fidelity, to scholars and laypersons alike. Herbal medicine's importance and the long-standing written record call for a better understanding of the mechanisms influencing the transmission of contemporary medicinal plant knowledge. Here we contextualize herbal medicine within evolutionary medicine and cultural evolution. Cumulative knowledge transmission is approached by estimating the causal effect of two seminal scripts about *materia medica* written by Dioscorides and Galen, two classical Greco-Roman physicians, on today's medicinal plant use in the Southern Italian regions of Campania, Sardinia, and Sicily. Plant-use combinations are treated as transmissible cultural traits (or “memes”), which in analogy to the biological evolution of genetic traits, are subjected to mutation and selection. Our results suggest that until today ancient scripts have exerted a strong influence on the use of herbal medicine. We conclude that the repeated empirical testing and scientific study of health care claims is guiding and shaping the selection of efficacious treatments and evidence-based herbal medicine.

Introduction

In contrast to the relatively homogenous human genome, human culture is characterized by diversity (Pagel and Mace, 2004). The origin of our cultural diversity and the question as to which parameters influence its dynamics are issues central to population genetics, anthropology and evolutionary biology (Guglielmino et al., 1995; Henrich and Boyd, 1998; Pagel and Mace, 2004). Human cultures and their persistence are grounded in the ability of individuals to learn from and copy each other in a process essential for cultural evolution termed “cultural transmission” (Cavalli-Sforza et al., 1982; Lehmann et al., 2010; Pennisi, 2010). While social learning and copying of cultural traits adds to the evolutionary success of animal species, particularly humans (Laland and Janik, 2006; Rendell et al., 2010), human cultures differ from other primate cultures by evolving constantly and cumulatively,

2 Published as: Leonti, M., Staub, P.O., Cabras, S., Castellanos, M.E., Casu, L., 2015. From cumulative cultural transmission to evidence-based medicine: evolution of medicinal plant knowledge in southern Italy. Frontiers in Pharmacology. 6, 207.

such that waves of innovations and trait modifications become continuously assimilated (Tennie et al., 2009). This essential difference has been explained by humans having a “theory of mind,” an ability to adopt another's point of view and understand the intentionality and purpose of action, and hence to innovate useful modifications to them, instead of the mindless copying that most non-human species engage in (Tomasello, 1999).

“Cultural traits” (Cavalli-Sforza and Feldman, 1981, p. 70) are units of transmittable knowledge hierarchically organized by scales of complexity and inclusiveness (O'Brien et al., 2010). Cultural change occurs when, in analogy to genetic evolution, traits are affected by mutation (incorrect knowledge transmission, loss of knowledge or traits, creation, and assimilation of new traits), recombination (mixture of traits), cultural drift (random processes) and guided by natural selection (Mesoudi et al., 2004; O'Brien et al., 2010; Cardoso and Atwell, 2011). Quantitative observations in cultural transmission are restricted to the study of cultural traits, which may also be described as units of cultural replicators propagated through imitation and termed “memes” (Dawkins, 1976, p. 189 ff.). With the concept of “memes” seemingly irrational behavior and religion can be equally well accounted for as technically complex recipes, whereas the success rate of memes or cultural traits is determined by their ability to spread between and lodge themselves in human minds and cultures (Dawkins, 1976; Strimling et al., 2009). Oblique knowledge transmission describes the passing down of cultural traits by members of one generation to extra-familial members of the next generation. A special case of oblique transmission that increases cultural homogeneity, results from teacher-pupil relationships (Cavalli-Sforza and Feldman, 1981, p. 54; Cavalli-Sforza et al., 1982). Also exclusive to humanity is the ability to transmit knowledge by means of language and symbology, via media such as scripts, art forms and telecommunication to subjects remote in space and time (Cavalli-Sforza and Feldman, 1981, pp. 3–4). The transmission of knowledge through print media results in a more precise and detailed passing down of information and hence dissemination of cultural traits (Diamond, 2005, p. 216). External storage of human knowledge, such as scripts, can act as interregional repositories and influence technological change, increase high-fidelity transmission, and preserve knowledge. Repositories increase the longevity as well as the diversity of cultural traits within a cultural group (Lewis and Laland, 2012; Mesoudi et al., 2013). The analysis of cultural transmission has been approached with the aid of proxies, such as archeological artifacts (e.g., O'Brien et al., 2010), or by means of animal or human behavioral experiments (Tennie et al., 2009; Rendell et al., 2010), phylogenetic inference (e.g., Barbrook et al., 1998) and using mathematical models (e.g., Strimling et al., 2009; Lehmann et al., 2010; Nunn et al., 2010; Lewis and Laland, 2012). Relative rarely knowledge transmission has been approached through statistical analyses of data obtained by means of real observations (but see: Hewlett and Cavalli-Sforza, 1986; Reyes-García et al., 2009; Leonti et al., 2010; Soldati et al., 2015).

Human knowledge about medicinal traditions and practices is well documented and can be traced back to the earliest writing, offering possibilities for diachronic studies (e.g., Heinrich et al., 2006; Pollio et al., 2008; Dal Cero et al., 2014). Historically, medicinal plants and their products have quantitatively dominated *materia medicae* and pharmacopeias. A pharmacopeia is a standard recipe book describing the preparation, formulation and application of medicines. The usefulness of a pharmacopeia is “determined by the periodical changes it has to undergo to keep pace with the latest progress in the sciences on which it is based” (Urdang, 1951, p. 577). Nonetheless, since medicinal plant knowledge and traditional medicine are at once adaptive yet deeply rooted in local traditions and history they show both conservative and progressive characters (Leslie, 1976, p. 1–17; Bye et al., 1995; Leonti, 2011). In modern societies and urban centers herbal medicine is frequently chosen as a treatment for mild or chronic ailments and as an adjuvant therapy. In rural and deprived areas, however, herbal medicine frequently constitutes the only affordable treatment option (Leonti and Casu, 2013).

Potentially, any plant or natural product can be used as a medicine and answers to questions such as "what is an accepted medicinal plant?" and "how many different plants are globally being used as medicines?," depend on the applied consensus or definition. The Kew Medicinal Plant Names Services currently catalogs around 13'500 medicinal plant species worldwide[3].

In general, cultural interactions (including factors such as exchange of biodiversity, associated knowledge, epidemics and political hegemony) can affect the continuity of medicinal plant use and may lead to recombination of traits and innovation. "Disjunction" describes a changing ethnomedical context applied to original remedies, "discontinuity" the giving up of a plant use and "synchronism" the substitution of a native species by a hitherto not considered species, or by introduced plants with similar semantic backgrounds (Bye et al., 1995). Medicine is, however, culture bound and includes rational (empirical) as well as irrational (symbolic) aspects and behavior. The placebo effect, or meaning response, for example, is a physiologically poorly described phenomenon and conceptualizes how subjective perception, expectation and cultural meaning influences the effectiveness of medicinal treatments (Etkin, 1988; Moerman and Jonas, 2002; Rief et al., 2011). Today, complementary and traditional medicines hold a multi-billion dollar market-share. Also therefore, it is important to understand the cultural dynamics and factors that influence the transmission of efficacious vs. non-efficacious medical treatments (Tanaka et al., 2009).

We and others have argued that scripts reporting and approving therapeutical uses of plants and remedies in general, may act as blueprints. Scripts facilitate high fidelity knowledge transmission and thereby shape the cultural and inter-cultural use of plant-based medicines (Leonti et al., 2009, 2010; Brown et al., 2014). The European Pharmacopeia and the use of herbal medicine have been influenced considerably by the Greco-Roman medical texts, their medieval Arabic interpretations, as well as by the Renaissance commentaries (Urdang, 1951; Mann, 1984; Heinrich et al., 2004). Dioscorides' and Galen's works were among the first printed medicinal texts, and Pietro Andrea Matthioli's translation of Dioscorides' *De Materia Medica*, remained the fundamental pharmacological text in Italy until the eighteenth century (Cosmacini, 2009). This well documented historical development, together with the wealth of historical records on *materia medicae*, provide a framework conductive to the quantitative analysis of high fidelity knowledge transmission of medical plant use, and the process of trait evolution.

Here we use causal inference, which is a statistical perspective designed to analyze the existence of causal connections between two categories of variables. The units of analysis are citations of plant use in herbal books and independent field studies, quantitatively arranged into medicinal use-categories. These plant taxon-use-category pairs are treated as cultural traits, compared, and analyzed with Bayesian statistical inference, and in particular with the Bayesian Additive Regression Trees (BART) model. Our aim is to determine the causal effect of the therapeutical recommendation of Dioscorides (first century CE) and Galen (ca. 130–200 CE) on contemporary (1970–2013) medicinal plant use in the Southern Italian regions of Campania, Sardinia and Sicily. *De Materia Medica* (henceforth *DMM*) written by Dioscorides probably in the second half of the first century CE, and Galen's *De simplicium medicamentorum facultatibus libri XI* (henceforth *DSMF*), written during the second half of the second century CE, are among the most copied and influential texts on herbal medicine in history (Singer, 1927; Arber, 1953; Riddle, 1985). The regions of Campania, Sardinia, and Sicily have experienced similar cultural impacts to varying degrees. While parts of Campania and Sicily belonged to Magna Graecia (800 BC onwards), after the first Punic war (264–241 BC) all three regions were

3 Kew Medicinal Plant Names Services (http://www.kew.org/mpns). (accessed: 14.08.2015).

absorbed by the Roman Empire (Saitta, 1967; Palmer, 1977). Greek, however, remained lingua franca in Southern Italy until the sixth century CE what facilitated the transmission of classical knowledge to later ages. The estimation of causal effects of historic therapeutical plant recommendations over contemporary medicinal plant knowledge is a problem of causal inference. The "causal effect" is determined by asking "how would the contemporary plant uses change (i.e., increase or decrease of specific contemporary plant-use combinations) if the authors (Dioscorides and Galen) had given the opposite indication?".

Addressing this research question is crucial for fostering the link between empirical "traditional" knowledge and biomedicine (see Etkin, 2001 for a comprehensive discussion): First, because it helps to understand the role and importance of texts in the transmission of medicinal plant knowledge and the development of pharmacopeias overall. Second, because it allows a critical discussion of the relevance of contemporary field surveys aiming at contributing to natural products research and conserving "traditional" knowledge in regions with a pronounced written tradition. We have approached this question before for the region of Campania with a limited set of data (Leonti et al., 2010), but now include a cross-cultural analysis considering two additional South Italian regions including all commonly used medicinal plant taxa described in Dioscorides' *DMM* and Galen's *DSMF*.

Materials and Methods

Data Sources and Sampling

Matthioli's (1501–1578) translation of Dioscorides' *DMM* from 1568 (reedited as a facsimile in 1967–1970) and the Latin-Greek transcription of Galen's *De simplicium medicamentorum facultatibus libri XI* (*DSMF*) by Theodorico Gerardo Gaudano, published by Gulielmum Rouillium (Guillaume Rouillé) in 1561 were used for extracting the historical therapeutical indications of medicinal plant taxa. These historical indications are treated as the influencing information. With respect to *DMM* and our previous analysis (Leonti et al., 2010) where we also included the recommendations made by Matthioli himself, here we only consider the text attributed to Dioscorides (*ex* Matthioli, 1568).

Data on contemporary medicinal plant use were compiled from 52 ethnobotanical studies on local medicinal plant use in the Italian regions of Campania (n_C = 11 study sites, including 1 study from the adjacent Basilicata), Sardinia (n_S = 20 study sites) and Sicily (n_{Si} = 21 study sites) published between 1970 and 2013 (Figures 3-1, 3-2, 3-3, Tables 7-2, 7-3, 7-4). The taxa concertedly mentioned in Dioscorides' *DMM* (*ex* Matthioli, 1568), Galen's *DSMF* (1561), and in the contemporary studies conducted in Campania, Sardinia and Sicily, are included in this analysis. Closely related plant species used interchangeably and forming use-complexes generally perceived as ethnotaxa, are treated as one taxon (e.g., *Anemone* spp. includes *A. coronaria* L., *A. hortensis* L., and *A. nemorosa* L.). Species synonymies were resolved following theplantlist.org (The Plant List 1.1). For a complete list of species considered see Supplementary Table 7-4.

Use-categories and Cultural Traits

The therapeutical indications of medicinal plants reported in Dioscorides and Galen, as well as those reported in the contemporary studies, were consistently allocated into 11 use-categories corresponding to organ or symptom-defined illness groups. Remedies and treatments of the eye, ear, and nose were classified as separate use-categories following Matthioli (1568) and Preuss (1971, pp. 300–341).

The eleven use-categories are: GAS, gastrointestinal disorders (including liver and spleen); URO, urological problems; RES, respiratory complaints (including angina, sore throat, pleurisy); DER, dermatologic problems (including oral cavity, varicose veins and hemorrhoids); SKM, skeleto-muscular disorders (including hematoma and gout); NER, central and peripheral nervous system (including headache, toothache, analgesic uses, epilepsy, insomnia); GYN, gynecology (application in women's medicine); FEV, fever, malaria; EYE, problems of the eye; EAR, problems of the ear; NOS, problems of the nose not related to respiratory diseases (epistaxis, polyps).

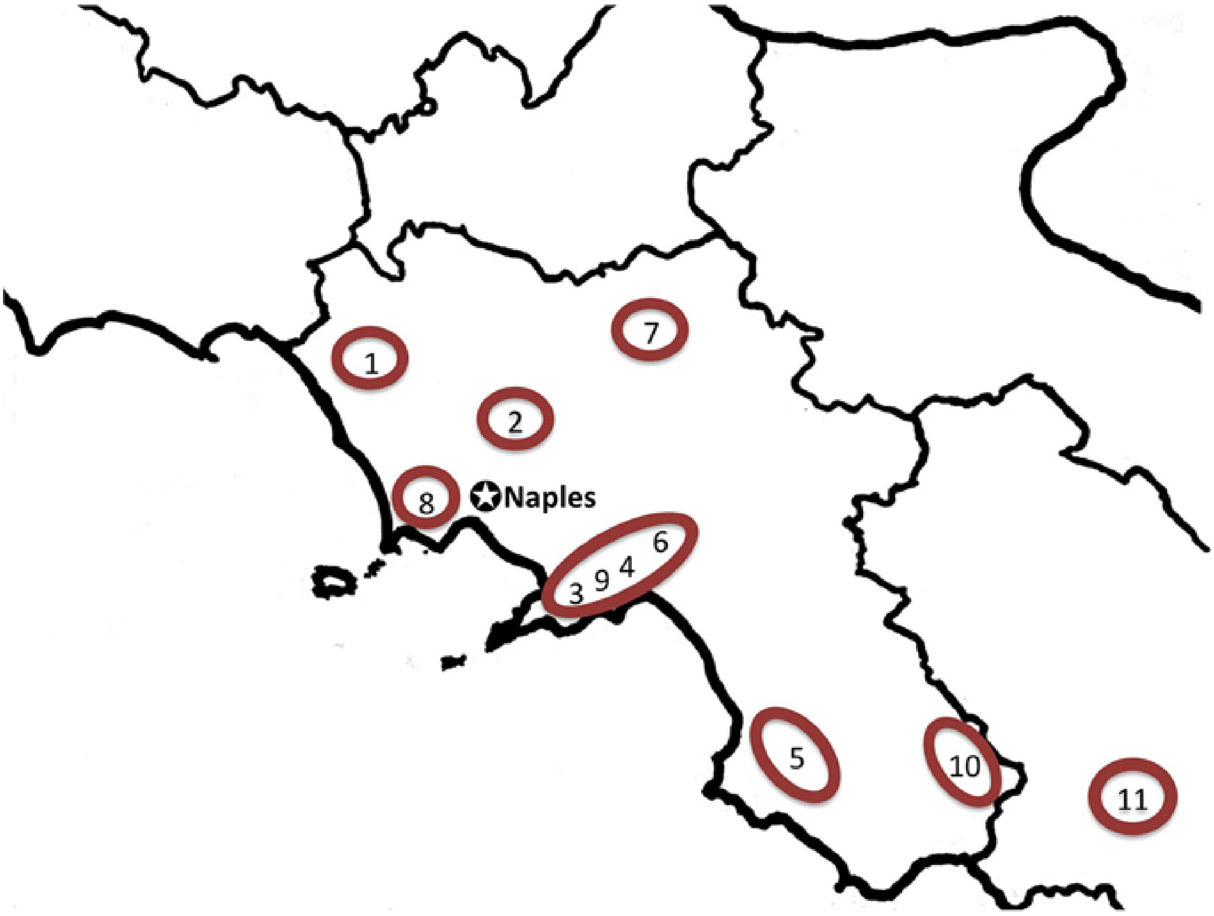

Figure 3-1 Map of Campania and adjacent regions indicating considered field studies addressing popular medicinal plant use.

1, Roccamonfina, Caserta (Antonone et al., 1988); 2, Caserta, Caserta (De Feo et al., 1991); 3, Peninsula Sorrentina, Napoli/Salerno (De Feo et al., 1992); 4, Coast of Amalfi, Salerno (De Feo and Senatore, 1993); 5, Monte Vesole and Ascea, Salerno (Scherrer et al., 2005); 6, Montecorvino Rovella, Salerno (De Natale and Pollio, 2007); 7, Sannio area, Benevento (Guarino et al., 2008); 8, Phlegraean Fields Regional Park (Motti et al., 2009); 9, Amalfi Coast (Savo et al., 2011); 10, National Park of Cilento and Vallo di Diano (Di Novella et al., 2013); 11, Rotonda, Pollino National Park (Di Sanzo et al., 2013).

Each plant taxon-use-category pair is treated as a separate cultural trait (cf. Leonti et al., 2010) or “meme” based on which the causal influence of Dioscorides' DMM and Galen's DSMF on local South Italian contemporary medicinal plant use is determined. For each of the three regions, contemporary plant use is scored with the number of studies where a plant taxon-use-category pair was cited. For the region of Campania the scores could thus take the values $c_{ij} = [0, 11]$, for Sardinia $s_{ij} = [0, 20]$ and for Sicily $s_{iij} = [0, 21]$ (Supplementary Tables 7-2, 7-3, 7-4). Historical plant use is scored in a binary fashion where each plant taxon-use-category pair was either recommended or not mentioned by Dioscorides, $d_{ij} = [0, 1]$ and by Galen $g_{ij} = [0, 1]$.

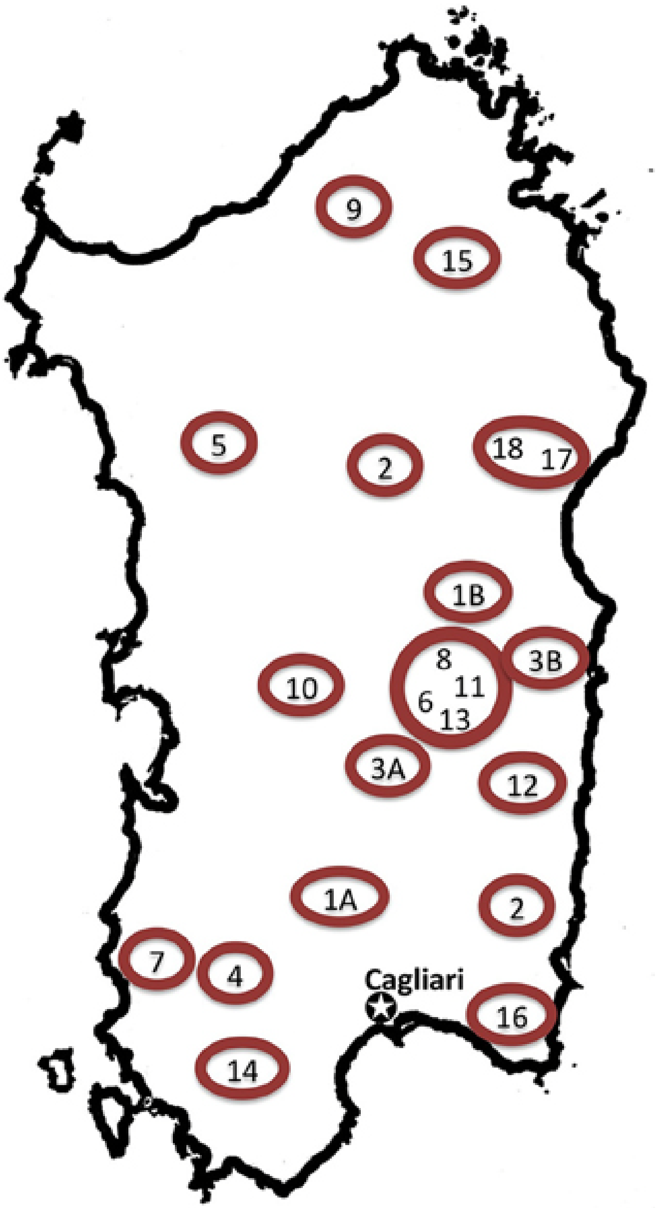

Figure 3-2 Map of Sardinia indicating considered field studies addressing popular medicinal plant use.

1A, Campidano; Cagliari (Bruni et al., 1997); 1B, Urzulei, Ogliastra (Bruni et al., 1997); 2, Sarrabus, Cagliari (Palmese et al., 2001); 3A, Escolca, Cagliari (Loi et al., 2005); 3B, Lotzorai, Ogliastra (Loi et al., 2005); 4, Marganai, Carbonia-Iglesias (Ballero and Fresu, 1991); 5, Monteleone, Sassari (Ballero and Poli, 1998); 6, Seui, Ogliastra (Ballero and Fresu, 1993); 7, Fluminimaggiore, Carbonia-Iglesias (Ballero et al., 2001); 8, Villagrande Strisaili, Ogliastra (Loi et al., 2004); 9, Tempio Pausania, Olbia-Tempio (Ballero et al., 1997); 10, Laconi; Oristano (Ballero et al., 1997); 11, Arzana, Nuoro (Ballero et al., 1994); 12, Perdasdefogu, Ogliastra (Ballero et al., 1997); 13, Ussassai; Ogliastra (Ballero et al., 1998); 14, Carbonia-Iglesias (Atzei et al., 1994); 15, Gallura; Olbia-Tempio (Atzei et al., 1991); 16, Villasimius, Cagliari (Ballero, 1982); 17, Dorgali (Camarda, 1990); 18, Monte Ortobene, Nuoro (Signorini et al., 2009).

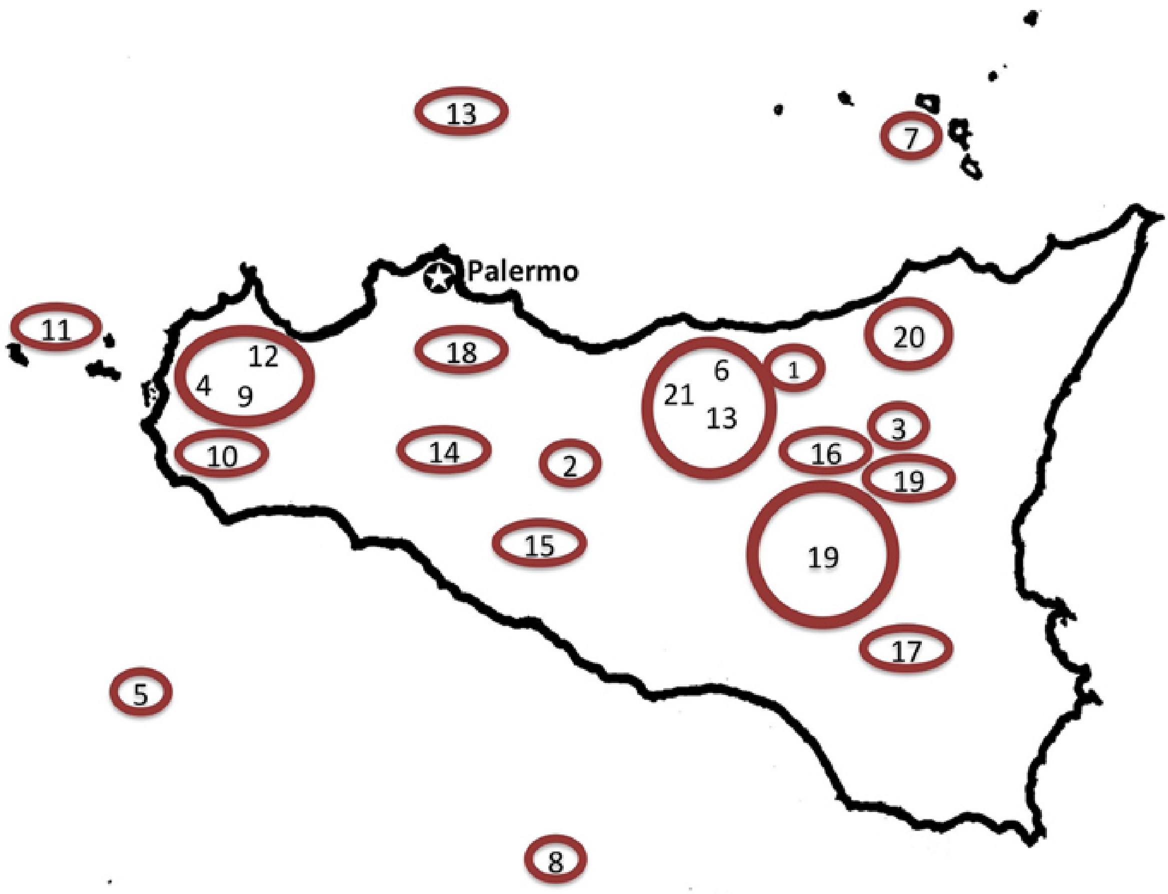

Figure 3-3 Map of Sicily indicating considered field studies addressing popular medicinal plant use.

1, Mistretta; Messina (Lentini and Raimondo, 1990); 2, Mussomeli; Caltanissetta (Amico and Sorge, 1997); 3, Cesarò; Messina (Barbagallo et al., 1979); 4, Erice; Trapani (Lentini and Aleo, 1991); 5, Pantelleria; Trapani (Galt and Galt, 1978); 6, Madonie, Palermo (Raimondo and Lentini, 1990); 7, Eolie, Messina (Lentini et al., 1995); 8, Pelagie, Agrigento (Lentini et al., 1996); 9, Trapani (Lentini, 1987); 10, Mazara del Vallo; Trapani (Lentini et al., 1987–1988); 11, Egadi; Trapani (Lentini et al., 1997); 12, Riserva Naturale Dello Zingaro; Trapani (Lentini and Mazzola, 1998); 13, Ustica; Palermo (Lentini et al., 1994); 14, Bivona, Agrigento (Catanzaro, 1970); 15, Sant'Angelo Muxaro, Agrigento (Lentini, 1996); 16, Bronte, Catania (Arcidiacono et al., 1999); 17, Monterosso Almo, Ragusa (Napoli and Giglio, 2002); 18, Mezzojuso, Palermo (Ilardi and Raimondo, 1992); 19, Sicilia centro-orientale (Barbagallo et al., 2004); 20, Alcara Li Fusi e Militello Rosmarino, Messina (Arcidiacono et al., 2007); 21, Madonie Regional Park (Leto et al., 2013).

General Statistical Procedure

In general, and when not explicitly specified, for studying the association between two categorical variables we make use of the Chi-square test. This is a statistical test useful for assessing the significance of the association between two categorical variables, for example the recommendations of Dioscorides and Galen. The rest of the analyses that involve more variables and complicated relation structures have been performed with techniques explained below. We furthermore cross-check plant-use traits not present in Galen and Dioscorides with the content of a popular book on herbal medicine issued in 1980 by Reader's Digest called “Segreti e virtú delle piante medicinali” (Secrets of the properties of medicinal plants) (Reader's Digest, 1980).

Probit Regression

The probit regression is a regression model where the response variable is handled as a proportion. The proportion is transformed into a variable that varies all over the real line. Subsequently, this variable is used as the response variable in the usual linear regression model. The transformation of the proportion is achieved by inverting the cumulative distribution function of the standard Gaussian law. This function is called “probit function” wherefrom the name “probit regression” derives.

With the probit regression (e.g., Dobson and Barnett, 2008; Hastie et al., 2009) we estimate the overall similarities in citations of plant-use combinations (traits) with respect to the regions, and the joint citations of Dioscorides and Galen and the eventual interactions between such joint citations and regions. The latter is necessary in order to answer the questions of whether Dioscorides' and Galen's joint recommendations increased the overall trait similarity among regions. Citation proportions (i.e., trait proportions) are regressed against the five effects: 1. Geography (region), 2. Plant taxon, 3. Use-category, 4. Joint recommendations by Dioscorides and Galen and 5. Interaction between joint recommendations and geography. The fifth effect “Interaction between joint recommendations and geography” is the one we are focusing on.

Causal Inference

We use a statistical analysis, suitable for non-experimental settings in order to measure the evidence for a causal effect of Dioscorides and Galen upon contemporary indications on medicinal plant use. This analysis is based on data for all plants, use categories and regions, and the response variable Y. Y is the number of contemporary studies reporting a specific plant-use-category pair for a certain region. The minimum value of Y is 0, while its theoretical maximum value is 21 (Sicily). Variable Y represents the possible outcome, in terms of frequency of mentioned uses, which may has been caused by Dioscorides and Galen. The degree to which the outcome Y has been influenced by the two classic authors needs to be estimated with the BART model. The BART model takes into account that different other effects may have affected Y, and thus, possibly confound the relation between the two authors and the variable Y. These variables are referred to as “confounding variables” and denoted by X. We assume that the specific plant taxon, the specific therapeutical indication as well as geographical particularities can themselves be the cause of, or shape the outcome, independently of Dioscorides' or Galen's recommendations. Therefore, X includes the confounding variables (i) plant taxon, (ii) therapeutical use, and (iii) geography into the causal relation and the estimation of the causal effect of Dioscorides and Galen on the contemporary observations:

(i) *Plant taxon*: The plant taxon determines the content of secondary metabolites and associated pharmacological properties. Plant identity also influences organoleptic properties of herbal drugs, which can have an impact on the assigned therapeutical indication and the mode of application.

(ii) Therapeutic use
: Each health problem has its own probability to be cured with medicinal plants

(iii) *Geography*: The local cultural history, regional epidemiology and the regional abundance of a taxon (biogeography) influences the probability that a plant taxon is used for medicine.

We assume that Dioscorides as well as Galen influenced contemporary medicinal plant knowledge and that the influence of Galen on contemporary traits may itself be conditioned by the influence exerted by Dioscorides' work. The arrows in the causal model (Figure 3-4) indicate the direction of the influence, which may contain a causal effect.

Recommendations by Dioscorides and Galen are denoted by *Z*, where $Z = 1$ means that one or both authors made a recommendation for a certain combination of a plant-use-category. Both *X* and *Z* may affect *Y* and therefore, we need to separate the effect of *Z* from the confounding variables *X*. That is, we want to estimate the causal effect of *Z* on *Y*. The first principle of causal statistical inference is: “Correlation is not causation.” This means that whatever correlation we observe between *Z* and *Y*, it does not necessarily describe a causal effect, unless we assume that there are no other influential variables that determined the outcome *Y*. In fact, due to the existence of confounding variables we cannot measure the causal effects directly (see Figure 3-4 for the causal model).

The parameter of interest is α, i.e., the difference between the number of actually observed values of *Y* (contemporary plant-use combinations) and the potential values we would have observed if the author had given the opposite recommendation of *Z*. Since the outcome $Z = 1$ or $Z = 0$ was observed, the not observed outcome ($Z = 0$ or $Z = 1$) is referred to as the counterfactual outcome. This counterfactual outcome is what is estimated with the BART model (Chipman et al., 2010). In practice we estimate the causal effect based on the number of records per plant use combination in the contemporary literature by estimating the outcome of that number in the counterfactual sense and the theoretical situation where Dioscorides and Galen would not have recommend that use, although they did (Leonti et al., 2010). We do not consider the opposite situation, i.e., the counterfactual outcome of uses not recommended by Dioscorides of Galen because not mentioning a certain use is different from an explicit recommendation that a certain taxon should not be used for a certain application. In fact, cases where authors (i.e., physicians) did explicitly reject medicinal plant uses are rather rare. According to Matthioli (1568) Galen writes in the second chapter of the “Facoltà dei cibi” that *Siliquae* (the fruits of *Ceratonia siliqua*) are difficult to digest, and that it would have been better to leave them in the Orient, instead of bringing them into “our countries” (Matthioli, 1568, Book 1, Chap. 131, p. 258).

Moreover, we are not able to assess the causal effect of Dioscorides on Galen because we lack information on the confounding variables at that time. Finally, we conceive the causal effect α as a random variable, while the BART model provides the estimation of the probability distribution of α conditionally on the observed data. This estimation is known as the posterior distribution of the causal effect. It allows us to calculate the most probable causal effect, its mean value and also its existence by estimating the probability that α differs from 0. Further details on the BART model and its use in estimating causal effects can be found in Hill (2011).

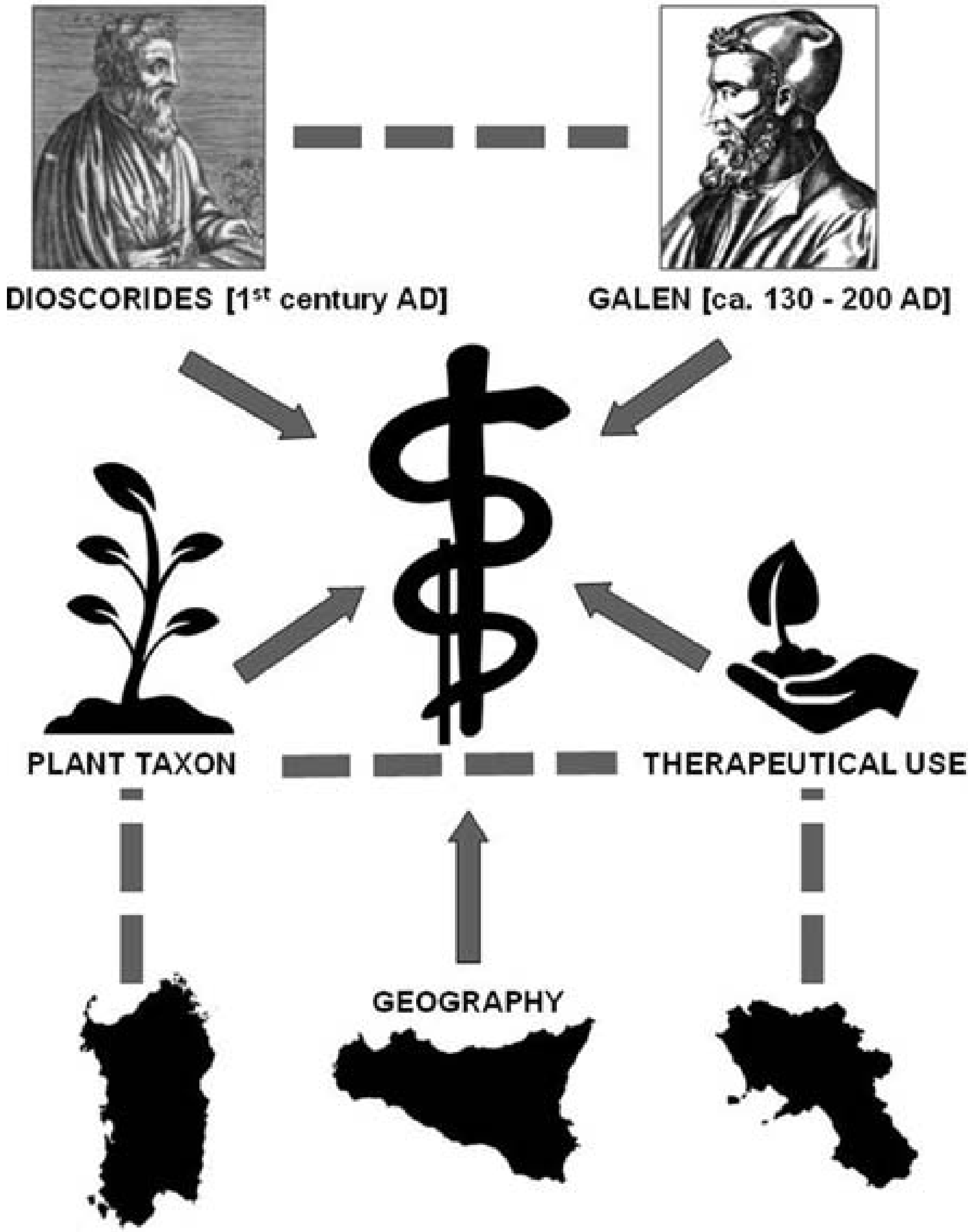

Figure 3-4 Causal model assuming that Dioscorides and Galen influenced contemporary medicinal plant use considering the confounding variables "plant taxon," "geography," "therapeutical use" and their interactions (segments)**.**

Arrows indicate the direction of the influence, which may exert a causal effect.

Results

General Data Matrix

A comparison and consensus analysis between Dioscorides' *DMM* (*ex* Matthioli, 1568) and Galen's *DSMF* (1561), and the plant uses reported for Campania, Sardinia and Sicily, resulted in a set of 87 commonly mentioned medicinal taxa (Table 3-1). Dioscorides and Galen highly agree ($p < 0.0001$) recommending the same therapeutical uses for the large part of the plant taxa although Dioscorides makes reference to more uses. Especially with respect to the smaller use-categories such as “eyes,” “ears,” and “nose” but also regarding women's medicine and skeleto-muscular disorders Galen mentions considerably fewer plants compared to Dioscorides. For the 87 taxa under analysis we collected 462 use-citations from *DMM* and 236 use-citations from *DSMF*. From a total of 957 [11 × 87] theoretically possible plant-use combinations 470 are mentioned neither by Dioscorides nor by Galen, 211 are recommended by both authors, 251 exclusively by Dioscorides and 25 by Galen alone.

Of the 3′104 citations of all three South Italian regions and 87 taxa together, 78% correspond with Dioscorides and 55% with Galen, while 23% of the uses mentioned in Dioscorides and 14% of those in Galen are not represented in contemporary traditions. Gastrointestinal (81.9–92.3%), dermatological (75.8–96.5%), and urological applications (50–80.5%) of contemporary ethnomedical knowledge in the three regions coincide the most with the recommendations in Dioscorides and Galen. Recent plant uses related to women's medicine shows high concordance with Dioscorides (83.3–87.5%) but a poor overlap with Galen (17.5–37.5%). The importance of the use-categories in terms of the number of included plant taxa shows considerable differences between the classic Greco-Roman and modern sources. For 59 of the 87 taxa, Dioscorides makes reference to a use related to women's medicine in relation to only 24 in Campania, 25 in Sardinia and 29 in Sicily. Also the remedies for eye (34) and ear problems (28) is considerably higher in Dioscorides with respect to the three South Italian regions, with 9–13 and 2–9 taxa indicated, respectively. Using herbal remedies for fever is, on the contrary, a cultural trait more common with the contemporary data where 14 taxa are used in Campania, 21 in Sardinia and 16 in Sicily, while Dioscorides recommends 9 and Galen only 2 out of the 87 taxa. For an overview see Table 3-1 and Supplementary Tables 7-2, 7-3, 7-4.

Probit Regression

The significance of the interaction between geography and joint recommendations is by far lower than that of the effect of geography taken alone. This means that the differences regarding citations proportions (or the number of use-citations relative to the number of examined papers) between regions are significant also for jointly recommended plant uses, but are less pronounced than the differences between regions considering all plant use combinations. Details are given in the Supplementary Material (Table 7-5).

Table 3-1 Plant taxa considered in this analysis derived from a consensus analysis between medicinal plants used in Campania, Sardinia, and Sicily, as well as those described in Dioscorides' *DMM* and Galen's *DSMF*.

Red: Dioscorides and Galen recommend the use; Yellow: Only Dioscorides makes the recommendation; Orange: Only Galen makes the recommendation. Numbers in cells correspond to the number of studies citing a plant taxon-use-category pair. GAS: gastrointestinal disorders (including liver and spleen); URO: urological problems; RES: respiratory complaints (including angina,sore throat, pleurisy); DER: dermatologic problems (including oral cavity, varicose veins, and hemorrhoids); SKM: skeleto-muscular disorders (including hematoma and gout); NER: central and peripheral nervous system (including headache, toothache, analgesic uses, epilepsy, insomnia); GYN: application in women's medicine (gynecology); FEV: fever, malaria; EYE: problems of the eye; EAR: problems of the ear; NOS: problems of the nose not related to respiratory diseases (epistaxis, polyps). * Eighth Book "Delle compositioni de medicamenti secondo I luoghi" by Galen (Matthioli, 1967–1970, pp. 535–536).

Taxon	Dioscorides' *DMM* (*ex* Matthioli, 1568), Book–Chap.	Galen's *DSMF* (1561)	GAS	DER	NER	SKM	GYN	RES	FEV	URO	EAR	EYE	NOS
Adiantum capillus-veneris L.	Adianto (IV–138)	Adiantum (p. 366)	4	10	4	1	18	13	0	3	0	1	0
Allium cepa L.	Cipolla capitata (II–140)	Crommyon–Caepa (p. 464–465)	7	13	2	2	1	12	0	12	2	0	1
Anagallis arvensis L. s.l.	Anagallide (II–169)	Anagallis (p. 377)	0	3	1	0	0	5	0	0	0	1	0
Anemone spp.	Anthillide (III–147)	Anemone (p. 378–379)	1	2	3	1	1	0	0	1	0	0	0
Apium spp.	Apio (III–69)	Selinon–Apium (p. 519)	7	2	0	4	0	5	1	11	0	0	0
Artemisia spp.	Abrotano, Assenzo, Assenzo marino, Artemisia, Artemisia delle frondi sottili (I–46; III–24–26, 121, 122; V–37)	Abrotonon, Artemisia, Absinthium (p. 353-360, p. 385, p. 388–389)	23	10	4	4	2	8	5	2	0	3	0
Arum spp.	Aro (II–156, 157)	Arum (p. 384–385)	0	8	0	5	0	1	0	1	0	0	0
Arundo spp.	Canna (I–95)	Calamus phragmites–Canna (p. 432)	1	16	1	1	2	1	1	5	1	0	0
Asparagus spp.	Asparago (II–114)	Asparagus (p. 385–386)	5	0	2	3	0	2	0	19	0	0	0
Asphodelus spp.	Asphodelo–Hastula regio (II–159)	Asphodelus (p. 387)	0	25	0	3	0	4	1	2	0	0	0
Avena spp.	Vena, Bromo (II–85; IV–142)	Aegilops–Avena (p. 366)	4	4	1	1	0	2	0	4	0	0	0
Brassica spp.	Brassica, Napi, Rapa (II–102, 103, 111)	Crambe–Brassica (p. 459–460, p. 166)	7	8	1	5	2	7	1	1	0	0	0
Calamintha nepeta (L.) Savi s.l.	Calamintha (III–38)	Calamintha–Nepitha (p. 429–431, p. 334)	10	8	5	4	1	5	0	1	0	0	0
Centaurium erythraea Rafn. s.l.	Centaurea minore (III–7)	Centaurium minus (p. 422–443)	7	5	1	0	1	0	12	0	0	0	0
Ceratonia siliqua L.	Silique (I–131)	Ceratonia (p. 444)	9	1	0	0	0	12	0	1	0	0	0
Ceterach officinarum Willd. s.l.	Aspleno (III–145)	Asplenum (p. 386)	4	2	1	0	1	5	1	15	0	0	0
Cichorium intybus L. s.l.	Cichoria salvatica (II–121)	Seris–Cichorium (p. 519 &*)	26	2	1	3	0	0	3	9	0	0	0
Convolvulus arvensis L.	Helsine (IV–49)	Elxine (p. 413)	7	4	0	3	0	0	0	0	0	0	0
Crataegus spp.	Oxiacantha (I–103)	Oxyacanthos (p. 497)	7	3	13	2	2	2	5	4	0	0	0
Cyclamen spp.	Ciclamino (II–153)	Cyclaminos–Rapu (p. 465–467)	3	4	0	1	2	0	0	0	0	0	0
Cydonia oblonga Mill.	Cotogno (I–132)	Cydonia (p. 168)	7	5	2	0	0	3	1	0	0	0	0
Cynara spp.	Cardo (III–14)	Scolymus (p. 524)	14	1	0	0	0	1	0	2	0	0	0
Cynodon dactylon (L.) Pers.	Gramigna (IV–3)	Agrostis–Gramen (p. 362)	18	3	1	2	1	8	2	32	0	0	0
Daucus carota L. s.l.	Pastinaca salvatica (III–54)	Daucus–Staphylinus (p. 402–403)	8	6	2	0	3	5	0	7	0	1	0
Ecballium elaterium (L.) A. Rich.	Cocomero salvatico (IV–156)	Sicyos agrios–Cucumis agrestrs (p. 522)	8	3	3	2	1	0	2	0	0	0	0
Equisetum spp.	Coda di cavallo (IV–48, 49)	Hippuris–Cauda equina (p. 424)	4	11	0	3	0	3	0	17	0	0	3
Ficus carica L.	Fichi (I–146)	Syca–Ficus (p. 529–530)	7	22	1	1	1	18	0	1	0	0	0
Foeniculum vulgare Mill.	Finocchio (III–76)	Marathrum–Foeniculum (p. 479–480)	27	3	1	1	7	8	0	8	0	2	0
Fumaria spp.	Fumaria (IV–112)	Capnios–Fumus (p. 433)	9	7	2	0	1	2	0	3	0	0	0
Hedera helix L. s.l.	Hedera (II–170)	Cissos–Hedera (p. 449–450)	2	18	6	7	2	10	0	0	0	0	0
Helichrysum italicum (Roth) G. Don s.l.	Helichriso (IV–59)	Amarantum (p. 373)	2	4	2	3	0	7	0	0	0	0	0
Helleborus spp.	Elleboro nero (IV–153)	Elleborus–Veratrum (p. 412)	0	2	3	1	2	0	0	0	0	0	0
Hordeum vulgare L.	Orzo (II–78)	Crithe–Hordeum (p. 461)	7	3	0	0	0	9	0	3	0	1	0
Hypericum spp.	Asciro, Androsemo (III–166, 167)	Hypericum (p. 542)	5	28	4	8	1	5	0	3	0	0	0
Juglans regia L.	Noci (I–142)	Carya–Nuces (p. 436–437)	7	7	2	1	0	3	0	1	0	0	0
Lactuca spp.	Lattuca (II–125)	Thridax–Lactuca (p. 422)	7	11	10	2	2	1	0	2	0	1	0
Laurus nobilis L.	Lauro (I–35, 87)	Daphne arbor–Laurus (p. 403)	44	6	6	13	4	17	3	3	1	0	0
Lavatera spp.	Althea (III–158–160)	Ebiscus–Althea (p. 406–407)	8	9	0	1	0	9	0	1	0	2	0

Taxon	Dioscorides' *DMM* (*ex* Matthioli, 1568), Book –Chap.	Galen's *DSMF* (1561)	GAS	DER	NER	SKM	GYN	RES	FEV	URO	EAR	EYE	NOS
Linum usitatissimum L.	Lino (II–94)	Linospermom–Lini semen (p. 475)	10	13	3	2	1	15	0	0	1	1	0
Lonicera implexa Aiton	Periclimeno (IV–15)	Periclymenos–Volucrum maius (p. 503)	3	2	1	3	1	2	0	2	0	0	0
Malva spp.	Malva (II–109)	Malache–Malva (p. 478–480)	40	36	8	1	5	24	2	14	0	5	0
Marrubium vulgare L.	Marrobio (III–113)	Prasium–Marrubium (p. 510–511)	12	3	4	7	4	13	7	0	0	0	0
Matricaria chamomilla L. & *Tanacetum* spp.	Anthemide, Camamilla, Parthenio (III–148, 149)	Anthemis aut Chamamelum (p. 380)	19	10	16	9	7	5	1	1	1	8	0
Mentha pulegium L.	Pulegio (III–31)	Glichon–Pulegium (p. 399, p. 334)	9	4	3	2	1	5	0	1	0	1	0
Mentha spp.	Menta, Sisembro (II–117; III–36)	Hediosmos–Menta (p. 418)	25	11	10	5	3	9	2	0	0	0	0
Morus spp.	Moro (I–144)	Morea–Morus (p. 488)	4	1	0	0	0	4	1	2	0	0	0
Muscari racemosum Mill. & *Leopoldia comosa* (L.) Parl.	Bulbo che si mangia, Bulbo che fa vomitare (II–160, 161)	Bulbos emeticos–Bulbus vomitorius (p. 394)	1	2	1	0	0	0	0	5	0	0	0
Myrtus communis L.	Mirto (I–129)	Myrrhine–Myrtus (p. 490–491)	12	14	3	2	2	9	0	4	0	1	0
Nasturtium officinale R. Br.	Sisembro acquatico (II–117)	Cardamum–Nasturtium (p. 435)	11	3	2	0	3	6	1	7	0	0	0
Ocimum basilicum L.	Basilico (II–130)	Ocimon (p. 550)	11	4	5	0	1	6	0	1	1	0	0
Olea europaea L.	Olivo salvatico (I–28, 117-121)	Elaea–Olea, Elaeon–Oleum (p. 407–411)	13	17	1	6	1	3	7	2	5	0	0
Origanum spp.	Origano, Maiorana, Sansucho (I–44; III–29, 42)	Origanus, Amaracon–Maiorana, Sampsycon–Maiurana (p. 498, p. 373, p. 518)	10	3	7	5	2	13	0	1	0	0	0
Papaver rhoeas L.	Papavero salvatico (IV–66)	Mecon–Papaver (p. 483–484)	2	2	30	1	0	12	1	0	0	0	0
Papaver somniferum L.	Papavero domestico (IV–67)	Mecon–Papaver (p. 483–485)	1	0	5	0	0	1	0	0	0	0	0
Parietaria spp.	Helsine (IV–88)	Elxine (p. 412–413)	27	26	8	10	1	9	3	31	1	1	0
Petroselinum crispum (Mill.) Fuss	Petroselino (III–72)	Petroselinum (p. 504)	14	5	5	1	8	1	0	10	2	1	1
Pinus spp.	Pino (I–71)	Pitys–Pinus (p. 507)	0	5	1	0	0	3	0	2	0	0	0
Pistacia lensticus L.	Lentisco (I–36, 37, 72)	Schinos–Lentiscus (p. 532)	6	14	4	4	0	7	2	0	0	0	0
Pistacia terebinthus L.	Terebintho (I–36, 73)	Terminthos–Terebinthus (p. 534)	2	4	2	2	0	4	0	1	0	0	0
Plantago spp.	Piantagine, Coronopo (II–115, 119)	Arnoglossum–Plantago (p. 383–384)	10	20	0	5	1	5	0	8	0	3	0
Polygonum aviculare L. s.l.	Poligono maschio (IV–3)	Polygonon–Seminalis (p. 508–509)	6	5	0	1	0	1	1	9	0	0	0
Prunus spp.	Ciregie (I–130)	Cerasus (p. 443–444)	6	0	0	3	0	5	0	7	0	0	0
Prunus dulcis (Mill.) D.A. Webb	Mandorle (I–31, 140)	Amygdala (p. 375–376)	8	3	0	0	0	5	0	0	0	0	0
Prunus persica (L.) Batsch	Pesco (I–132)	Melea persice–Malus persica (p. 486)	4	1	1	0	0	0	0	1	0	0	0
Punica granatum L.	Melagrano (I–128)	Rhoea–Malum granatum (p. 516, p. 169, p. 318)	11	1	1	1	2	2	1	2	0	0	0
Ranunculus spp. & *Ficaria verna* Huds.	Ranunculo, Batrachio, Chelidonia minore (II–166, 172)	Batrachium (p. 391)	0	6	1	5	0	1	0	0	0	0	0
Ricinus communis L.	Ricino (IV–165)	Cici–Ricinus (p. 446)	7	2	1	1	1	0	0	0	0	0	0
Rosa spp.	Rosa (I–39, 104, 111, 112)	Rhodos–Rosa, De rosaceo (p. 515–516, p. 134 ff.)	8	5	0	0	1	4	0	3	0	5	0
Rosmarinus officinalis L.	Rosmarino coronario (III–83)	Libanotides (p. 474)	22	6	9	8	2	13	0	3	0	0	0
Rubus spp.	Rovo (IV–39)	Batos–Rubus (p. 391–392)	19	28	1	0	2	6	0	5	0	1	0
Rumex spp.	Lapatio, Rombice (II–106)	Lapathum (p. 470)	6	13	2	1	0	1	2	5	0	0	0
Ruscus spp.	Rusco, Lauro Alessandrino (IV–148, 149)	Daphne herba (p. 403)	4	7	2	4	0	0	0	13	0	0	0

Taxon	Dioscorides' *DMM* (*ex* Matthioli, 1568), Book –Chap.	Galen's *DSMF* (1561)	GAS	DER	NER	SKM	GYN	RES	FEV	URO	EAR	EYE	NOS
Ruta spp.	Ruta (III–47)	Perganon–Ruta (p. 505)	28	7	7	17	8	2	1	1	2	6	0
Sambucus nigra L.	Sambuco (IV–175)	Acte–Sambucus–Ebulus (p. 370)	13	15	8	14	0	13	2	5	2	9	0
Senecio spp.	Senecio (IV–99)	Herigeon (p. 420)	4	1	0	1	6	1	0	2	0	0	0
Solanum nigrum L.	Solatro hortolano (IV–73)	Trychnon (p. 539–541)	0	12	8	6	0	2	0	1	0	0	0
Sonchus spp.	Soncho (II–120)	Sonchus (p. 527)	8	7	2	2	0	1	0	4	0	0	0
Tamus communis L. (now: *Dioscorea communis* (L.) Caddick & Wilkin.)	Vite nera (IV–184)	Ampelos melana–Vitis nigra (p. 375)	0	1	1	10	0	0	0	1	0	0	0
Thymus spp.& *Thymbra capitata* (L.) Cav.	Tragorigano, Thimo, Serpillo (III –30, 39, 41)	Thymum (p. 423)	12	7	4	3	1	16	1	2	0	1	0
Trigonella foenum-graecum L.	Fiengreco (II–93)	Telis–Foenum graecum (p. 536)	1	1	1	0	1	2	0	1	0	0	0
Triticum spp.	Grano (II–77, 81)	Pyros–Triticum (p. 513)	4	10	4	3	1	3	0	0	0	0	0
Tussilago farfara L.	Tossilagine (III–120)	Bechium–Tussilago (p. 393)	0	8	1	1	0	9	1	0	0	0	0
Ulmus spp.	Olmo (I–93)	Ptelea–Ulmus (p. 511–512)	0	8	0	4	0	1	1	0	0	0	0
Umbilicus spp.	Ombelico Venere (IV–94)	Cotyledon–Umbilicus veneris (p. 458)	2	23	2	0	0	1	0	2	0	0	0
Urtica spp.	Ortica (IV–96)	Acalephe–Urtica (p. 368)	19	36	5	17	3	6	1	12	1	0	3
Verbascum spp.	Verbasco (IV–106)	Phlomos–Verbascum (p. 543–544)	3	16	2	0	0	8	0	1	0	0	0
Verbena officinalis L.	Verbenaca (IV–62)	Peristereon–Verbena (p. 503)	6	6	6	7	1	3	8	0	0	0	0
Total			759	713	273	262	128	455	84	346	20	55	8

Causal Inference

The estimation of the causal effect is measured as the increment in the probability that a plant taxon is used in contemporary local herbal medicine for a specific use due to Dioscorides or Galen accounting for the confounding effects. The posterior distribution of the causal effect of the two authors for the 87 plant taxa over all three South Italian regions together is summarized in Figure 3-5. The mean effect α (point) along with its 95% credible intervals are reported. These intervals, although located at larger values, are compatible with the results obtained in our previous study (Leonti et al., 2010), and a causal effect of the two authors almost certainly exists for all three regions.

The overall causal effect of Dioscorides' *DMM* (*ex* Matthioli, 1568) on the uses of the 87 plant taxa in the three regions is 27.6% (15.1–51.7%), while the effect of Galen's *DSMF* is 36.4% (14.3–66.2%). *DMM* causally influenced the medicinal use of the 87 plant taxa between 27.3 and 27.9% in all three regions (Figure 3-6). Galen causally influenced popular use of the 87 plant taxa of 26.6% in Campania, 41.6% in Sardinia and 41.7% in Sicily (Figure 3-6).

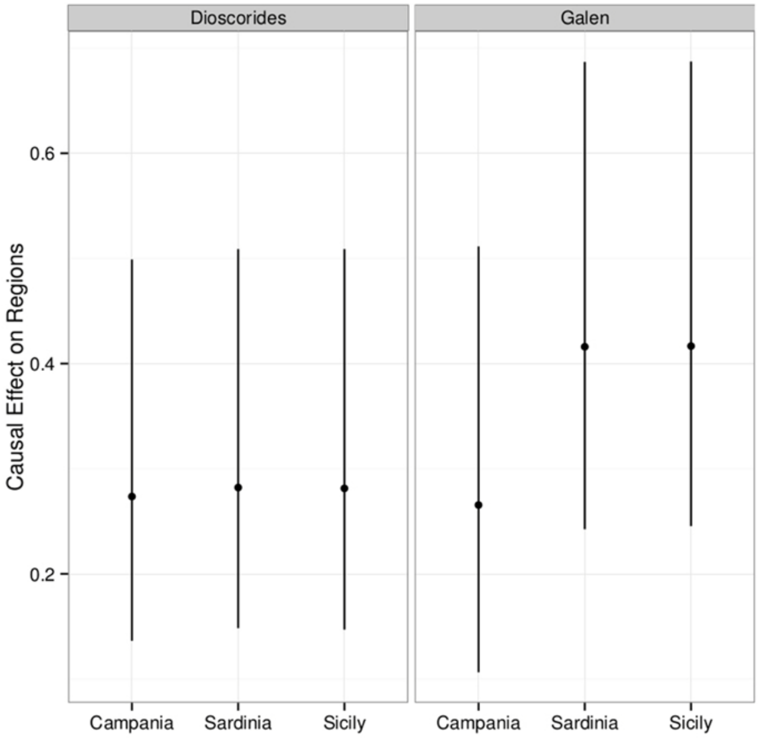

Figure 3-5 Overall posterior distribution of the causal effect of Dioscorides and Galen on the contemporary plant use traits over all 87 taxa, 11 uses-categories and for all three regions together.

The plot shows the mean effect (point) along with the 95% credible interval.

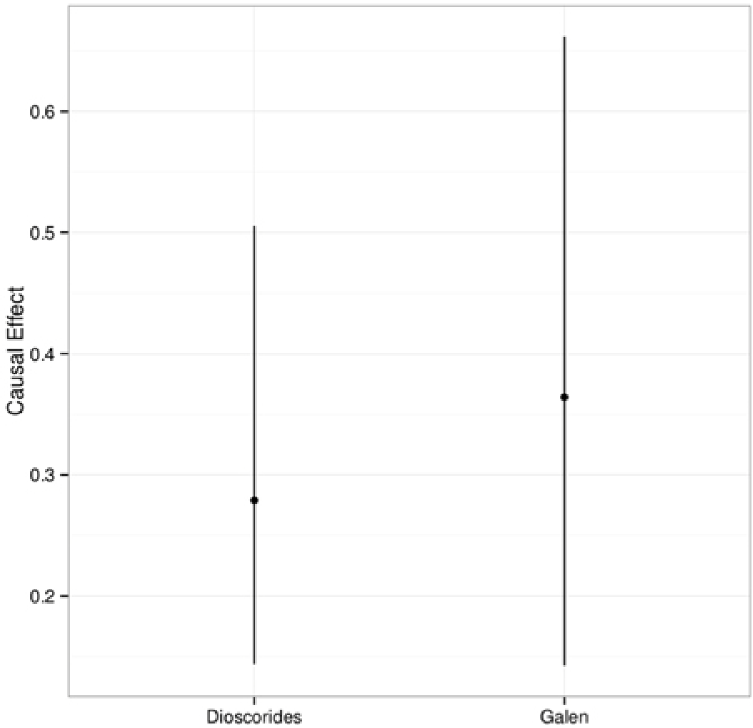

Figure 3-6 Posterior distribution of the causal effect of Dioscorides and Galen on the contemporary plant use traits of the 87 taxa conditioned by the region of Campania, Sardinia, and Sicily.

The plot shows the mean effect (point) along with the 95% credible interval.

Contemporary Traits Not Coinciding with Dioscorides and Galen Cross-Checked with the Content of a Popular Book on Herbal Medicine

Practically all of the most frequently reported contemporary plant use traits not mentioned in Dioscorides' and Galen's works are described in Reader's Digest (1980). Exceptions are few, such as applying parsley (*Petroselinum crispum*) for ear problems and the perceived analgesic properties of *Sambucus nigra*. In fact the emollient and diuretic properties of *Parietaria officinalis* are reported in the popular book, as well as its use against lithiasis and toothache (p. 223). *Rosmarinus officinalis* is recommended for sprains, asthma and cellulitis (p. 252) as well as hair loss (p. 381). The trait of using *Ruscus aculeatus* to treat hemorrhoids and varicose veins is reported on page 243, while the sedative properties of *Crataegus* sp. and its use to treat anxiety is described on page 78. The sedative and calming properties of *Malva sylvestris* and its use to treat bronchitis, asthma, cough, toothache, nervousness and as an eye cleanser, are referred to on page 192, while on page 261 *Sambucus nigra* is recommended for bronchitis and *Papaver rhoeas* praised for its beneficial effects against angina and bronchitis (p. 253). The application of *Tanacetum vulgare* against contusions and strains is recommended on page 283, and the usefulness of *Tamus communis* (syn.: *Dioscorea communis*) for arthritis and contusions is highlighted on page 282. The emmenagogue properties of *Senecio vulgaris* and its use in menstruation problems is explained on page 273, while the febrifuge properties of *Centaurium erythraea* and *Marrubium vulgare* are mentioned on page 106 and 194, respectively.

Discussion

General Analysis

Overall, the present analysis is more reliable than our previous approach (Leonti et al., 2010) because we considered a larger amount of data and included an additional confounding variable. The intervals (Figures 3-5, 3-6), although located at larger values are compatible with our previous results (Leonti et al., 2010). A causal effect of the two authors exists almost for sure for all three regions. In our previous approach we estimated that one out of five plant uses stems directly from Matthioli's work (including the uses mentioned by Dioscorides as well as those recommended by Matthioli himself). This corresponded to a 20% average increment of the probability of finding a plant taxon mentioned for a certain use-category indicated by Matthioli during the sixteenth century. The results of the present analysis suggest, however, that around one in three (Galen) and one in four (Dioscorides) plant uses recorded in the three South Italian regions stem directly from the recommendations made by the two physicians some 2000 years ago. This corresponds to a slightly stronger effect than the one observed for Campania for a smaller set of taxa and the recommendations taken from *DMM* as well as Matthioli's comments.

We assume that the joint recommendations by Galen and Dioscorides equalize interregional citation proportions because of the causal effect we have found with the causal inference approach. In concordance with other studies (Hallpike, 1988; Guglielmino et al., 1995), our results suggest that the transmission of knowledge has been influenced more by cultural determinants than by ecological or geographical factors.

However, Dioscorides has not invented the tradition of writing herbals but was influenced by works of other scholars whom he cites in his work. Dioscorides has taken inspiration and instruction from Sextius Niger and Krateuas, and also from Iollas of Bithynia and Herakleides of Tarentum, while he quotes from works ascribed to Theophrastus and Hippocrates (Singer, 1927; Matthioli, 1967–1970). Galen, in his turn, has acknowledged Dioscorides' authority citing his name several times in *DSMF* (Galenus, 1561; Riddle, 1985). Overall, by reading Dioscorides' and Galen's texts it becomes clear that both report on a perceived cultural consensus of medicinal plant use enriched by their personal experiences.

Cavalli-Sforza et al. (1982) pointed out how oblique knowledge transmission through one or a few teachers creates an increase in trait homogeneity and allows for fast cultural change within a population, but at the same time may lead to greater variation between populations. An effect leading to a similar outcome has been described with models of cultural evolution, which suggest that natural selection favors psychological mechanisms that lead to conformist transmission influencing social learning behavior (Henrich and Boyd, 1998). Adaptive conformist transmission entails the adjustment and alignment of individuals' behavior in concordance with that of other group members, and in a cross-cultural context might explain the maintenance of between-group differences (Henrich and Boyd, 1998). Concerning the context of our research question, however, the three South Italian regions, (Campania, Sardinia, and Sicily), although having experienced distinct historic developments, have gradually grown into a more or less coherent cultural area since the Roman conquest. It can therefore be assumed that the scaling down of cultural barriers facilitated conformist transmission in Southern Italy and promoted the adoption of "new cultural traits."

Impact of the Scientific Sphere on the Frequency of Popular Plant Use Traits

External storage of human knowledge, such as writing, influences technological change, preserves knowledge and allows the transmission of knowledge between populations distant in time and space. At the same time populations adapt their pharmacopeia to the latest scientific progress trying to keep pace with the epidemiological situation and therapeutical needs. The advancements in pharmacology and epidemiology clearly allowed for a more Darwinian perspective on herbal medicine, including the isolation of pure biologically active principles. Globalization and modernization have led to new medical thinking, in both professional and popular spheres, moving away from Galenic humoral theory and the doctrine of signatures. In the course of the introduction of vaccinations and prescription drugs during the early twentieth century, herbal medicine lost its appeal and importance in the more industrialized countries. The turnaround that started some decades ago, accompanied by a changing epidemiology where cancers, cardiovascular and other chronic illnesses superseded infectious diseases, is culminating in the ever-growing popularity of nutraceuticals (Etkin, 2006).

The comparison of antique with contemporary plant uses suggests that hormonal birth control and systematic clinical controls considerably reduced the need and popularity of using herbal remedies in women's medicine. Likewise, herbal remedies are today rarely indicated for the treatment of sensory organs such as the eyes and ears in Southern Italy. For eyes and ears prescription drugs are generally preferred, such as isotonic and sterile eye drops as well as antibacterials, which -notwithstanding their precise indications, are used against all kind of infections, whether bacterial or not. This indiscriminate prescription and use of antibacterial drugs, however, afflicts Italy with a particularly high incidence of methicillin-resistant *Staphylococcus aureus* strains (Porretta et al., 2003; Tiemersma et al., 2004). In fact, the effectiveness of infection therapies are difficult to evaluate on a popular level, as proper immune response usually leads to the elimination of germs and the restoration of health. In such cases, the recovery of the patient may be ascribed to a remedy applied, which at best was ineffective. In this context it has been argued that therapeutically ineffective and therefore repeatedly practiced treatments have a greater chance of being copied and transmitted (Tanaka et al., 2009). However, rarer and less frequently mentioned plant uses such as those to treat eye and ear problems, might also have a higher chance of being replaced or abandoned with respect to more common applications due to random effects (Leonti, 2011). Thus, besides the introduction of real innovations and the creation of new cultural traits cultural changes can occur also through cognitively biased or incorrect knowledge transmission and random processes.

Exchange of Cultural Traits between the Popular and the Scientific Sphere and the Loss of Local Knowledge

Oral and written knowledge influence each other creating what has been described as a feedback loop of knowledge transmission mediated through cultural exchange between popular and science-based knowledge systems (Leonti, 2011). This process was -and is- far from straightforward, and involves modifications of traits, i.e., recombination of plant-uses, as well as the diffusion of completely new traits within the popular and scientific spheres. In terms of quality there is no need to divide between oral and written knowledge transmission (Totelin, 2009) although writing permits knowledge transmission with higher fidelity. However, written transmission of knowledge has a higher quantitative potential and can be traced back in time. It can be anticipated that with increasing magnitude the transmission of plant use traits lies within the domain of the written scientific sphere. Today, apart from biomedicine and evidence-based phytotherapy, a wealth of alternative treatment options, including different herbal medicinal systems, such as Ayurveda or Chinese Medicine, are widely available to the European citizen. This development is paralleled by the correct perception by ethnobotanists that plant use traits involving the local flora are becoming less important on the local level. We assume that high-fidelity knowledge transmission through scripts and advertisement has led to an overall diversification of plant use traits since antiquity at the expense of the medicinal importance of native floras. Ethnobotanists mourn this loss of importance of the local flora for medicinal purposes, claiming a pressing need for the documentation of the remaining knowledge arguing that such information is crucial for local health care, the development of herbal remedies and bioprospecting. However, considering that even contemporary plant uses in Southern Italy not discussed by Dioscorides and Galen can be found in a randomly chosen popular book on herbal medicine from the second half of the twentieth century, such argumentations appear to have a weak basis as most of the knowledge has already been documented. Where and when exactly these traits evolved and to which extent popular books on herbal medicine influenced local herbal practices, goes beyond the scope of this analysis. However, the traits not reported by Dioscorides and Galen are evidently well documented elsewhere.

Cultural Evolution and Evidence-based Medicine

The experimental search for effective natural remedies by individuals and populations is generally referred to as the “trial and error” approach. Especially the emergence of new epidemics (e.g., diabetes, cardiovascular disorders, HIV) and the introduction of “exotic” plant species, guides the popular experimentation with old and new remedies for new and old diseases. As herbal medicine and phytotherapy research are striving to build an evidence base, ethnopharmacology takes popular plant use traits or memes and subjects them to laboratory and clinical testing in order to select for the most beneficial traits. This aspect of cultural mutation and evolution is different from genetic evolution as it arises from problem solving and is directional, purposeful, and non-random with respect to its adaptive consequences (Kronfeldner, 2007; Cardoso and Atwell, 2011). The cognitive capacity of the human mind to select effective and appropriate applications of plants as medicine, adds to the cultural success of such traits or memes, as well as to the fitness of the human population adopting that trait. On the other hand, traits of plant use may become obsolete because scientific progress has led to the development of more effective treatments and preventions, or because the disease has been eradicated. In this sense, a quotation from R. Dawkins: “Nothing is more lethal to certain kinds of memes than a tendency to look for evidence” (1976, p. 198), describes perfectly the goal of evidence-based (herbal) medicine.

Conclusion

We have provided further evidence for how repeated cumulative transmission of cultural traits through written sources shapes consensus on the use of medicinal plants. The teacher-like oblique transmission of Dioscorides' and Galen's medico-botanical treatises, exert a causal and homogenizing effect on contemporary medicinal plant use in Southern Italy. Cumulative knowledge derived from the repeated empirical testing of natural remedies over the past 2000 years in Southern Italy, Europe and elsewhere, have led to a selection of applications, memes or cultural traits with perceived favorable healing outcomes. Evidence-based medicine exposes anecdotal treatment reports to pharmacological testing, chemical analysis and clinical trials, in an attempt to falsify or verify the hypothesis of efficacy. The subsequent divulgence and commercial exploitation of the scientific data adds to the fitness of human cultures and, in a self-reinforcing process, leads to the emergence of new cultural traits at the local level, in turn leading to a homogenizing effect between local, global and scientific medical realities. We conclude that cultural interactions lead to new challenges, which can be approached in a most creative way by mixing cultural traits, which eventually helps to solve problems and may lead to innovation and progress.

Author Contributions

ML together with SC and MC designed the study; LC and PS collected the data and SC together with MC carried out the statistical analysis. ML wrote the paper and all authors commented on and approved the manuscript.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

Translation of Galen's chapters by Ettore Casu and a critical reading of the manuscript draft by Antony Challenger and Michael Heinrich are kindly acknowledged.

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Chapter 4 Classifying diseases and remedies in ethnomedicine and ethnopharmacology

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Abstract

Ethnopharmacological relevance: Ethnopharmacology focuses on the understanding of local and indigenous use of medicines and therefore an emic approach is inevitable. Often, however, standard biomedical disease classifications are used to describe and analyse local diseases and remedies. Standard classifications might be a valid tool for cross-cultural comparisons and bioprospecting purposes but are not suitable to understand the local perception of disease and use of remedies. Different standard disease classification systems exist but their suitability for cross-cultural comparisons of ethnomedical data has never been assessed. Depending on the research focus, (I) ethnomedical, (II) cross-cultural, and (III) bioprospecting, we provide suggestions for the use of specific classification systems.

Materials and methods: We analyse three different standard biomedical classification systems (the International Classification of Diseases (ICD); the Economic Botany Data Collection Standard (EBDCS); and the International Classification of Primary Care (ICPC)), and discuss their value for categorizing diseases of ethnomedical systems and their suitability for cross-cultural research in ethnopharmacology. Moreover, based on the biomedical uses of all approved plant derived biomedical drugs, we propose a biomedical therapy-based classification system as a guide for the discovery of drugs from ethnopharmacological sources.

Results: Widely used standards, such as the International Classification of Diseases (ICD) by the WHO and the Economic Botany Data Collection Standard (EBDCS) are either technically challenging due to a categorisation system based on clinical examinations, which are usually not possible during field research (ICD) or lack clear biomedical criteria combining disorders and medical effects in an imprecise and confusing way (EBDCS). The International Classification of Primary Care (ICPC), also accepted by the WHO, has more in common with ethnomedical reality than the ICD or the EBDCS, as the categories are designed according to patient's perceptions and are less influenced by clinical medicine. Since diagnostic tools are not required, medical ethnobotanists and ethnopharmacologists can easily classify reported symptoms and complaints with the ICPC in one of the “chapters” based on 17 body systems, psychological and social problems. Also the biomedical uses of plant-derived drugs

[4] Published as: Staub, P.O., Geck, M.S., Weckerle, C.S., Casu, L., Leonti, M., 2015. Classifying diseases and remedies in ethnomedicine and ethnopharmacology. Journal of Ethnopharmacology. 174, 514–519.

are classifiable into 17 broad organ- and therapy-based use-categories but can easily be divided into more specific subcategories.

Conclusions: Depending on the research focus (I–III) we propose the following classification systems:

I. Ethnomedicine: Ethnomedicine is culture-bound and local classifications have to be understood from an emic perspective. Consequently, the application of prefabricated, “one-size fits all” biomedical classification schemes is of limited value.

II. Cross-cultural analysis: The ICPC is a suitable standard that can be applied but modified as required.

III. Bioprospecting: We suggest a biomedical therapy-driven classification system with currently 17 use-categories based on biomedical uses of all approved plant derived natural product drugs.

Introduction

Many ways exist to analyse ethnographic field-data. The selection of the most appropriate methodology depends on the focus of a study and the research questions. Usually, at a certain stage of the project, collected data are categorized for an overview and further analysis. Ellen (2006, p. 31) argued that “we cannot think about the world unless we assign it to categories”. Any object or cultural trait can be classified according to different criteria. For instance, a car can be classified based on its colour, engine-power, number of seats or maximum speed. Also cultural traits can be classified according to a variety of parameters. Remedies, for example, can be classified according to body-system disorders and/or the symptoms against which they are indicated, the mode of application, the philosophical-therapeutical frame, organoleptic properties, mode of preparation, availability, and more. Classifying remedies into organ- and symptom-defined categories has a historic legacy. For example, Renaissance physician Matthioli [1501-1578] grouped all therapeutics in his augmented edition of Dioscorides' [1st century CE] *De Materia Medica* based on body parts, symptoms and therapeutical effects, beginning with the head and ending with laxatives and emetics (Matthioli, 1968–1970, 6th Book).

A central objective in ethnopharmacological research is to understand and experimentally assess ethnomedical systems and their medicinal products (Leonti and Weckerle, 2015). With respect to ethnopharmacological field-studies, classification of medicines into use-categories helps to get an overview of the therapeutical diversity. When the numbers of individual use-reports are considered, such classifications can be used as a proxy for estimating the epidemiological situation, i.e. the preponderance of diseases and afflictions within a community.

However, culture defines medicine and disease etiologies vary between ethnomedical systems. For example, the manifestation of anxiety disorders has been shown to be heavily influenced by the sociocultural context (Hofmann and Hinton, 2014). Also effectiveness of medicines and treatments relate to disease etiologies and depend on the sociocultural context (Etkin, 1988). Thus specific cultural context influences illness experience, expression and responses to therapeutic interventions (Nichter, 1992, pp.: 223–259). Therefore, the emic perception and categorisation of illness has to be understood for the development of meaningful use categories and a culturally appropriate classification system (Heinrich et al., 2009). The emic perspective is generally understood to come from within a culture and is opposed to the etic point of view, which is that of an outsider (e.g., a researcher). However, in practise this dichotomy is not static but can be viewed as stages in a dialectic intercourse (see e.g. Headland, 1990; Hickerson, 1992).

Disease concepts and etiologies can be assessed qualitatively through interviews and participant observation, while more or less coherent groups of remedies can help in demarcating and visualising emic categories. The Sierra Popoluca people of southern Mexico, for instance, use the same plant-based remedies to treat fever and headache and *vice versa*, applying them in the same way, i.e. as a body shower. The Popoluca informants generally cited these symptoms together, in the same context. Therefore the emic Popoluca perspective is best reflected with a use-category including fever *and* headache (Leonti et al., 2001). Categorizing the associated use-reports and plant taxa separately, firstly as "fevers" or "infections" and a second time as "analgesics" or "headaches", would not reflect the emic perception and would thus not reflect the appropriate cultural context.

Appropriate use-categories and classification systems also allow for cross-cultural comparisons. While classification systems based on emic use categories may show considerable overlap for geographically proximate and culturally related ethnic groups (e.g. Heinrich et al., 2014), emic use categories of unrelated cultures show poor congruence and might not be suitable for cross-cultural comparative analysis. This would suggest the need for a different approach to compare use-categories between culturally distinct ethnic groups. Generally, biomedically defined standard disease classifications such as the International Classification of Diseases (ICD) by the WHO or the Economic Botany Data Collection Standard (EBDCS) are used to define use-categories in cross-cultural comparisons.

Problem statement

To the best of our knowledge, the suitability of the International Classification of Diseases (ICD) and the Economic Botany Data Collection Standard (EBDCS) for ethnopharmacological and ethnomedical research has never been assessed or discussed in a broader scientific context, although they are widely used. However, what we have come across is a self-evaluation by the Economic Botany Subgroup of the Taxonomic Databases Working Group (TDWG) revealing that those who were not implementing the EBDCS were discouraged "finding the printed version cumbersome and difficult to interpret" (Daphne, 2002). Here, the limitations of the currently used biomedical classification systems for cross-cultural analyses in ethnomedicine and ethnopharmacology are addressed, and an alternative classification system accepted by the WHO, the International Classification of Primary Care (ICPC), presented. Since classification systems and use-categories may also be used as a starting point for selecting remedies for laboratory work, we also introduce a biomedicine informed classification, which applied as baseline data can help to guide drug discovery from ethnomedical sources.

The International Classification of Diseases (ICD) and its limitations for ethnomedicine and ethnopharmacology

The International Classification of Diseases (ICD) by the WHO (http://www.who.int/classifications/icd/en/) distinguishes over 20 different categories. The purpose of the ICD is to be used as a standard diagnostic tool in epidemiology, as defined by the WHO on its website:

"The International Classification of Diseases (ICD) is the standard diagnostic tool for epidemiology, health management and clinical purposes. This includes the analysis of the general health situation of population groups. It is used to monitor the incidence and prevalence of diseases and other health problems, providing a picture of the general health situation of countries and populations".

The structure of the ICD is disease based and has been developed for hospital data systems and is dependant on a precise diagnosis (Users Guide ICPC-2 Plus, 1998). This latter aspect makes it unpractical for ethnopharmacological research, as field-workers do not have the necessary diagnostic devices at their disposal. Moreover, most fieldwork is directed towards the recording of past experiences and events, making diagnostic examinations impossible. The accounts of the informants and the descriptions of medicines do not allow for detecting the causative agent or the etic disease etiology, which would be the basis for the use of the WHO classification system. It is thus difficult if not impossible to apply the ICD to ethnomedical records. Therefore, although the WHO's International Classification of Diseases is an excellent guide for explaining how clinical medicine classifies and distinguishes diseases from symptoms, its practical application for ethnopharmacologists and ethnobotanists is limited.

The “Economic Botany data collection Standard” (EBDCS) and its limitations for ethnomedicine and ethnopharmacology

The so-called “Economic Botany Data Collection Standard” (EBDCS) largely follows the ICD but lacks its diagnostic rigour. It was proposed by Cook (1995) and results from “discussions at the International Working Group on Taxonomic Databases for Plant Sciences (TDWG) between 1989 and 1992” and “provides a system whereby uses of plants (in their cultural context) can be described, using standardized descriptors and terms” (Kew.org Economic Botany Data Standard, http://www.kew.org/tdwguses/).

Besides the lack of a proper clinical or pharmacotherapeutical basis, the EBDCS is a mixed classification system with heterogeneous use-categories, which in some cases adhere to the ICD, and in others combine both disorders and pharmacological effects in a rather imprecise and confusing way. For example, chilblains and frostbites are filed under “muscular–skeletal system disorders” and the use-category “injuries” subsumes abscesses, bites, blisters, burns, wounds and bruises as well as cerebrovascular haemorrhage. Sunburns, however, are classified under “skin/subcutaneous cellular tissue disorders”. Furthermore, the EBDCS proposes “inflammation” as a separate use-category, although inflammation is a symptom associated with different kinds of pathologies ranging from oncological diseases, through autoimmune diseases to all kinds of infections. Including “social uses” as another, separate use category, also makes little sense, as all medicinal uses are “social” by their very nature.

Remarkably, Gruca et al. (2014) suggested that “cultural diseases and disorders”, which they also refer to as “culture-bound syndromes”, and occasionally are referred to as “folk illnesses” (Browner et al., 1988) should be included as a separate medical category in the EBDCS. They suggest that this would “give a more accurate insight into traditional medicine”. As examples for “culture-bound syndromes” the authors cite amongst others “susto” (“fright”; also “espanto”) and “evil eye” (Gruca et al., 2014). These are emotional states, which are treated with medicinal plants but frequently also with rituals and ceremonies (Foster and Anderson, 1978; pp. 65–67, Quinlan, 2010). According to Foster (1951) “a sudden shock, and unexpected encounter with supernatural beings, a fall, or […] fear of death from purely natural causes” may cause “espanto”. If the illness is believed to be caused by spiritual entities such as deities, gods, ghosts, ancestors, or demons, or by spells and black magic, diagnoses are often accompanied by oracles or spiritual sessions involving ritual specialists and healers (Foster and Anderson, 1978). In cases where the cause of illness is attributed to the material world, such as injuries, the diagnosis adhere more to the visible and observable universe. A strict dichotomy does not exist and healing ceremonies appeasing nature gods might be involved in both, personalistic and naturalistic etiological systems (Foster and Anderson, 1978). However, there exists a variety of “cultural syndromes” associated with the manifestation of psychological distress across cultures (Nichter, 2010), which biomedicine would diagnose as “nervousness”, “stress”, “mental illnesses” or “depression” (Quinlan, 2010; Foster and Anderson, 1978). Consequently, lab-based ethnopharmacologists screen plants used against e.g. “susto” for their influence on anxiety disorders (Bourbonnais-Spear et al., 2007). According to the EBDCS such reports would need to be classified as “mental disorders”.

However, not all cultural syndromes are associated with the psychological equilibrium of humans. For example, Berlin et al. (1993) revealed that the Tzeltal and Tzotzil Maya ethnomedical syndrome “Me' winik” (palpitating mass around mid abdomen) corresponds to the biomedical equivalent of gallbladder diseases, which according to EBDCS should be categorized under “Digestive System Disorders”.

In the light of the above, the inclusion of “culture bound syndromes” or “cultural diseases and disorders” into the EBDCS is not necessary: Firstly, psychological disorders are already included under the EBDCS category “mental disorders” (http://www.kew.org/tdwguses/rptLevel1_2States.htm), and secondly, classification mainly relies on symptoms rather than the etiology of diseases and many of the so-called “cultural diseases and disorders” can therefore be classified in biomedical categories. Last but not least “culture-bound syndromes” is a rather out-dated term as every aspect related to health and illness is culture-bound (e.g. Etkin, 1988; Nichter, 2010).

International classification of primary care (ICPC) and its limitations for ethnomedicine and ethnopharmacology

An alternative classification system accepted by the WHO is the International Classification of Primary Care (ICPC; http://www.who.int/classifications/icd/adaptations/icpc2/en/). The ICPC is an empirically designed tool created to classify patient data using the concept of “episodes of care” (Soler et al., 2008). The ICPC was designed by the ICPC working party and published by WONCA (World Organisation of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians) in 1987. The ICPC allows the classification of the three crucial elements of the health care encounter: (i) reasons for encounter, (ii) diagnosis or problems and (iii) process of care (Miller et al., 2009). The ICPC is intended for the use of primary health professionals such as primary care physicians, general practitioners and family physicians providing first-time consultation to patients within a health care system. It is a tool for monitoring and analysing epidemiological data and can be used to inform health services and health economics (User Guide ICPC-2 Plus, 1998). The concept of the ICPC induced a paradigm shift in family practise, away from the practitioner centred view. According to the ICPC approach, the patient's reason for seeking medical help, that is, the presentation of a health problem or disease to a health care provider, should be at the centre of the classification, rather than the diagnosis made by a medical doctor (Lamberts and Wood, 2002 and Soler et al., 2008).

The ICPC has a biaxial structure with 17 chapters on one axis (15 are based on body systems, one concerns psychological problems and one social problems) and 7 components on the other axis (Table 4-1; Miller et al., 2009):

The 17 chapters are: **A**) General and unspecified; **B**) Blood, blood forming organs, lymphatics and spleen; **C**) Digestive; **D**) Eye; **E**) Ear; **F**) Circulatory; **G**) Musculoskeletal; **H**) Neurological; **I**) Psychological; **J**) Respiratory; **K**) Skin; **L**) Endocrine, metabolic and nutritional; **M**) Urology; **N**) Pregnancy, childbirth and family planning; **O**) Female genital system and breast; **P**) Male genital system; and **Q**) Social problems;

The 7 components are: **1**) Symptoms and complaints; **2**) Diagnostic, screening and preventive procedures; **3**) Medication, treatment and procedures; **4**) Test results; **5**) Administrative; **6**) Referrals and other reasons for encounter; and **7**) Diagnosis and diseases (Table 4-1; Miller et al., 2009).

In an ethnomedical context the ICPC components **2**) “Diagnostic, screening and preventive procedures” and **7**) “Diagnosis and diseases” depend on the cultural (emic) disease etiology system and can be compared qualitatively. The ICPC components **4–6** are not intrinsically part of ethnomedical systems but through biomedical health care providers test results (**4**), such as diagnosis of diabetes and infectious diseases are communicated to patients, who although receiving and accepting biomedical care, often rely on their cultural medical system in parallel.

Table 4-1 Biaxial structure of the International Classification of Primary Care (ICPC).

A) General and unspecified; B) Blood, blood forming organs, lymphatics and spleen; C) Digestive; D) Eye; E) Ear; F) Circulatory; G) Musculoskeletal; H) Neurological; I) Psychological; J) Respiratory; K) Skin; L) Endocrine,metabolic and nutritional; M) Urology; N) Pregnancy,childbirth and family planning; O) Female genital system and breast; P) Male genital system; and Q) Socialproblems.

	Components	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
1	Symptoms, complaints																	
2	Diagnostic, screening and preventive procedures																	
3	Medication, treatment and procedures																	
4	Test results																	
5	Administrative																	
6	Referrals and other reasons for encounter																	
7	Diagnosis and diseases																	

The varying degree of complexity we face when categorizing ethnomedical data into disease categories is nicely illustrated with the 7 colour codes, applied to the 17 chapters of the 2nd edition of the ICPC by the Wonca International Classification Committee (WICC). While symptoms and complaints (green) are the least problematic and define the 17 chapters, the categories of infections (yellow) and neoplasms (blue) pose considerable difficulties in an ethnomedical context (www.kith.no/upload/2705/ICPC-2-English.pdf).

Classifying ethnomedical uses – ways forward

The most appropriate way for classifying diseases and remedies based on ethnomedical data largely depends on the research focus. In the following we propose three different approaches (I–III) based on whether the aim of the study is reflecting the emic perception, comparing medical practises across cultures or identifying leads for drug development.

I. Research focus: Understanding local and indigenous medical systems

Different populations and ethnic groups have different cultural perceptions and values. Since medicine is defined by the respective culture, during fieldwork ethnopharmacologists and medical anthropologists aim at understanding the classification of diseases and illnesses from within the culture, i.e. from an emic perspective. Consequently, standardized biomedical models might suppress cultural traits and are of limited value to such research endeavours as the focus lies on *ethno*-pharmacology not on ICD-, EBDCS- or ICPC-pharmacology.

II. Research focus: Cross-cultural comparisons and the search for uniqueness and similarities

Uniform, biomedical classification systems can be useful for cross-cultural comparisons of medicinal floras and medical uses. Field ethnopharmacologist interview traditional practitioners, whose diagnostic procedure usually differ greatly from that of medical doctors. The ICPC is a closer approximation to ethnomedical reality, than the ICD or the EBDCS because the categories are built according to patient's perceptions and are little influenced by clinical medicine. For example, under the umbrella term “Genitourinary System Disorders” the ICD as well as the EBDCS subsume women's medicine, andrology and urological diseases. However, women's medicine and urological problems are particularly broad, well-established categories in ethnomedicine and herbal medicine alike, generally equipped with a specific therapeutical armamentarium. Therefore, it would make more sense to classify women's medicine, andrology and urological diseases separately. The ICPC not only separates women's problems, andrology (“male genital system”) and urology, but differentiates also within women's medicine between “pregnancy, childbirth, family planning” and “female genital system and breast” (Table 4-1; Miller et al., 2009).

For medical ethnobotanists and ethnopharmacologists it should be relatively easy to classify the reported symptoms and patients' complaints as well as the applied remedies with the ICPC by using component 1) “Symptoms and complaints” and component 3) “Medication, treatment and procedures” (Table 4-1). This appears more practicable than applying the ICD or the EBDCS system.

In working towards a classification system suitable for the comparison of ethnomedical records, therefore, we advocate a compromise, suggesting that the ICPC standard be used as a template, which can be modified as required. For example, including a separate category for infectious diseases under “General and Unspecified”, together with the symptoms of fever and chills (http://www.kith.no/upload/2705/icpc-2-english.pdf), might be appropriate for a classification system for ethnomedical records. In fact, due to inter-cultural exchange with the western medical system, some endemic infectious diseases such as malaria, dengue, and sleeping sickness are often correctly identified or known by local healers and laypersons since public health care clinics provide screenings and treatments.

The example given above regarding the symptoms “fever and headache”, classified by the Popoluca into one category, with the ICPC would need to be classified into “General and Unspecified” (fever, A03) and “Neurological” (headache, N01), while “susto” (fright) would need to be classified under “Psychological” (Acute stress action, P02) with the ICPC (see http://www.kith.no/upload/2705/icpc-2-english.pdf). We furthermore showcase the applicability of the ICPC system for ethnopharmacological records through the classification of therapeutic indications made by Dioscorides (*ex* Matthioli, 1968–1970):

The seeds, the root and the herb of the wild and cultivated fennel (*Foeniculum vulgare* Mill., Apiaceae) are recommended for the production of milk (“genera copiosamente latte”), as a diuretic (“provoca ella l’orina”) and to calm pain and problems of the kidney and the bladder (“conferisce a i dolori delle reni, and mali della vesica”; p. 821). Furthermore, *F. vulgare* is indicated for the treatment of [kidney and/or bladder] stones (“rompono le pietre”) and for inducing the menses and expelling the afterbirth (“provoca i mestrui”, “purga le femine di parto”; p. 821). According to the ICPC these reports would need to be classified among “Pregnancy, Childbearing, Family Planning” (Breast/lactation symptom/complaint, W19), among “Urological” (Urinary symptom/complaint other, U29; Bladder symptom/complaint other U13; Kidney symptom/complaint U14; and urinary calculus, U95), as “Female Genital” (Menstruation absent/scanty, X05), and again among “Pregnancy, Childbearing, Family Planning” (Post-partum symptom/complaint oth., W18). With the ICD or the EBDCS, however, the above indications would all be classified among “Genitourinary System Disorders”.

Moreover, since “the remedy” does not stand at the centre of the ICD, EBDCS and ICPC, the manner of its application is not taken into consideration, but for ethnomedical systems it may be useful to use the mode of application as a key for classification. For example, systemic as well as topical forms of applications for haemorrhoids and varicose veins exist in ethnomedical systems and it may thus be meaningful to either classify use-reports or citations among circulatory system or dermatological disorders according to the mode of application.

III. Research focus: Bioprospecting - classifying ethnomedicine into categories as a basis for drug discovery

When selecting local medicines for chemical and pharmacological investigation we generally rely on a detailed description of the application and mode of preparation of the remedies together with an evaluation of the available chemotaxonomic information. In order to direct the local remedies towards the most appropriate biomedical screening systems, a translation of the emic to the etic perspective is required (Leonti and Weckerle, 2015). We argue that the existing biomedical standard classification systems (see 3, 4 and 5) are inadequate for this purpose, because they rely neither on plant-derived pharmacology, nor the associated clinical applications.

We suggest considering the biomedical uses of all approved, plant-derived drugs to develop use-categories suitable for drug discovery. The seminal work by Zhu et al. (2011), which itself is based on Newman and Cragg (2007) surveyed all approved natural product derived drugs, clinical trial and preclinical trial drugs. Below, by way of example, we have classified all clinical and pre-clinical applications of the 225 angiosperm and gymnosperm plant taxa reported by Zhu et al. (2011), which currently contribute to the development of plant-derived drugs into 17 broad use-categories, which by hierarchical taxonomy unite more specific subcategories:

ANT: Antidote (DigiFab, digoxin toxicity) **AND**: Andrology (erectile dysfunction) **CAN**: Cancer (benign prostatic hypertrophy, oncological diseases) **CAR**: Cardiovascular diseases (antiarrhythmic, antihypertensive, antithrombotic, capillary fragility, haemostatic, hypertension, vasodilator) **DER**: Dermatologic disorders (antiacne, antipsoriatic, leukoderma, rubefacient, skin photodamage, vitiligo, vulnerary) **EYE**: Ophthalmic problems (antiglaucoma) **FOO**: Food (antioxidant, flavouring agents, sweetener) **GAS**: Gastrointestinal problems (antihepatotoxic, antiulcer, choleretic, chronic idiopathic constipation, laxative) **GYN**: Gynaecology (abortifacient, oxytocic, uterine haemorrhage) **INF**: Infections (antibacterial, antifungal, antiplasmodial, antiviral, dental plaque inhibitor) **MET**: Metabolic syndromes (Addison's disease, anti-allergic, anti-hyperprolactinaemia, anti-obesity, antityrosinaemia, homocystinuria, immunological–inflammatory and related diseases, lipoprotein disorders) **NER**: Nervous system (ADHD, analeptic, Alzheimer's disease, analgesic, anticholinergic, Parkinson's disease, anxiety and psychosis, cerebral stimulant, major depressive, narcolepsy, neuropathic pain, vascular dementia) **PAR:** Parasites; metazoan (anthelmintic chemotherapy) **POI**: Poisons (insecticide, piscicide) **RES**: Respiratory complaints (antitussive, bronchodilator, expectorant) **SKE**: Skeleto-muscular system (antispasmodic, muscle relaxant, skeletal muscle relaxant) **URO**: Urology (diuretic).

This classification system is derived from biomedical therapy. The specific uses are identical to the ones reported in Zhu et al. (2011) and broadly classified into organ- and therapy-based categories. It is likely that the future will bring further discoveries of plant-derived products with additional uses, which can eventually be classified into new use categories. In the meantime, the current uses and use-categories reflect the present state of clinical applications and form a solid evidence-base, which can inform both natural product research and, when compared to ethnomedical uses, ethnopharmacology.

Conclusions

The answer to the question as to the most appropriate biomedical classification system for ethnomedicine, depends on the context provided by the research purpose. Absolute “one size fits all” standards cannot be appropriate. Focusing on the understanding of local or indigenous medicine warrants an emic or cultural approach (6.I), while cross-cultural comparisons would benefit from adopting the ICPC system because it is patient informed, rather than dependant on clinical examinations and the availability of medical diagnostic devices (6.II). A biomedical therapy driven classification system (6.III) might be instructive for projects focusing on drug discovery from medicinal floras. The most important prerequisite for cross-cultural comparisons is a transparent, coherent and congruent disease classification, based on criteria described in a way that anyone can understand.

Acknowledgements

We are thankful to Antony Challenger for his valuable comments. The research leading to these results has received funding from the People Programme (Marie Curie Actions) of the European Unions 7th Framework programmeFP7/ 2007/2013 under REA Grant agreement no. PITN-GA-2013-606895 – MedPlant.

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Chapter 5 Screening of herbal drugs from *De Materia Medica* for inhibition of fatty acid amide hydrolase

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Abstract
The endocannabinoid system (ECS) is a neuronal lipid signaling network involved in a variety of human physiological functions such as appetite, memory, mood and pain sensation. Today, there is increasing evidence that ECS-modulating compounds are more widespread in the plant kingdom than initially thought. Hence, we performed a systematic study of herbal drugs for inhibition of fatty acid amide hydrolase (FAAH), a major target of the ECS. Since for the discovery of bioactive metabolites directed approaches are more efficient than random screenings, plant species were selected based on traditional knowledge sourced from Dioscorides' *De Materia Medica* (*ex* Matthioli, 1568).

Out of 436 screened herbal drugs, 34 (8%) decreased FAAH activity to 40% or less. Four of strongest hits were *Glycyrrhiza glabra* root (licorice; 2.6%), *Medicago arborea* leaves (12.1%), *Zingiber officinale* rhizome (ginger; 12.4%) and *Anacyclus pyrethrum* root (26.6%). Although all but one of the 34 hits had at least one therapeutic use in a category with a potential link to the endocannabinoid system, specific categories of use were of limited predictivity for the obtained FAAH inhibitory effects. Further, the considerable number of hits obtained from common food plants and spices calls for further research on the role of phytocannabinoids in human diet.

Given the sustained interest in exploiting the ECS for pharmacotherapy, the present screening provides a basis for future research on 1) the distribution of phytocannabinoids in the plant kingdom; 2) the chemical diversity of FAAH inhibitor scaffolds; 3) cannabinomimetic natural products; and 4) the relation of therapeutic uses and FAAH inhibitory activity.

Introduction
Dioscorides' *De Materia Medica* (*DMM*) is one of the most influential historical texts on Euro-Mediterranean pharmacy, summarizing knowledge on the use over 1000 drugs (Riddle, 1985). Historical medical texts have recently entered drug discovery attempts as their contents may inspire the search for novel leads (Adams et al., 2011; Buenz et al., 2004; Holland, 1994). This prompted us to evaluate the herbal remedies in *DMM* using a modern pharmacological approach.

The Endocannabinoid System (ECS) is a neuronal lipid signaling network comprising at least two $G_{i/o}$-protein-coupled cannabinoid receptors (CB1 and CB2), their endogenous ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG), dubbed endocannabinoids (eCBs), as well as several eCB synthesizing, transporting and degrading enzymes (e.g. Di Marzo et al. 1998, Iannotti et al., 2016). Functionally, the ECS is involved in many aspects of mammalian physiology and has thus been implied in various pathophysiologies, including inflammation, neurological and psychiatric ailments, eating disorders, pain and cancer (De Petrocellis et al., 2000; Di Marzo, 2008; Iannotti et al., 2016; Lutz et al., 2015; Mackie, 2006; Matias et al., 2006).

While for decades the phenylterpenoid Δ^9-THC and its derivatives from *Cannabis sativa* L. were the only phytocannabinoids known, recently, several plant species besides hemp were found to produce compounds interacting with the ECS (Gertsch, 2010; Russo, 2016; Sharma et al., 2014). Some of these natural products are *N*-alkylamides (NAAs) from *Heliopsis helianthoides* var. *scabra* (Dunal) Fernald, *Lepidium meyenii* Walp. and *Echinacea purpurea* (L.) Moench; N-acylethanolamines (NAEs), for example found in cocoa seeds and soy beans; isoflavonoids, such as genistein and daidzein; the N-isobutylamide guineensine from *Piper* spp., the chiefly Umbelliferous polyyne falcarinol as well as the widespread sesquiterpene β-caryophyllene (Chicca et al., 2009; di Tomaso et al., 1996; Gertsch et al., 2008, 2010; Hajdu et al., 2014; Leonti et al., 2010; Nicolussi et al., 2014; Thors et al., 2007, 2008). The emerging reports of natural products mediating specific effects on the ECS suggest a more comprehensive search for phytocannabinoids in plants.

Purpose and aims

The present study was conducted with the aim to perform a systematic screening of vascular plants for *in vitro* inhibition on fatty acid amide hydrolase (FAAH), a key target of the ECS. Hereto, the tested plant species were selected based on traditional knowledge, as this search strategy may be more efficient than random approaches in detecting specific pharmacological effects (Ramesha et al. 2011). In order to target plant species that are culturally significant, *De Materia Medica* (*DMM*) was selected as a reference. Due to its thematic coverage of a wide range of (herbal) drugs and health conditions, *DMM* appears to have been written as a guide to general medicine. Hence, the choice of *DMM* as a template for the screening was assumed to ensure the analysis of plants with diverse phytochemical signatures and pharmacological profiles.

Since many of the herbal drugs described in *DMM* are recommended for the treatment of pain, skin inflammation and excrescences, psychiatric disorders and other ECS-related health conditions, the present study aimed to systematically test these drugs for cannabinomimetic effects. Specifically, 436 herbal drugs were screened for *in vitro* inhibition of FAAH, which is a membrane-bound serine hydrolase chiefly responsible for the breakdown of AEA, thereby regulating eCB tone (Cravatt et al., 1996). The specific aims were, 1) to discover herbal drugs previously not known to exert cannabinomimetic effects; 2) to promote research on the chemical diversity of scaffolds of FAAH inhibitor; and 3) to study cannabinomimetic plant natural products; and 4) to investigate the relation of therapeutic uses as described in *DMM* and FAAH inhibitory activity. Moreover, a toxicity screening was conducted to test for unspecific cytotoxic effects.

Material and Methods

Historical source

Quantitative data on the herbal drugs described in *DMM* were sourced from the 1568 commentary edition by Renaissance physician Matthioli (see Chapter 2 for methodological details and the analyzed dataset). The basic units of analysis were individual therapeutic plant uses, which, for the present purpose, were classified into 54 organ- and symptom-based categories of use (Supplementary Table 7-7).

Plant collection

Extensive botanical fieldwork in Europe and the Mediterranean between 2014 and 2016 aimed at collecting all identifiable herbal drugs described in *DMM* (Supplementary Figure 7-3, Table 7-8). For every herbal drug, at least one botanical voucher per plant species together with one or more bulk samples of the mentioned plant organ(s) were collected. Additional plant samples were cultivated in domestic gardens or obtained from commercial suppliers. Plants were identified using the Flora Europaea (Tutin et al., 1968–1993), species names were checked against The Plant List 1.1 (2013 and references therein) and family names follow the Angiosperm Phylogeny Group 4 (APG IV, 2016). Botanical vouchers were deposited at the Herbaria of the University of Geneva (G) and National and Kapodistrian University of Athens (ATHU). Samples were dried at 40 – 60° C and stored in plastic containers for further analysis. For botanical fieldwork in Greece, photography and collection permits (7ΨΞ24653Π8-NMA and 6Ω8K4653Π8-AK7) were obtained from the Greek Ministry of Environment and Energy (Supplementary Figures 7-4 and 7-5).

Phylogenetic tree

A species-level phylogeny of all plant taxa was constructed based on a recently published, ultrametric supertree of land plants (i.e. Embryophytes; Zanne et al. 2014). Species not present in this tree were added by attaching them to the most recent common ancestor (MRCA) of the respective genus or, if absent, the family. Branch lengths of the inserted taxa were adjusted to retain ultrametricity. From this modified phylogeny a tree comprising all analyzed taxa was pruned out. All tree manipulations were done in R (R Core Team 2013) using the packages APE, CAPER, PHYTOOLS and DIVERSITREE (FitzJohn, 2012; Orme et al., 2013; Paradis et al., 2004; Revell, 2012).

Reagents

Compounds and chemicals were of purest possible grade. Anandamide (AEA) and (3-aminocarbonyl[1,1-biphenyl]-3-yl)-cyclohexylcarbamate (URB597) were purchased from Cayman Chemicals Europe. Fetal bovine serum, albumin from bovine serum essentially fatty acid free (BSA), and RPMI-1640 medium were purchased from Sigma-Aldrich (Germany). Analytical grade chloroform, dichloromethane and methanol were supplied by Grogg Chemie AG (Switzerland) and ethyl acetate was obtained from VWR International (Italy). [*Ethanolamine*-1-3H]-AEA (60 Ci/mmol), was purchased from American Radiolabeled Chemicals. MTT (3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide).

Plant extraction

Drug samples (3 g) were extracted in ethyl acetate by overnight maceration (50 ml) and subsequent percolation (100 ml) at room temperature. Solvent was removed using rotary-evaporation (40°C, 240 mbar; Heidolph Laborota 4000-Pump system: PC 3001 VARIO) to obtain dry extracts.

Cell culture

U937 human monocytic leukemia and HeLa cells were purchased from American Type Culture Collection (Manassas, VA) and cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS). Cells were cultured in an incubator at 37 °C with a 5% CO_2 humidified atmosphere.

FAAH inhibition screening

FAAH mediated hydrolysis of [^{3}H]-AEA was determined using U937 cell homogenates (1×10^6 cells/ml). Enzyme activity was assessed by addition of vehicle, URB597 (positive control) or extract in 0.6 µl DMSO to 294 µl homogenate in 10 mM Tris HCl, 1 mM EDTA, 0.1% (w/v) BSA fatty acid free, pH = 8 and incubation for 15 min at 37°C. After, 6 µl of a mixture of AEA plus [*ethanolamine*-1-3H]-AEA (0.5 nM) at final 100 nM was added to 294 µl of the homogenates and again incubated for 15 min at 37°C. The tested concentrations were thus 10 µg/ml for plant extracts and 100 nM for URB597 controls. The reaction was stopped by addition of 0.6 ml ice-cold $CHCl_3$:MeOH (1:1) followed by vigorous vortexing. Phase separation was achieved by centrifugation (10,000 × g) at 0°C for 10 min. Radioactivity of the separated aqueous phase (upper phase; 475 µl) containing the hydrolysis product [^{3}H]-ethanolamine was measured by liquid scintillation counting on a Tri-Carb

2100 TR liquid scintillation analyzer after addition of 3 ml Ultima Gold scintillation cocktail (PerkinElmer). Results are expressed as hydrolysis of tritium substrate in percent of vehicle treated control. Data are reported as mean values of two independent experiments.

Cytotoxicity assay

The cytotoxic potential of the extracts was investigated against a human cancer cell line (HeLa) using the colorimetric MTT assay. For this, HeLa cells (20,000 cells/ml) were suspended in RPMI 1640 medium (supplemented with 10% inactivated FBS) and incubated in 96-well plates (100 µl/well) for 24 h at 37 °C in 5% CO_2 atmosphere. Upon addition of culture medium (100 µl), containing either 50 µg/ml of plant extract or DMSO (control), plates were incubated for another 72 h at 37 °C in 5% CO_2 atmosphere. After removing the supernatant 100 µl of new RPMI medium were added to each well. To start the color reaction, 6.6 µl of a 7.5 mg/ml solution of MTT (3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide) in PBS were added to each well, resulting in a final concentration of about 0.5 mg/ml in the culture medium. After incubation for another 4 h at 37°C in 5% CO_2 atmosphere, the resultant formazan crystals were dissolved in DMSO (200 µl/well). Absorbance intensities were spectrophotometrically determined at 550 nm. The reported percentages express the relative viability of extract-treated cells compared to untreated controls. Data are reported as means of three independent experiments.

Results and Discussion

Overall, 34 out of 436 tested plant extracts (Top34) reduced fatty acid amide hydrolase (FAAH) activity to 40% or less as compared to vehicle treatment. Most of these hits have so far not been reported to produce phytocannabinoids (Gertsch, 2010; Russo, 2016; Sharma et al., 2014). Four of the extracts showing the strongest inhibitory effects were the subterranean parts of *Glycyrrhiza glabra* L. (2.6 %), the leaves of *Medicago arborea* L. (12.1%), *Zingiber officinale* Roscoe. (12.4 %) and the roots of *Anacyclus pyrethrum* (L.) Lag. (26.6%). To visualize the phylogenetic distribution of the measured effects, FAAH inhibitory potential was mapped onto a phylogenetic tree of all tested plant taxa (Figure 5-1).

Glycyrrhiza glabra (Fabaceae)

The strongest inhibitory effects were obtained from the root extract of *Glycyrrhiza glabra* L. (licorice), which decreased FAAH activity to 2.6% (cell viability of 14.5%). Licorice is a herbaceous perennial native to Southeastern Europe and parts of Asia, and is the most well-known member of the genus *Glycyrrhiza*. Like many other species of this genus, licorice is used for a variety of purposes, such as food, flavoring and medicine. So far, about 400 different phytochemicals were identified from *G. glabra*. It contains 2-15% of triterpene saponins, most notably the characteristically sweet glycyrrhizin, whose aglycon moiety is 18β-glycyrrhetinic acid. Further, about 40 different flavonoids (totaling 0.65-2%) were identified, such as the chalcone isoliquiritigenin and the flavon liquiritigenin, and their derivatives, as well as prenylated flavanones, flavanololes, flavones, isoflavones, isoflavanes, isoflav-3-enes and pterocarpanes. Additionally, it contains some volatile compounds (0.04-0.06%), polysaccharides (10%), and coumarins, such as umbelliferone (Wichtl, 2002 and references therein).

Licorice extract showed an inhibitory effect with a potency comparable to that of the synthetic FAAH inhibitor URB597 (100nM). Compounds from licorice which may have contributed to this strong FAAH inhibitory activity are isoflavones such as genistein, daidzein or kaempferol (Kim et al., 2016 and references therein) as these were shown to inhibit FAAH concentration dependently in the low µM range (Thors et al., 2007, 2008). Interestingly, licorice and its constituents have previously been found to interact with the ECS. Specifically, one of its major triterpenoids, 18β-glycyrrhetinic acid, showed inhibition of AEA-mediated Ca^{2+} flux in a concentration-dependent fashion (IC_{50}=1.96; Park et al., 2014).

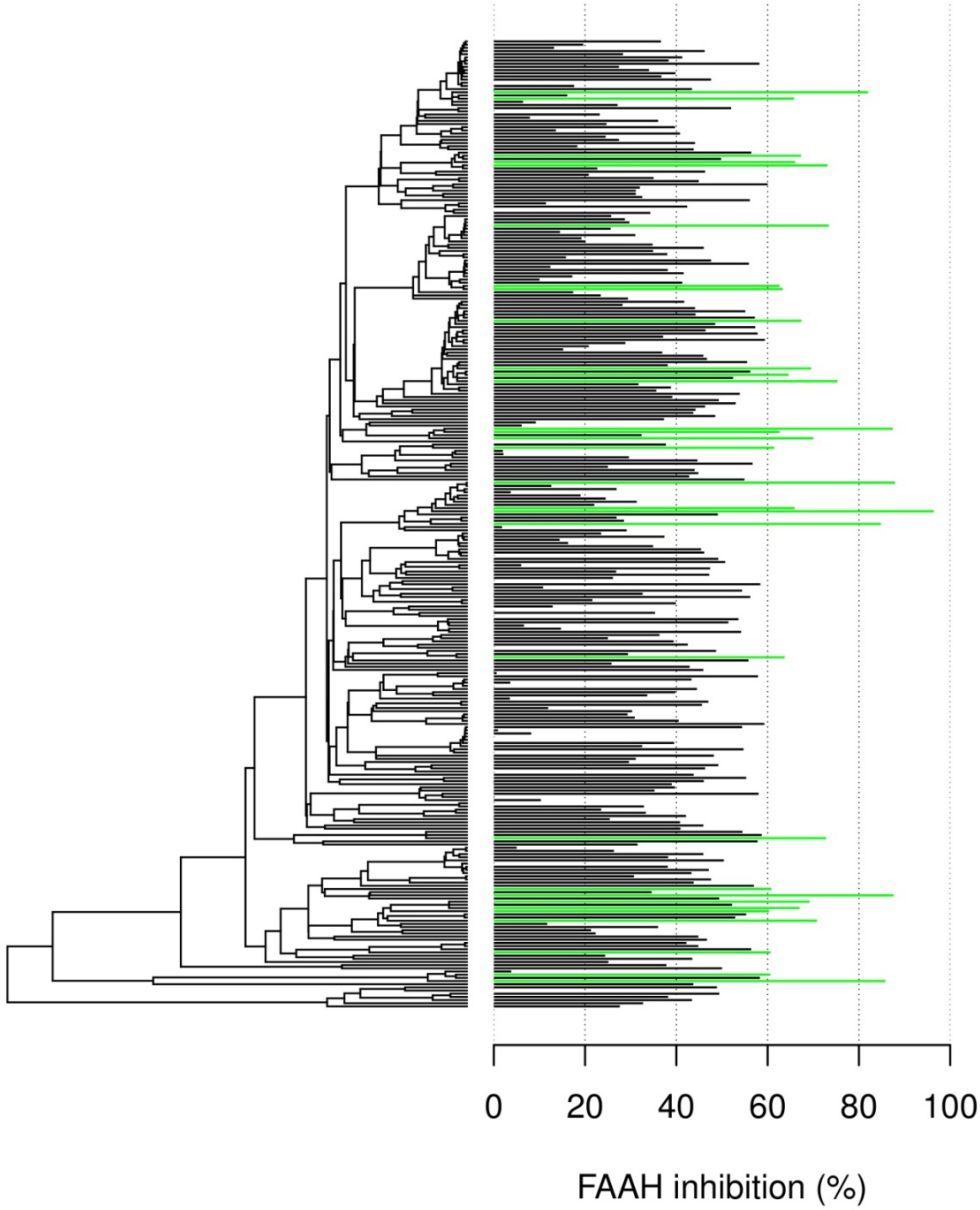

Figure 5-1 Ultrametric phylogeny of all screened plant taxa and FAAH inhibitory effects of their respective drugs.

For plant taxa with more than one tested herbal drug, the drug with the strongest activity was selected. Screening data are reported as means of two independent experiments. Green bars indicate plant taxa with FAAH inhibitory effects of 60% or more.

In *DMM* (Book 3, Chap. 5: *Glicirrhiza*), licorice is recommended for various health conditions: externally applied it is mentioned for the treatment of wounds, problems of the liver and pterygia (i.e. a benign growth of the conjunctiva); internally administered it is indicated against roughness of the trachea, kidney pain, bladder ailments, and chest and stomach inflammations. Insofar that pathologies described in historical texts are comprehensible from a modern perspective (Lardos, 2015), these therapeutic uses - at least in part - may be linked to the therapeutic modulation of FAAH. For example, FAAH inhibition, and the consequent (indirect cannabinomimetic) rise in eCB levels, is a comparably well-explored strategy in the treatment of certain types of pain and inflammation (Schlosburg et al., 2009). Likewise, FAAH inhibition is thought to be a promising pharmacotherapeutic approach in wound healing (Sasso et al., 2016) and to treat cutaneous inflammations (Oláh et al., 2016).

So far, *G. glabra* and its secondary metabolites were demonstrated to exert anti-inflammatory effects via three different pathways (see Asl and Hosseinzadeh 2008, for a review). First, β-glycyrrhetinic acid was shown to inhibit glucocorticoid metabolism in human skin and lung by inhibiting 11 β-Hydroxysteroid hydroxigenase, thus reducing the conversion of anti-inflammatory cortisol into inactive cortisone (Schleimer, 1991; Theelucksingh et al., 1990). Second, glycyrrhizin and glycyrrhetinic acid were found to inhibit 5α- and 5β-reductase activity in rat liver preparations, hence, too, potentially delaying the metabolism of corticosteroids and prolonging the half-life of cortisol (Tamura et al., 1979). Third, crude licorice extract efficiently suppressed eicosanoid and leukotriene formation in cell-free systems, suggesting direct inhibitory activity on both Cyclooxygenase-2 (COX-2) and Arachidonat-5-Lipoxygenase (5-LO) (Herold et al., 2003). Insofar as the herein detected cannabinomimetic activity can be translated into an *in vivo* setting, FAAH inhibition could represent a novel potential mechanism by which licorice and its secondary metabolites exert anti-inflammatory effects.

Medicago arborea **(Fabaceae)**

The second-strongest hit was the leaf extract of *Medicago arborea* L., which reduced [^{3}H]-AEA hydrolysis to 12.1% (cell viability of 71.1%). *M. arborea* is a woody shrub native to the northern half of the Mediterranean basin, where it serves as an important forage plant for small ruminants (Amato et al., 2004). Studies on its phytochemistry identified flavonoids, such as isomyricitin, kaempferol, quercetin, medicarpin and vestitol; triterpene saponins including for instance the glycosides of medicagenic, zanhic acid, hydroxyoleanolic acid, and soyasapogenol B; as well as simple aromatic compounds like ferulic acid; carbohydrates (Bisby and references therein, 1994; Tava et al, 2005).

Just like licorice, also *M. arborea* is a member of the isoflavone-rich Fabaceae (Kaufmann et al., 1997), and thus, also this hit may be conditioned by this class of compounds. Indeed, daidzein, genistein, and structurally related compounds are characteristic of many *Medicago* species, in which they have been detected in total amounts of up to 52.33 mg/kg dry weight (Rodrigues et al., 2014). Furthermore, also in this case, the flavonoid kaempferol may have contributed to the measured FAAH inhibitory effects (Bisby, 1994; Thors et al., 2008). Another explanation may be the presence of *N*-acylethanolamines (NAEs), which, apart from many other plant taxa, also have been found in the genus *Medicago* (Venables et al., 2005). In fact, NAEs are well known to modulate the ECS by reducing FAAH-mediated breakdown of AEA. Specifically, *N*-palmitoylethanolamide (PEA; NAE 16:0) and *N*-linoleoylethanolamine (NAE 18:2) was found to weakly inhibit AEA hydrolysis by substrate competition (Di Marzo et al., 1998; di Tomaso et al., 1996; Katayama et al., 1999). Moreover, PEA has been shown to increase eCB tone in the long term by decreasing FAAH expression levels (Di Marzo et al., 2001). This latter effect, however, is probably not relevant here as [^{3}H]-AEA hydrolysis product was quantified already after 30 minutes in the assay.

In *DMM* (Book 4, Chap. 115: *Citiso*), only two therapeutic uses are reported for *M. arborea*, one of which may be potentially linked to ECS-modulation. According to *DMM*, its ground leaves, externally applied as a bread poultice, are beneficial against early-stage skin tumors (‘*tumori*’). This therapeutic use could theoretically imply indirect cannabinomimetic effects, given that increasing eCB levels were found to decrease growth, proliferation, angiogenesis and metastasis of melanoma tumor cells (Blazquez et al., 2006). Moreover, it was shown that in the treatment of B16 melanoma cells *N*-

palmitoylethanolamide concomitantly applied with URB597 may increase the antiproliferative and cytostatic actions of AEA. Due to the fact that *M. arborea* leaves showed strong FAAH inhibitory effects, together with its potentially high levels of PAE, this herbal drug merits further attention in terms of potential cytostatic and anti-proliferative effects.

Zingiber officinale (Zingiberaceae)

Another strong hit was obtained with the extract of ginger (subterranean parts of *Zingiber officinale* Roscoe.), which diminished FAAH activity to 12.4% (cell viability of 86.0%). Ginger is an herbaceous perennial cultigen, possibly of Indian origin (Mabberley, 2008), and is widely used for its aromatic rhizome in food, cosmetics and medicine.

Ginger contains gingerols, shogaols, 3-dihydroshogaols, paradols, 1-dehydrogingerdiones, diarylheptanoids, and their derivatives. Moreover, it yields about 1-3% of essential oil composed of over 50 components, such as the monoterpenoids β-phellandrene and curcumene, and the sesquiterpenoids α-zingiberene (30–70%) and β-sesquiphellandrene (15–20%). The pungent taste of fresh ginger is primarily due to gingerols (most importantly [6]-gingerol), which are a series of phenols with alkyl chain residues of variable length. However, the pungency of dry ginger is mainly caused by shogaols (mainly [6]-shogaol), which are degradation products of gingerols (Ali et al., 2008 and references therein).

Though yet no compound from ginger has been reported to interact with the ECS, gingerols and shogaols were found to activate transient receptor potential vanilloid 1 (TPRV1) *in vitro* and *in vivo* (Iwasaki et al., 2006). Interestingly, gingerols and shogaols share some striking structural similarities with N-alkylamides (NAAs), such as those from *maca* (*Lepidium meyenii*; Hajdu et al. 2014), particularly regarding their aromatic head and alkyl tail. These NAAs which are also referred to as macamides, were found to inhibit FAAH to various degrees, likely by mimicking its native substrates, such as oleamide (Hajdu et al., 2014; Wu et al., 2013). Hence, it would be interesting to investigate whether gingerols and/or shogaols have contributed the observed FAAH inhibitory effects.

According to *DMM* (Book 2, Chap. 149: *Gengevo*), apart from being mentioned as a food and spice, ginger is also recommended as an antidote, digestive and ophthalmic drug. While the therapeutic use of ginger for ophthalmology could in theory involve ECS-modulation (Cairns et al., 2016), the text passage in *DMM* dealing with this use is too generic and hence, does not allow for any detailed interpretation. Further, also the use of ginger to as a digestive may be partly due to cannabinomimetic effects, given that FAAH inhibition is a potential strategy to treat nausea and gastrointestinal pain and inflammation (Parker et al., 2011; Salaga et al., 2014). However, the digestive and anti-emetic potential of ginger and its compounds has already been well-explored and is thought to be due to the activation of muscarinic acetylcholine and 5-HT receptors by gingerols and shogaols (Giacosa et al., 2015). In terms of the anti-inflammatory properties, gingerols, shogaols, and other constituents were found to weakly inhibit components of proinflammatory signal transduction pathways, such as NF-kB, protein kinase C as well as the inducible NO synthase, cyclooxygenase (COX)-1/-2, and lipoxygenase *in vitro* (Kim et al., 2007; Lee et al., 2009; Nurtjahja-Tjendraputra et al., 2003; van Breemen et al., 2011). Moreover, ginger constituents were shown to concurrently inhibit i/cPLA_2 and prostanoid production, representing yet another potential anti-inflammatory mechanism (Nievergelt et al., 2011). Insofar as the herein detected indirect cannabinomimetic effects of ginger extract are relevant in mediating anti-inflammatory effects *in vivo*, FAAH inhibition may represent a novel potential mechanism, by which ginger and its compounds exert anti-inflammatory effects.

Anacyclus pyrethrum **(Asteraceae)**

Another strong hit was obtained with the extract of the root extract of *Anacyclus pyrethrum* (L.) Lag., which lowered FAAH activity to 26.6% (cell viability of 72.6%). *A. pyrethrum* is a perennial herb native to the Western Mediterranean, and has recently been listed as vulnerable in the 2015 IUCN red list (Rankou et al., 2015). Phytochemically, this plant is mainly known for containing *N*-alkylamides (NAAs) that cause a characteristic tingling sensation when chewed. NAAs are a class of compounds with a comparably well-explored distribution in the plant kingdom (Boonen et al., 2012) and have attracted scientific interest for their modulatory effects on the ECS (Raduner et al., 2006). For example, certain NAAs from *Echinacea spp*., *Heliopsis helianthioides* var. *scabra* and *Lepidium meyenii*, which likely mimic eCBs, were shown to interact with CB1 and CB2 receptors, and FAAH in the low mM range and below (Hajdu et al., 2014). Hence it is very likely that the FAAH inhibitory effects measured here might have been caused by NAAs. According *DMM* (Book 3, Chap. 80: *Pirethro*), the roots of *A. pyrethrum* are useful to treat toothache, chilled and paralyzed limbs and prolonged tremors. Since pain and inflammation are two major pathophysiologies for which FAAH is considered a potential pharmacotherapeutic target (Petrosino and Di Marzo, 2010; Ahn et al., 2009), the rationale behind the therapeutic uses of *A. pyrethrum* may, at least in theory, involve cannabinomimetic effects.

Overall therapeutic use patterns

Next, the medicinal plant knowledge in *DMM* was correlated with the measured FAAH inhibitory effects to test if specific therapeutic indications predict the cannabinomimetic potential of a herbal drug. To this end, all plant uses, classified into 54 categories of use, were matched against a list of pathologies for which FAAH inhibition has been implied as a potential therapeutic strategy (Table 5-1). Figure 5-2 shows the therapeutic uses of the 34 strongest extracts (Top34), in relation to the uses of all screened drugs. All but one of the Top34 herbal drugs had at least one therapeutic indication potentially involving cannabinomimetic effects. However, categories of use with potential link to FAAH inhibitory effects (green bars) did not have higher shares of Top34 plant uses than categories without such a link (gray bars). In terms of relative importance, the most prevalent Top 34 plant uses potentially involving cannabinomimetic activity were various nervous ailments (four uses) and cardiovascular conditions (one use). However, due to the low number of overall plant uses in both categories, stochastic effects are mainly responsible for these high relative frequencies. In absolute numbers, the relevant categories of use comprising the highest above-average use counts were skin infections/inflammations (18 uses), various types of ulcers (14 uses), ophthalmological complaints (14 uses), various forms of pain and inflammation (ten uses), skin injuries (ten uses), headache (six uses), diarrheal conditions (six uses) and intestinal pain (five uses). This clustering of potentially ECS-relevant plant uses among the Top34 hints at that some categories of use may predict the cannabinomimetic potential of herbal drugs. However, as the relative numbers of uses in these categories were only slightly above the average number of Top34 plant uses (9.2%), predictivity was marginal (Figure 5-2). There are several possible reasons for why the plant knowledge in *DMM* served - at best - only as a weak indicator of FAAH inhibitory effects: 1) For most, if not all therapeutic conditions, FAAH or the ECS are not the only possible pharmacological targets. Hence, by screening the extracts against more molecular targets the overlap between the screening data and the therapeutic knowledge in *DMM* may be increased; 2) a considerable share of the plant uses described in *DMM* may be anecdotal and hence devoid of underlying pharmacological bases; 3) the large-scale translation of *in vitro* to human *in vivo* data is not trivial and depends on various factors such as bioavailability, pharmacodynamics and pharmacokinetics; 4) the therapeutic uses described in *DMM* could result from polypharmacological effects and thus may not be not comprehensible through the ‘one drug, one target and one disease’ paradigm (Ulrich-Merzenich et al. 2009).

Table 5-1 Pathologies for which FAAH inhibition has been implied as a potential therapeutic strategy and the corresponding therapeutic categories of use.

Categories of use were grouped based on an organ- and symptom-defined classification scheme (see Supplementary Table 7-7)

Potential therapeutic target	Corresponding category of use	References
Excitotoxic events, including seizures	Epilepsy Various neurological ailments	Naidoo et al. (2011) Naderi et al. (2012)
Abnormal gastrointestinal motility and Inflammatory bowel disease	Gastric function Diarrheal conditions Gastrointestinal pain	Bashashati et al. (2012) Petrosino and Di Marzo (2010) Fichna et al. (2014)
Gastric ulcers	Ulcers	Sasso et al. (2012), Kinsey et al. 2011
Skin inflammation, pruritus	Dermatitis	Schlosburg et al. (2009) Oláh et al. (2016)
Cutaneous wounds	Skin injuries Snakebites	Sasso et al. (2016)
Mental illnesses (incl. anxiety, depression and related disorders)	Psychiatric disorders	Petrosino and Di Marzo (2010) Marco et al. (2015) Ahn et al. (2009)
Nausea, vomiting, anorexia	Gastric function	Parker et al. (2011) Soria-Gómez et al. (2006)
Cancer	Skin excrescences	Petrosino and Di Marzo (2010) Malfitano et al. (2011) Hamtiaux et al. (2012) Blázquez et al. (2006)
Pain and inflammation	Unspecific pain and inflammation Headache/Toothache	Petrosino and Di Marzo (2010) Ahn et al. (2009)
Glaucoma	Ophthalmology	Cairns et al. (2016)
Cardiovascular dysfunction	Cardiovascular disorders	Godlewsky et al. (2010) Carnevali et al. (2015)
Cough	Cough	Wortley et al.(2015)

However, regardless of the specific reason(s) for why specific plant uses described in *DMM* only weakly predicted a drugs' FAAH inhibitory potential, the finding in itself has an important implication for historical ethnopharmacology. Specifically, the failure to find connections between therapeutic uses and screening data casts doubt over one of the key assumptions in this field, namely that historical knowledge may inform the drug discovery process more efficiently than random approaches (Adams et al., 2011; Buenz et al., 2004; Holland, 1994).

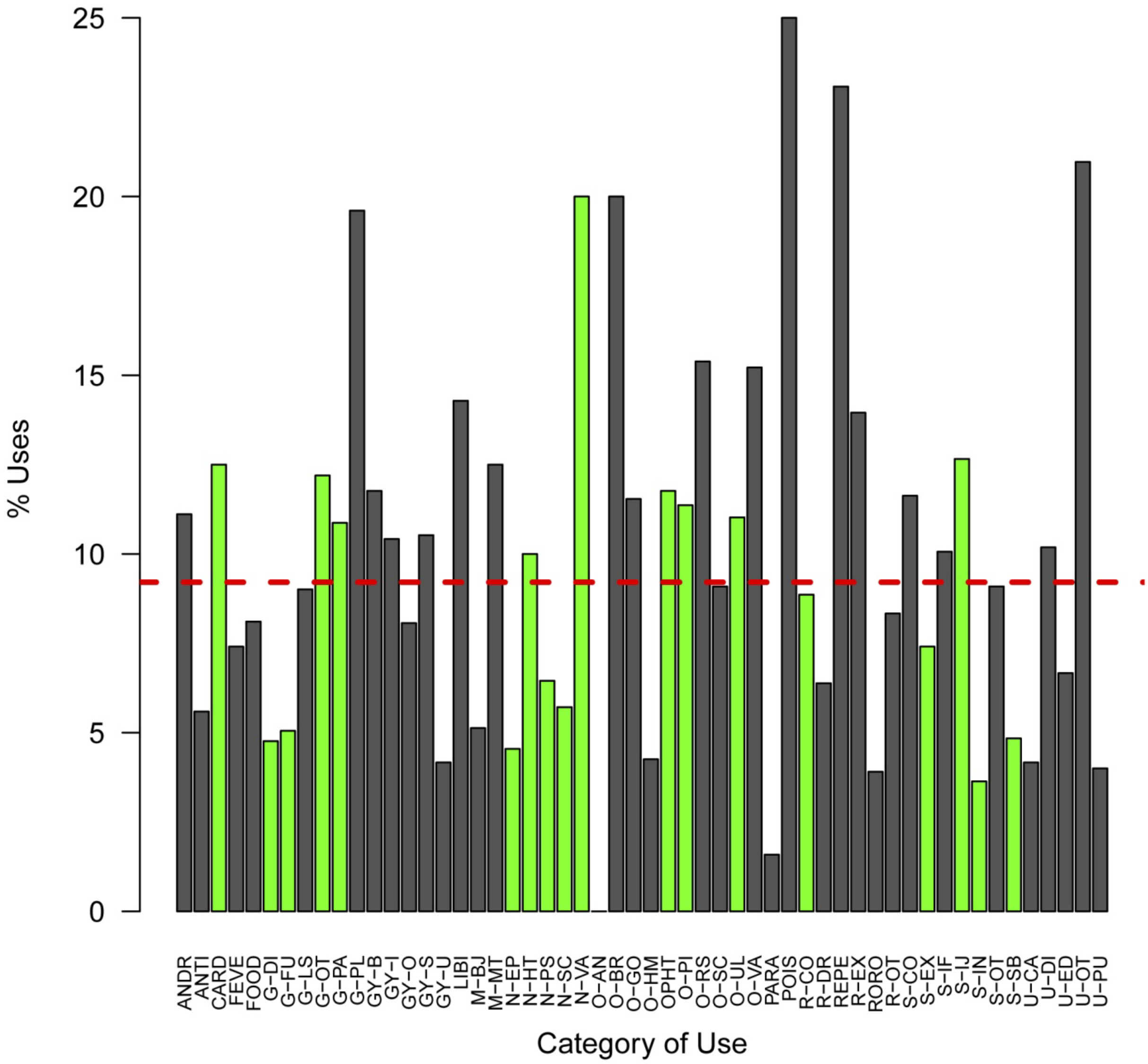

Figure 5-2 Share of the therapeutic uses of the Top34 dugs (N=297) in relation to the uses of all screened drugs (N=3225).

Uses are classified into 54 symptom- and organ based categories of use (see Table 7-7). Bars representing categories of use with a potential link to FAAH inhibition are green. The dashed line (red; 9.2%) indicates the total share of uses accounted for by the Top 34 herbal drugs.

Dietary phytocannabinoids

Another intriguing aspect of this analysis is the considerable number of spices and food plants that showed FAAH inhibitory activity. Apart from ginger and licorice, three additional hits among the Top34 are widely used foodstuffs. This supports the view that dietary fats may play a hitherto underestimated role in ECS modulation (Bisogno and Maccarone, 2014). Some recently discovered dietary phytocannabinoids are 1) the ubiquitous sesquiterpenoid β-caryophyllene, which is a potent CB2-mediated cannabinomimetic in mice (Gertsch et al., 2008); 2) falcarinol, which is found in vegetables like carrots, celery and fennel and shows affinity to both CB1 and CB2 (Leonti et al., 2010); and 3) guineensine from pepper species, which inhibits AEA re-uptake *in vitro* and *in vivo* (Nicolussi et al., 2014).

Given the overarching role of the ECS in regulating food intake and energy balance (e.g. Di Marzo et al., 2009, Di Patrizio and Piomelli, 2012), the emerging role of ECS-modulating plant natural products indicates that humans may have integrated phytocannabinoids into their cooking cultures on purpose. Indeed, a recent review presenting an evolutionary perspective on dietary phytocannabinoids proposed that ECS-modulation might have played an important role for coping with the changing dietary patterns as part of the Neolithic Revolution (Gertsch 2016). Specifically, Gertsch (2016) suggested that during the transition from the hunter-gatherer to the agriculturist lifestyles, the decreasing consumption of fats and increasing reliance on carbohydrates may have required the consumption of compensatory foodstuffs to re-balance CB1/CB2 signaling ratio (i.e. to reduce inflammatory reactions through enhanced CB2 signaling and to decrease the risk of metabolic pathologies through CB1-antagonism). The considerable number of hits obtained from commonly used foods and spices thus calls for further research on the role of phytocannabinoids in human diet.

Limitations

Despite their importance in drug discovery, *in vitro* screenings of crude herbal extracts have some limitations. Plant extracts are typically complex mixtures of compounds that may affect one or more target in additive, synergistic or antagonistic ways (Wagner and Ulrich-Merzenich, 2009). Hence, only further research, such as bioactivity-guided isolation and metabolic profiling may pinpoint compound(s) responsible for the observed effects (Atanasov et al., 2015). Further limitations of the study were that 1) the extracts were only tested at one concentration (10 µg/ml), which does not allow to assess dose-response-relationships; 2) the extracts were screened for only one target within the ECS; and 3) only one bulk sample was tested per herbal drug ignoring the fact that plant chemical profiles typically depend on various genetic, environmental and ecological variables (Anttonen and Karjalainen, 2005).

Further challenges arise from the modern (viz. bio-scientific) medico-botanical interpretation of historical texts, which is notoriously difficult (Lardos, 2015; Touwaide, 2010). Here, two particularly relevant issues were the identification of pre-Linnaean plant descriptions, and the interpretation of ancient disease terminology. Although both of these aspects may have affected the analyzed therapeutic knowledge to some degree, previously proposed methods were followed to ensure the reliability of the generated data (cf. Staub et al., 2016).

Conclusions

The endocannabinoid system (ECS) is an emerging neuromodulatory system implied in a variety of pathophysiologies. Fatty acid amide hydrolase (FAAH) is an important target of the ECS, hydrolyzing endocannabinoids (eCB) and thus regulating eCB tone. Here, 34 of 436 screened plant extracts decreased FAAH activity to 40% or less, suggesting that cannabinomimetics are much more widespread in land plants than previously thought. Since the majority of the hits are new, this screening stresses the need for further research on the pharmacology, phytochemistry and evolution of phytocannabinoids in plants. As the tested herbal drugs were selected based on traditional knowledge, their therapeutic uses were analyzed for their predictive value as indicators of FAAH inhibitory potential. Although all but one of the 34 strongest hits had at least one therapeutic use in a category with potential link to FAAH inhibition, specific categories of use were, at best, only weak predictors of the measured FAAH inhibitory effects. Finally, the considerable number of hits obtained from food plants and spices, supports the view that phytocannabinoids likely play an underestimated role in human food intake and energy balance.

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Chapter 6 Flavors of the past: Chemosensory selection of herbal drugs in European tradition

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Abstract

Taste and smell have emerged as important criteria for the selection of medicinal plants. Yet, reports on how flavor cues encode therapeutic information about herbal drugs are fragmentary. By using Dioscorides *De Materia Medica* (*ex* Matthioli, 1568) as a model pharmacopoeia, we systematically tested how plant chemosensory features influence the knowledge on herbal drugs in European tradition.

Experimentally assessed chemosensory profiles of 697 herbal drugs derived from 404 plant species were analyzed with previously surveyed data on their therapeutic use. A Bayesian model for multivariate categorical data was fitted to test for statistical dependencies.

The results confirm previous research suggesting that plant chemosensory features have guided the compilation of *De Materia Medica*. We reiterate the view that chemosensory cues are important criteria for the selection of food and medicinal plants, supporting and expanding specific flavor use-links reported in the literature. Moreover, plant flavor bouquet complexity appears to drive therapeutic use complexity, what represents a hitherto disregarded phenomenon in medicinal plant selection.

Prospective studies might profile an equivalent set of “non-medicinal” plants to elucidate if herbal drugs having specific flavors are selectively chosen from the environment. Moreover, it might be worthwhile to explore Dioscorides’ system of drug classification using the presented data. Finally, we propose that future studies might adopt a phylogenetic framework to account for evolutionary non independence among plants, and to test if plant chemosensory properties are constrained to evolutionary plant lineages. These approaches could shed more light on the development of pharmacopoeias, historical concepts of medicinal plant classification and may highlight interesting candidate species that warrant examination in the laboratory.

Introduction

The perception of environmental chemicals is important for the survival of every living organism (Harborne, 1993). In humans, chemosensory abilities have been shaped largely by the niches of our hominid ancestors and, in particular, by the nutrients they sought (Breslin, 2013). As omnivores, we encounter a wide range of potential foods and thus, reliable detection of noxious or deteriorated substances is vital (the omnivore’s dilemma; Rozin and Todd, 2016). Similar to human food choice, the selection of plants for medicine may be grasped as the search for beneficial (i.e. therapeutic) metabolites and the concurrent avoidance of toxins (Brett and Heinrich, 1998; Casagrande, 2000). Indeed, chemosensory features are used by various cultures not only to identify medicinal plants but also to evaluate plants in terms of their therapeutic potential (Ankli et al., 1999; Barbulescu, 2015; Brett, 1998; Casagrande, 2000; Etkin, 1988; Frei et al., 1998; Geck et al., 2017; Gollin, 2004; Heinrich, 1998; Johns, 1990; Leonti, 2002; Messer, 1991; Shepard, 2004; Weimann and Heinrich, 1998). While chemosensation is essentially a physiological process driven by genetic and environmental factors, the perception and interpretation of chemical cues largely depends on individual and cultural backgrounds (e.g. Classen et al., 1997; Melis et al., 2015; Prutkin et al., 2000; Shepard, 2004; Sorokowska et al., 2014). Hence, the chemosensory selection of herbal drugs has basically a dual nature: From a chemical-ecological perspective, olfactory and gustatory cues may indicate presence of specific classes of compounds, while from a semantic perspective, interpretations of such cues may shape medical belief, and through mnemonic association, facilitate the transmission of therapeutic knowledge (Bennet, 2007; Brett and Heinrich, 1998; Casagrande, 2000; Etkin, 2006; Leonti, 2011; Shepard, 2004).

The European Pharmacopeia and the use of herbal medicine have been influenced largely by Greco-Roman medical scripts, their medieval Arabic interpretations, and Renaissance commentaries (Mann, 1984; Urdang, 1951). Arguably one of the most influential and comprehensive medico-botanical texts in European tradition is *De Materia Medica,* written by Dioscorides of Anazarbos (Asia Minor; 1st century CE; Riddle, 1980). In about 800 chapters Dioscorides monographed over 600 different kinds of plants, 35 animals and 90 minerals and summarized what was considered efficacious medicine (Riddle, 1971). To compile the treatise, Dioscorides is thought to have relied on a system of ‘drug affinity’ (Riddle, 1985), which appears to loosely follow therapeutic, taxonomic, organoleptic and other principles (Scarborough, 2013; Touwaide, 1998).

Previous studies provided crucial insights into the chemosensory selection of medicinal plants, yet left several methodological issues unaddressed. For example, some approaches were based on only small datasets such as in terms of herbal drugs, plant uses and/or sensory attributes (e.g. Casagrande, 2000; Pieroni and Torry, 2007), what limits generalizations about entire medicinal floras. Other studies relied on rudimentary or no explicit sensory methodology (e.g. Messer, 1991; Weimann and Heinrich, 1998), or did not assess flavor data experimentally (e.g. De Medeiros et al., 2015), limiting the validity of the data. Another problem relates to ‘retrofitting’ or ‘circular logic’, which may occur when both plant flavor and use data are obtained from the same primary source, such as books or local informants. ‘Circular logic’ can cause epistemological problems as it may lead to the documentation of only preconceived or ideal typical flavor-use-links, which primarily fit with prevalent medical theory. The problem can be exemplified with, but is not limited to, the study by Gilka and Barbulescu (2015), who studied three Ayurvedic standard books and correlated the taste and ethnopharmacological actions (EPAs) of herbal drugs described therein. Based on several strong associations between specific plant tastes and actions, the authors concluded that “Ayurveda theory of relationships between taste (*rasa*) and EPAs (*karman*) is valid” (Gilca and Barbulescu, 2015:473). Such an interpretation from an emic (i.e. cultural) perspective is fine, though the finding that each *rasa* encodes specific healing properties (*karman*) reveals little more than standard Ayurvedic theory (Srivastava, 2013:195). However, when the researchers conclude that the findings might also be of use for bioprospecting, it gets problematic, because the analyzed taste and EPA data were not collected independently and are thus inherently biased by ‘circular logic’. Put in other words, it is reasonable to assume that in the employed Ayurvedic textbooks, *rasa* data were brought into line with *karman* data, and vice versa, and hence, cannot reasonably be grasped outside of Ayurvedic theory. Therefore, we argue that only experimentally assessed chemosensory data can overcome ‘circular logic’ in this context, and provide data that are significant beyond the emic perspective.

Purpose and Aims

The present study aimed to rigorously test how plant taste and smell shaped knowledge on the use of herbal medicine in European tradition. Hereto, Dioscorides' *De Materia Medica* (*ex* Matthioli, 1568) was selected as a model pharmacopoeia, providing quantitative knowledge on herbal drugs. To base the analysis on chemosensory data that are independent of the knowledge described in this treatise, plant taste and smell properties were experimentally assessed by means of a trained sensory panel.

The research questions were:

1) How do specific chemosensory properties of herbal drugs correlate with specific therapeutic uses?

2) How does overall chemosensory complexity of herbal drugs correlate with their overall use profile complexity?

Addressing these questions is important for several reasons. First, many herbal drugs described in historical scripts are still in use today (dal Cero et al., 2014; De Vos, 2010; Lardos et al., 2011; Leonti et al., 2009, 2015), and thus insights into their past selection and classification may help to better contextualize modern phytopharmacy (Heinrich, 2006; Helmstädter and Staiger, 2014). Second, chemosensory properties provide clues to plant secondary metabolites, which may inform phytochemical and pharmacological research (Beauchamp et al., 2005; Brett and Heinrich, 1998; Shepard, 2004). Third, a better understanding of how cultures select medicinal plants sheds more light on the mechanisms that drive the evolution of the pharmacopoeias (Leonti, 2011).

Materials and Methods

Text source

Knowledge on herbal drugs was extracted from *De Materia Medica* (hereafter referred to as *DMM*) in a previous survey of Renaissance physician Matthioli's 1568 commentary of the treatise (see Chapter 2 for details). In brief, Matthioli's translation was chosen as a proxy for Dioscorides' text because (I) unlike the current standard edition (Wellmann, 1906–1914), Matthioli (1568) facilitates the identification of the often ambiguously described plants; (II) Matthioli's authority resulted in practical yet qualified interpretations of the Dioscorides' text; and (III) the text is written in a modern language (Italian) and thus easily comprehensible to readers without any knowledge of Latin or Ancient Greek. Specifically Matthioli's edition from 1568 was selected because it is easily available in facsimile and one of Matthioli's later and hence, repeatedly revised versions of the text. The present analysis relied on the variables of 1) plant taxon, 2) plant part and 3) category of use, as presented in Chapter 2. Moreover, therapeutic uses were re-classified into 54 more specific organ- and symptom based categories of use to allow for more relevant predictions (Supplementary Table 7-7).

Plant collection

Extensive botanical fieldwork in Europe and the Mediterranean between 2014 and 2016 aimed at collecting all herbal drugs putatively described in *DMM* (Supplementary Table 7-8). Fieldwork included the collection of at least one botanical voucher per species together with one or more bulk samples of the plant organ(s) that have therapeutic properties. Since the identification of historical (viz. Pre-Linnaean) plant descriptions is often ambiguous (e.g. Reveal, 1996), drug collection was restricted to (one of) the most plausible species per chapter (see Lardos et al. (2011) for an adoption of the 'label species' concept in the context of historical ethnopharmacology; Linares and Bye, 1987). Plant material that could not be collected in the wild was either cultivated in domestic gardens or obtained from commercial suppliers. Gathered material was identified using the Flora Europaea (Tutin et al., 1968–1993), species names were checked against The Plant List 1.1 (2013 and references therein) and family names follow the Angiosperm Phylogeny Group 4 (APG IV, 2016). Botanical vouchers were deposited at the Herbarium of the University of Geneva (G) and the Herbarium of the National and Kapodistrian University of Athens (ATHU). Samples were dried at 40 – 60° C and stored in plastic containers for further analysis.

Chemosensory analysis

Chemosensory profiles of collected herbal drugs were experimentally assessed using Conventional Profiling (ISO 11035). This is an intersubjective assessment technique for the standardized evaluation of sensory attributes for a given set of samples. Sensory evaluation took place at the Hospital of *San Giovanni di Dio* (Cagliari, Italy) during a period of 5 months in 2016. The panel consisted of 11 healthy Caucasian volunteers (6 males / 5 females; age: 29.6±6.7). Working language was Italian. All panelists were familiarized with sensory panels, procedures and techniques. Based on a subset of all samples, four initial training sessions were held to develop a set of descriptive terms on which all panelists agreed. As part of this training, hedonic (e.g. “good” or bad”), self-referential (e.g. “minty” for *Mentha* spp.) and infrequent terms were excluded to reduce subjectivity and to increase discriminative power of the analysis. Moreover, closely related terms (e.g. “astringent” and “tannic”) were pooled to reduce attribute redundancy. The resulting set of sensory attributes consisted of 26 externally defined chemosensory descriptors, which were used for the sensory modalities of both smell and taste (Table 6-1). For simplicity, the terms astringency, sliminess and woodiness, which are primarily describing qualities of texture, were assumed to be chemosensory properties. The possible attribute intensities for descriptor ranking were: absent, weak, medium and strong. However, due to statistical model choice (see below), herein, attribute intensities were analyzed as binary absence-presence data.

Sample material for sensory evaluation was labeled with random three digit codes and randomly assigned to individual panelists. Samples (0.1 to 2 g) were presented in identical plastic containers of 125 ml and served at room temperature. For each sensory trial a separate ballot sheet was used for attribute ranking (Supplementary Figure 7-6). Panelists were instructed to first smell and then taste the sample, to spit the sample out, to rinse the mouth with drinking water and to take breaks between consecutive samples.

Table 6-1 Chemosensory descriptors, their definition and English meaning.

Descriptors were used for the sensory modalities of smell (O) and/or taste (G).

Modality	Code	Descriptor	English gloss	Reference
G / O	ACID	aspro / acido / agro	sour	lemon
G / O	AFFU	affumicato	smoky	smoke
G / O	AMAR	amaro / amarognolo	bitter	coffee beans
G / O	AMID	amido	starchy	rice
G / O	AROM	aromatico / speziato	aromatic	rosemary
G	ASTR	astringente / tannico	astringent	oak aged wine
G / O	BALS	balsamico / eterico / canforato	ethereal	eucalyptus
G / O	BRUC	bruciante / piccante	hot (like chiles)	chili peppers
G / O	CALD	caldo	warming	chocolate
G / O	DOLC	dolce / dolciastro	sweet	sugar

G / O	ERBA	erbaceo / clorofilla	herbal	herb
G / O	FLOR	floreale / fiorito	floral	rose
G / O	FRUT	fruttato / agrodolce	fruity	orange
G / O	LEGN	legnoso	woody	wood
G / O	LETA	letame / stalla	like manure	manure
G / O	MUFF	muffa / fungo / umidità	moldy	humidity
G / O	MUSK	muschiato / ambrato / incenso	musky	nard
G / O	NOCI	di noci	nutty	walnut
G / O	PAGL	paglia / fieno	strawy	straw
G / O	PUNG	acuto / pungente / pizzicore / frizzante	pungent	ginger
G / O	PUZZ	puzzolente / sgradevole	unpleasant	excrement
G / O	RINF	rinfrescante	refreshing	mint
G / O	SALT	salato / umami / brodo	salty / umami / broth	salt
G / O	SAPO	sapone / profumo / deodorante	soapy	soap
G / O	TERR	terroso / bosco	earth	earth
G	VISC	viscido	mucilaginous	mucous

Statistical analysis

To test for statistical dependencies, a Dirichlet process mixture of products of multinomial distributions model (DPMPM) was fitted to the data. This is a nonparametric Bayesian model for multivariate unordered categorical data (Dunson and Xing, 2009; Si and Reiter, 2013). The DPMPM was chosen to adopt a rather general approach, providing results that are conditioned by the observed data without the need for the infinite re-sampling as commonly done in non-Bayesian inference. We consider the DPMPM appropriate as it can deal with large frequency tables, which arise from the crossing of many multilevel categorical variables. We are interested in estimating the conditional probability, denoted π, of some of the crosses between two levels of two categorical variables, given all possible crosses of the collected data. This model is designed to use a prior distribution with full support on the space for all πs, so that variable dependencies are not restricted *a priori*.

To elucidate how specific chemosensory properties predict medicinal plant use, we estimated the conditional probabilities of an herbal drug being recommended for some use, given some sensory attribute. Further, the Cramér's V statistic (Cramér, 1946:282) was computed to determine how much of variance in the therapeutic data (dependent variables) is explained by specific chemosensory attributes (independent variables). Cramér's V is a normalized Chi-Square metric that varies from 0 (no association) to 1 (full association) and was calculated by averaging over the predictive posterior probability distribution of the cell counts. All estimations have been done using 60000 Gibbs sampling steps, hence reported means (of π and Cramér's V) have a standard error of $1/\sqrt{(60000)}= 0.004$.

In a second step, the model output was used to test if herbal drugs with more complex chemosensory properties also tend to have more complex therapeutic use profiles. Hereto, the number of sensory attributes used to profile a herbal drug was regressed against the number of use categories and the total number of uses it is mentioned for. The reported numbers of descriptors and categories per drug express mean values sampled from the posterior distribution of all π. Statistical analyses and plotting were done using R and several add-on libraries (R Core Team, 2016; Venables and Ripley, 2002; Wang et al. 2016; Wickham, 2011).

Ethics and legal issues

Sensory analysis was performed in accordance with the Declaration of Helsinki (World Medical Association, 2013) and the ethics guidelines of the Institute of Food Science & Technology (2015). All human subjects were informed about the aim, scope and procedures of the study and gave written informed consent. Moreover, the Ethics Committee of the University Hospital of Cagliari approved the study design and procedures (Supplementary Figure 7-7). For botanical fieldwork in Greece, photography and collection permits (7ΨΞ24653Π8-NMA and 6Ω8K4653Π8-AK7) were obtained from the Greek Ministry of Environment and Energy.

Results

Chemosensory profiling

Chemosensory properties of 697 herbal drugs deriving from 404 plant species were profiled in 4026 sensory trials, with an average of 366±177 trials per panelists and 5.8±1.3 trials per drug. Overall, the sensory modality of taste received slightly more (10892) descriptor rankings than smell (8594). In terms of taste, bitter was the most frequent descriptor (1497 rankings), followed by herbal (1105), aromatic (758), pungent (684) and woody (675); while for smell, aromatic (1021), herbal (1006), woody (536), musky (532) and fruity (515) were most commonly selected (Figure 6-1).

To study how specific taste and smell features (hereafter jointly referred to as flavors) determine herbal drug use according to *DMM* we estimated the conditional probability for each category of use, given that the herbal drug has a specific chemosensory property (Figure 6-2). Chemosensory attributes explained about 4% of the therapeutic data (indicated by Cramèr’s V). Differences in conditional probabilities were most pronounced with sweet, fruity, nutty and starchy flavors, astringency and mucilaginous taste (lower third of the dendrogram on the left). In turn, the categories of use with particularly distinct probabilities were cough, food, gastric function, otolaryngology, diarrheal conditions, diuretics, antidotes, various skin disorders and ulcers (right half of the upper dendrogram).

Uses of food plants showed comparably high conditional probabilities for fruity, salty, starchy and sweet flavors as well as acid and nutty taste. Likewise, the related category of gastric function had rather high probabilities for sweet and fruity flavors as well as nutty taste. Plant uses against diarrheal conditions were strongly predicted by astringency as well as fruity, sweet, starchy and woody flavors. Further, astringency, together with dungy taste were moderate predictors for drugs to *staunch* vaginal discharge (i.e. menstrual and other vaginal effluxes), but conversely, remedies to *induce* menstrual fluxes and abortive drugs had moderate probabilities for aromatic, balsamic, hot, musky, refreshing, pungent, soapy, floral, smoky and warm flavors. In turn, antidotes were chiefly predicted by hot and smoky smells and dungy tastes and to moderate extent by aromatic, pungent, musky and refreshing flavors. Otolaryngological remedies had particularly high probabilities with astringency and mucilaginous taste. Further, mucilaginous taste also had comparably high probabilities for anti-ulcer, various dermatologic ailments and cosmetic uses, the latter of which was also moderately predicted by nutty taste.

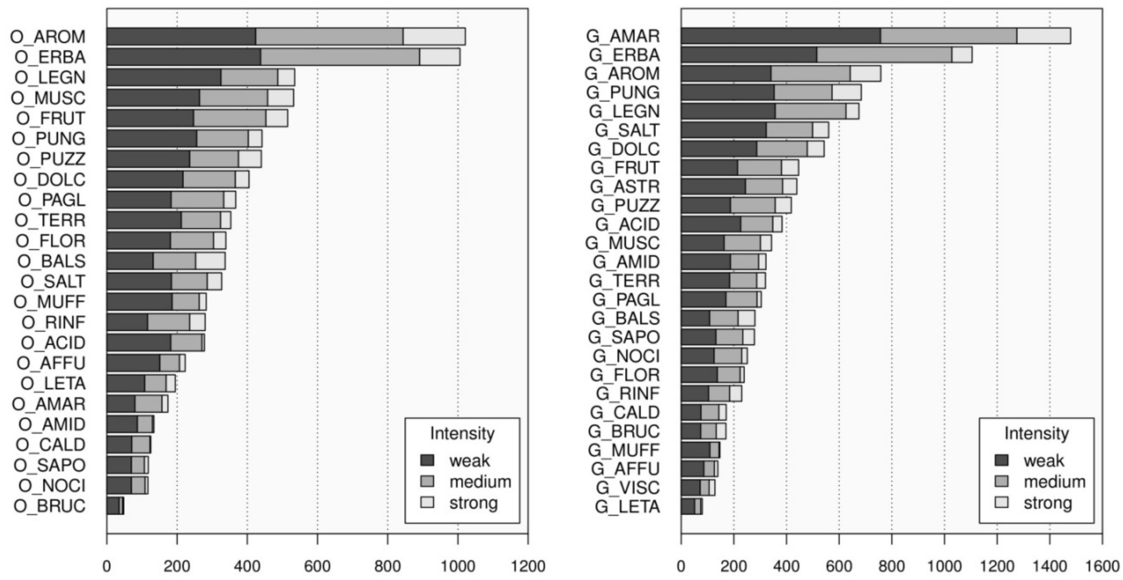

Figure 6-1 Total number of attribute rankings per sensory descriptor for the modalities of smell (left) and taste (right).

Descriptor codes are abbreviated following the legend of Table 6-1.

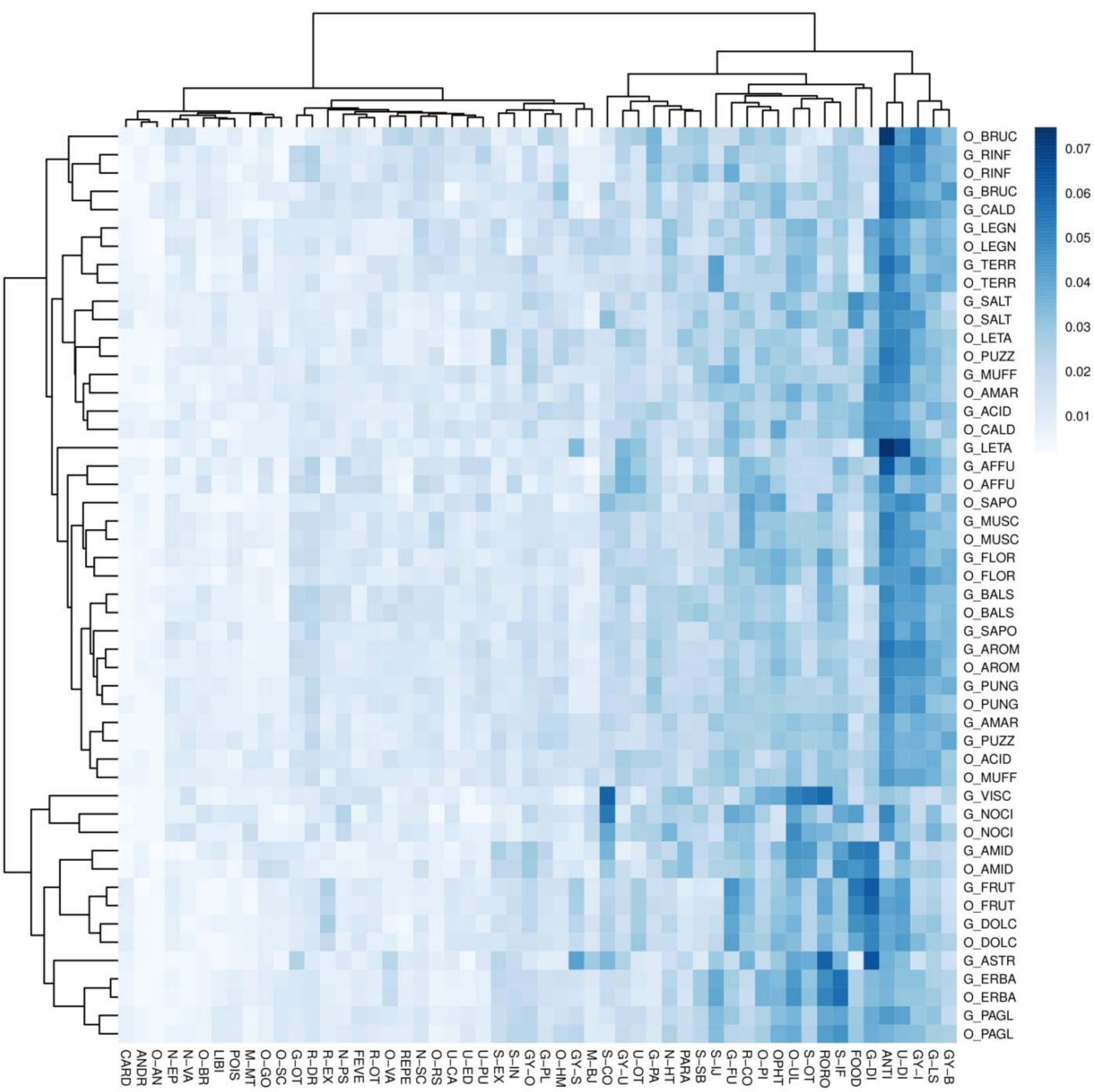

Figure 6-2 Heatmap depicting conditional probabilities of herbal drugs being mentioned for some category of use (bottom), given a certain chemosensory feature (right).

Cluster dendrograms illustrate relative similarities among sensory attributes (left) and categories of use (bottom). Abbreviations for descriptors and categories of use follow the legends of Table 6-1 and Table 7-7, respectively.

In contrast to these examples of high predictivity, some categories of use had particularly low conditional probabilities for specific attributes. For instance, food plants were largely devoid of astringency, whereas anti-diarrheal remedies almost never elicited hot tastes. Further, bitter and unpleasant tastes were largely unpredictive of any therapeutic category of use.

In spite of these intriguing links between the plant flavor and use, specific chemosensory attributes explained only about 4 % of the therapeutic data. Therefore, in a second step, chemosensory profile complexity was regressed against overall use complexity, to test if the chemosensory richness of herbal drugs (regardless of specific attributes) influences their overall therapeutic profiles (regardless of specific uses). Two regressions showed that herbal drugs with more complex tastes and smells accounted for both more (R^2= 0.43; Figure 6-3a) and more diverse uses (i.e. mentioned in more different categories; R^2= 0.9; Figure 6-3b).

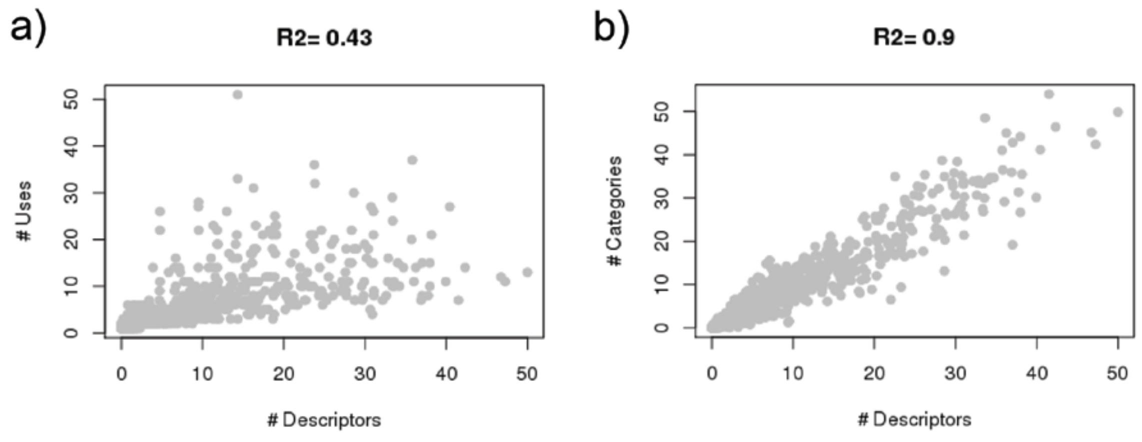

Figure 6-3 Regression of the number of chemosensory attributes used to profile herbal drug against the number of categories of use and the total number of individual uses they are recommended for.

Herbal drugs with more complex flavor bouquets accounted for both more (a) and more diverse uses (i.e. in more different categories; (b)). The reported values express mean numbers of chemosensory attributes or therapeutic uses sampled from the posterior distribution of all conditional probabilities.

Discussion

By systematically analyzing chemosensory profiles of 697 herbal drugs together with their therapeutic use, we revealed interesting chemosensory principles of drug classification that seem to have partly guided the compilation of *De Materia Medica*. Overall, the identified links between plant flavors and specific use reiterate the notion that chemosensory properties are important criteria in the selection and classification of medicinal plants. Bitter taste and aromatic flavors were by far the most frequent chemosensory attributes, which is in line with previous research on traditonal pharmacopoeias (Ankli et al., 1999).

Chemosensory cues structure therapeutic use

Food plants were well predicted by acid, fruity, nutty, salty-brothy, starchy and sweet flavors. These flavor-use links are comparably well-known principles in human food choice: The selection of sweet, starchy foods likely reflects the need for caloric intake; the preference for salty items ensures electrolytic balance; and the drive for sour and fruity aliments is hypothesized to guarantee Vitamin C supply (Breslin, 2013). Some stereotypical examples are the fruity-sweet fruits of *Crataegus azarolus* L. and *Mespilus germanica* L.; starchy legumes and cereals, such as rice (*Oryza sativa* L.) and lentil (*Lens culinaris* Medik.); nutty-tasting poppy seeds (*Papaver* spp.), walnuts (*Juglans regia* L.) and almonds (*Prunus dulcis* L.); as well as various salty-brothy-tasting parts of *Allium* spp., *Apium graveolens* L. and *Crithmum maritimum* L. Notably, astringency was virtually non-predictive of food plant uses, possibly because astringent secondary metabolites typically function as feeding deterrents (Bate-Smith 1972; cf. Gottlieb, 1995). Notably, bitter taste was largely absent with plants in this category, despite the importance of bitter green leafy vegetables in contemporary Mediterranean diet (Nebel et al., 2006).

Similar to uses of food plant, sweet and fruity flavors also predicted remedies in the category of gastric function (i.e. anti-flatulent, appetizing, digestive, or emetic uses). This overlap largely reflects that in *DMM* food plant monographs often include specific health benefits (functional food), and illustrates the fuzzy distinction between ancient dietetics and pharmacology (Totelin, 2015). Two examples in this continuum are the fruits of *Celtis australis* L. (Book IV, Chap. 135) and *Prunus domestica* L. (Book IV, Chap. 138), which, apart from being edible, also have constipating and laxative properties, respectively.

Further, anti-diarrheal remedies were strongly predicted by astringency and fruity, sweet, starchy and woody flavors. Some examples include starchy rice (*Oryza sativa* L.) and lentils (*Lens culinaris* Medik.), sweet-fruity grapes (*Vitis vinifera* L.) and peaches (*Prunus persica* (L.) Batsch.) as well as the fruity-astringent fruits of date palm (*Phoenix dactylifera* L.) and service tree (*Sorbus domestica* L.). The preference for fruity remedies to treat diarrheal conditions may partly mirror the beneficial effects of fruit-derived pectin on stool volume and quality (Rabbani et al, 2001). The selection of sweet and starchy anti-diarrheals, in turn, could be based on the positive action of sugars (e.g. glucose) on water absorption from the intestinal lumen. Specifically, as glucose is transported across the intestinal epithelium via Na+-glucose symports, salt is concomitantly absorbed and water follows osmotically (Field, 2003). Moreover, the application of astringent antidiarrhoeals is a well-established principle in ethnomedicine (Ankli et al., 1999; Frei et al., 1998; Gollin, 2004; Heinrich, 1998; Leonti, 2002) and Western phytotherapy (Schulz et al., 2004:340) and likely reflects the soothing action of polyphenols (i.e. tannins and proanthocyanidins) on irritated or inflamed intestinal membranes. Astringency was also predictive of anti-ulcer and otolaryngological remedies as well as cosmetics and drugs to staunch vaginal discharge Likewise, these uses may be due to the binding, antihemorrhagic and disinfecting properties of polyphenols. Typical astringents include the barks and herbs of *Pistacia lentiscus* L., *Quercus ilex* L. and *Tamarix* sp. Conversely, drugs to *induce* menstrual bleedings and fluxes, together with obstetric remedies had moderately high probabilities for aromatic, balsamic, hot, musky, refreshing and warming flavors. Characteristic examples are cinnamom (*Cinnamomum* spp. bark), labdanum (*Cistus ladanifer* L. exudate), pepper (*Piper nigrum* L.), white mustard seeds (*Sinapis alba* L.) and cardamom (*Elettaria cardamomum* (L.), Maton fruits), which are rich in essential oil. This clustering of odoriferous remedies for gynecology may relate to the ancient Greco-Roman medical belief of the “wandering womb”, which was considered the cause of various pathologies and which could be treated by returning the uterus to its proper position through the use of either attracting (fragrant) or repelling (fetid) remedies (Slavney, 1990:14). Further, the reliance on aromatic, essential-oil containing remedies in traditional midwifery is a widespread trait and may be explained through variety of pharmacological, psychological and social effects (Ankli et al., 1999, Zumsteg and Weckerle, 2006).
Particularly interesting were antidotes, as these had particularly high probabilites for hot, smoky and manure-like flavors. Examplary drugs are the hot-smelling ginger (*Zingiber officinale* Roscoe.), pepper (*Piper nigrum* L.) and fringed rue seeds (*Ruta chalepensis* L.), the smoky-tasting subterranean parts of *Cyperus rotundus* L. and *Rheum rhaponticum* L., as well as manure-flavored *Valeriana celtica* L. roots and *Athamanta cretensis* L. seeds. Antidotes were also moderately predicted by other ‘salient’ attributes, such as aromatic, musky, floral, balmy and pungent flavors. Altogether, this is in support of Norton (2006), who found that many herbal ingredients of *mithridatum*, a famous compound antidote from the 1st century BCE, are strikingly odoriferous.

Bitterness is commonly considered an allegory of medicine (Johns, 1990). Yet notwithstanding, bitter taste was virtually non-predictive of any category of use, despite, or maybe because it was the most frequently selected attribute (Figure 6-1). This is not too surprising, given that bitter taste can be elicited by a plethora of secondary metabolites (Rodgers et al., 2005; Wiener et al., 2012) and mediated via about 25 different bitter receptors (Behrens and Meyerhof, 2006). This finding is in agreement with Casagrande (2000), who found bitter plants in the Tzeltal Maya pharmacopoeia not to be correlated with any particular therapeutic use. Casagrande (2000) hypothesized that this might be due to the lack of resolution in human taste abilities in differentiating bitter phytochemicals. In indirect agreement, studies on other indigenous group reported bitter remedies to be variously used as antidotes, in obstetrics and against cough, diabetes, gastrointestinal disorders, snakebites, pain and fever (Ankli, 1999; Casagrande, 2000; Frei et al., 1998; Heinrich, 1998; Leonti, 2002; Weimann and Heinrich, 1998). This blurriness in the therapeutic interpretation of bitterness among different cultures may reflect 1) the broad chemical and hence pharmacological spectrum of bitter secondary metabolites (Ankli, 1999); 2) cross-cultural differences in healing philosophies (Shepard, 2004); or 3) differences in study design (e.g. sampling size; cf. Casagrade, 2000). In any case, whether the frequency of bitter tasting drugs in *De Materia Medica* (Table 6-2) is due to their general abundance in the environment, or due to their specific selection cannot be elucidated based on the present data. Ankli et al. (1999), who studied medicinal plant uses among Yucatec Mayan communities, reported that medicinal plants were equally likely to be bitter as non-medicinals.

Another striking aspect is that, although bitterness is canonically assumed to indicate toxins (Glendinning, 1994), not even the category of poisons (e.g. comprising *Aconitum napellus* L., *Nerium oleander* L. and *Veratrum album* L.) had an elevated conditional probability for the attribute of bitter taste. Yet, many strongly bitter herbal drugs, although not cited as poisons in *DMM*, actually do have considerable toxic potential from a modern perspective (Frohne and Pfänder, 2004; Wink, 2009). This suggests differences in ancient and modern conceptions of toxic or dangerous substances.

Table 6-2 Strongly bitter herbal drugs and some of their bitter principle(s)

Family	**Herbal drug**	**Bitter principle**	**Reference**
Apiaceae	*Smyrnium perfoliatum* L. root	sesquiterpene lactones	Gören and Ulubelen (1987)
	Thapsia garganica L. root	sesquiterpene lactones	Andersen et al. (2015)
Asphodelaceae	*Aloe* sp. exudate	anthracene derivatives: aloin	Schelton (1991)
Asteraceae	*Achillea millefolium* L. herb	sesquiterpene lactones	Wichtl (2002)
	Arctium lappa L. leaf	sesquiterpene lactones	Machado et al. (2012)
	Tanacetum parthenium (L.) Sch.Bip. herb	sesquiterpene lactones flavonoids: quercetin	Pareek et al. (2011)
Capparaceae	*Capparis spinosa* L. subterranean parts	flavonoid glycosides, rutin, quercetin	Sher and Alyemeni (2010)
Cucurbitaceae	*Citrullus colocynthis* (L.) Schrad. fruit	cucurbitacins	Rehm et al. (1957)
	Ecballium elaterium (L.) A.Rich. root	cucurbitacins	Rehm et al. (1957)
Gentianaceae	*Gentiana lutea* L. root	secoiridoids: gentiopicroside, swertiamarin, amarogentin; disaccharides: gentiobiose	Wichtl (2002)
Lamiacaeae	*Teucrium polium* L. herb	diterpenes: picropolin	Malakov et al. (1979)
	Ajuga chamaepitys L. herb	diterpenoids: ajugapitin, chamaepitin	Coll and Tandrón (2008)

	Marrubium vulgare L. seeds	diterpenoids: marrubiin	Knöss et al. (1997)
Papaveraceae	*Chelidonium majus* L. root	alkaloids: sanguinarine, chelidonine	Tomè and Colombo (1995)
	Glaucium flavum Crantz root	isoquinoline alkaloids: glaucine, magnoflorine, sanguinarine	Wink (2009)
Salicaceae	*Salix alba* L. bark	salicin	Palo (1984)
	Populus alba L. bark	salicin	Palo (1984)
Solanaceae	*Mandragora officinalis* Mill. root	tropane alkaloids: hyoscyamine, atropine, scopolamine	Hanus et al. (2005)
Verbenaceae	*Verbena officinalis* L. root	iridoid glycosides: verbenin and verbenalin	Xu et al. (2010)

Flavor bouquets structure therapeutic use complexity

Apart from links between specific flavors and categories of use, also overall chemosensory bouquets of herbal drugs emerged as important drivers of therapeutic plant use (Figure 6-2). This implies that drugs with strong smells and tastes are more often and more diversely used in herbal medicine because of overall chemosensory salience. Similarly, Ankli et al. (1999) and Leonti et al. (2002) found that among two independent indigenous communities plants with salient chemosensory features were more often considered medicinal, than plants without any particular smell and/or taste.

From a chemical-ecological perspective, the connection between flavor and use profile complexity suggests that, apart from specific chemosensory cues, the overall flavor bouquet of a herbal drug may provide humans with an rough idea about its phytochemical signature and, as a corollary, its overall therapeutic potential. In this context, prospective studies might investigate the presented data in the light of apparency theory (Feeny, 1976), which posits that plants that are more ‘apparent‘ to herbivores tend to produce more quantitative chemical defenses (e.g. tannins and lignins), whereas ‘non-apparent‘ species will rather invest in qualitative allelochemicals (e.g. alkaloids and terpenoids). From a historical perspective, the correlation between chemosensory and use profile complexities highlights the therapeutic significance of aromatic drugs in European medical tradition. Herbal drugs that showed both multifaceted chemosensory as well as therapeutic profiles were: sweet flag (*Acorus calamus* L.), spikenard (*Nardostachys jatamansi* (D.Don) DC.), labdanum (*Cistus ladanifer* L.), black cardamom (*Amomum subulatum* Roxb.), chaste tree seeds (*Vitex agnus-castus* L.) and *Thymbra capitata* (L.) Cav. Indeed, it is well-known that these and other strongly odoriferous substances, also referred to as *aromata*, played a major role in the ancient Mediterranean dispensatory, being important constituents of perfumes, incenses (*thumiamata*), ointments, flavored wines, preservatives (*condimenta*), medicines and spices (Miller, 1969:3). Particularly emblematic of their therapeutic pluripotency is that *aromata* were often used as antidotes and thus formed key ingredients of panaceas like theriac and mithridate (Norton, 2006). However, by the 18th-19th centuries and possibly in relation to advances in modern chemistry and pharmacy, the belief in the efficacy of antidotes was declining, what resulted in their removal from the European dispensatory (Norton, 2006; Jackson, 2002). This notwithstanding, many herbal antidotes, and *aromata* in general, remained important in the West as spices.

The selection of medicinal plants with appealing, salient or repugnant flavors is not just due to pharmacological reasons but possibly also because of their semantic potential. Sensory features of medicinal plants are well-known for being important in the cultural construction of medical efficacy (Etkin, 1988). Moreover, plant organoleptic properties may also function as mnemonic devices, facilitating the transmission of associated therapeutic plant knowledge (Ankli, 1999; Bennet, 2007; Leonti et al., 2002). Given the sustained interest in the food-medicine continuum (Etkin, 2006; Leonti, 2012; Totelin, 2015), the organoleptic, therapeutic and historical links between ancient antidotes and present-day spices merits further attention in ethnopharmacology.

Limitations

This study has several limitations: First, the used set of descriptors may not have appropriately covered the entire chemosensory variability. For example, some panelists expressed difficulty in profiling the typical taste of Legumes based on the employed set of descriptors. Second, due to time constraints, only a limited number of replicates could be assessed per herbal drug. However, even though this may have reduced overall statistical power, the chosen statistical model is specifically designed to cope with problems related to item non-response (Xi and Reiter, 2014). Third, for each herbal drug only one representative bulk sample was profiled, which is few given that plant chemical profiles depend on a range of genetic, environmental and ecological variables (Anttonen and Karjalainen, 2005). Forth, since sensory analysis extended over multiple months changes in the sensory quality of the samples (e.g. due to storage) was inevitable. Likewise, in some cases, drying of the material resulted in the loss of salient chemosensory features (e.g. the characteristically caustic properties of *Euphorbia* spp. latex). However, drying and storage were assumed to have affected the outcomes only marginally, first, because the employed sensory descriptors were rather broad and second because this would have most likely affected statistical power, but not the revealed flavor-use-links *per se*.

Of course, many factors beyond chemosensory properties may have shaped the plant knowledge contained in *DMM*. Other sensory modalities, such as vision and touch, were shown to be important in medicinal plant selection (Leonti, 2002; Moerman and Jonas, 2002; Shepard, 2004). Moreover, prevalent medical philosophies, such as humoral theory or the doctrine of signatures, likely have influenced which remedies were considered efficacious (Bennet 2007, Effert and Grethen 2016). Other aspects that may have shaped the European botanical pharmacopoeia include historical knowledge exchange (Lardos and Heinrich 2013; Touwaide and Appetiti 2013), cultural migration history (van Andel et al. 2014), the available flora (Moerman et al. 1999), local prevalent diseases (Cohen and Armelago 1984) and plant ecology (e.g. Stepp and Moerman, 2001).

Conclusions

This study revealed a sophisticated chemosensory system of drug classification that seems to have guided the compilation of *De Materia Medica*. The results reiterate the view that chemosensory cues are important criteria in the selection of plants for food and medicine, supporting and expanding specific flavor use-links reported in the literature. Further, flavor complexity of herbal drugs is quantitatively shown to drive therapeutic use complexity, which represents a yet unexplored phenomenon in medicinal plant selection. Methodologically, this study represents a first attempt to systematically profile herbal drug by the means of a trained sensory panel.

Prospective studies might test if herbal drugs in European tradition differ in their sensory features from “non-medicinal” plants to elucidate if plants with specific flavors are deliberately selected from the environment. Also, it might be interesting to explore how plant chemosensory features and therapeutic uses relate to Dioscorides’ own classification system of ‘drug affinity’. Finally, we propose that future studies may adopt a phylogenetic framework to account for evolutionary non independence among the tested herbal drugs and to trace secondary metabolites more effectively. Such an approach could shed more light on historical concepts of medicinal plant classification and may highlight interesting candidate species that warrant examination in the laboratory.

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Chapter 7 Appendix

Supplementary material of Chapter 2

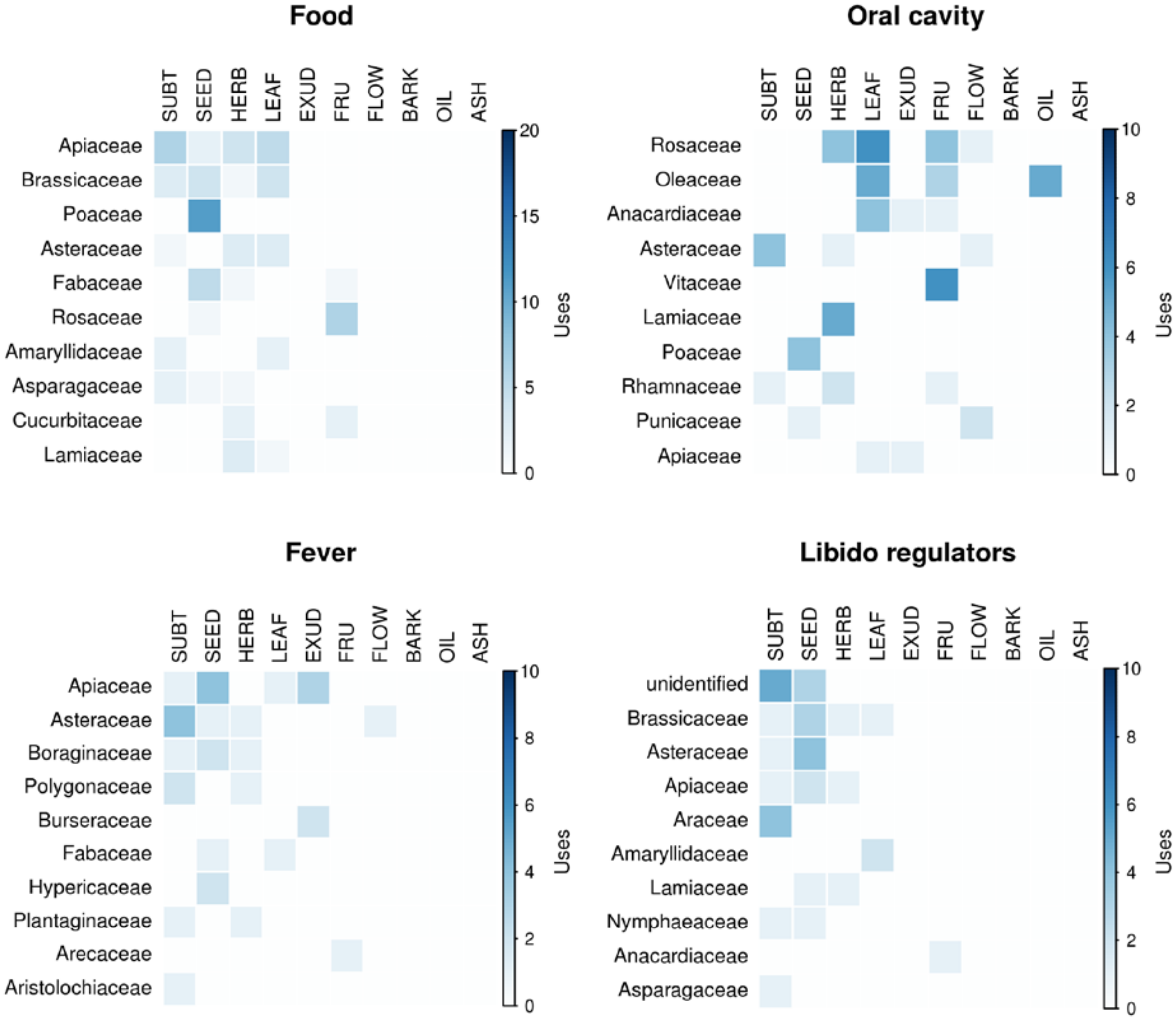

Figure 7-1 Quantification of uses for the categories of food, oral cavity, fever and libido regulators. Plant part abbreviations follow the legend of Figure 2-3.

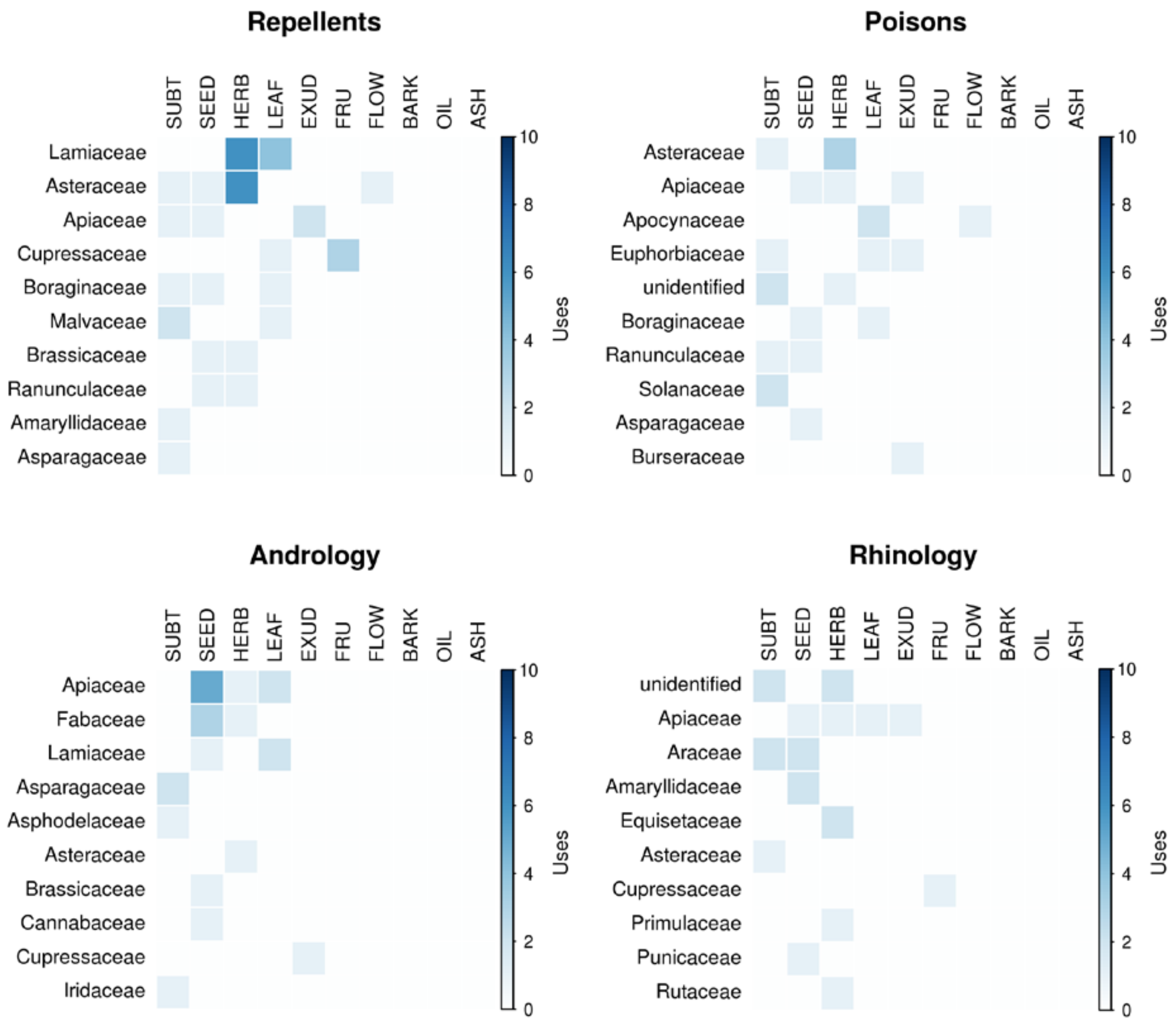

Figure 7-2 Quantification of uses for the categories of repellents, poisons, andrology and rhinology. Plant part abbreviations follow the legend of Figure 2-3.

Table 7-1 Compact list of the vascular plant uses described in *De Materia Medica* (*ex* Matthioli, 1568).

[1] Family names follow the APG IV (2016) classification. [2] Generic and subgeneric taxon names follow The Plant List 1.1 (2013 and references therein). [3] The differentiated plant parts/products are (11): ASH: Ashes; BARK: barks; FLOW: flowers; FRU: fruits; HERB: herbs; LEAF: leaves; OIL: oils; EXUD: exudates; SEED: seeds; SUBT: subterranean parts and WOOD: wood. [4] The differentiated uses categories are (21): ANDR: Andrology; ANTI: antidotes; CARD: cardiovascular problems; DERM: dermatology; FEV: fever; FOOD: food; GAST: gastroenterology; GYN: gynecology; LIBI: libido regulators; MUSK: musculoskeletal ailments; NERV: neurology; ORAL: oral cavity; OPHT: ophthalmology; OTH: others; OTO: otology; PARA: parasites; POIS: poisons; REPE: repellents; RESP: respiratory system; RHI: rhinology and URO: urology. [5] The suggested routes of administration (given in brackets) are (four): INT: Internal; EXT: external; FUM: fumigations and CLY: clysters. For more details on the employed classification system consult the methods section. [6] Each combination of use category and route of administration for any given taxon is only listed once, regardless of the actual number of respective mentions in the text. A detailed version of this table specifying individual uses was tabulated into a separate data file.

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Acacia spp.	Fabaceae	EXUD	I 114	Acacia	DERM (EXT), GAST (INT), GYN (CLY), GYN (INT), MUSK (EXT), OPHT (EXT), ORAL (EXT)
Acanthus mollis L.	Acanthaceae	SUBT	III 017, III 018	Acantho, Acantho salvatico	DERM (EXT), GAST (INT), MUSK (EXT), OTH (INT), RESP (INT), URO (INT)
Achillea ageratum L.	Asteraceae	HERB	IV 061	Agerato	GYN (FUMI), URO (FUMI)
Achillea millefolium L.	Asteraceae	FLOW, HERB	IV 038, IV 105	Achillea, Stratiote millefoglio	DERM (EXT), GAST (INT), GYN (CLY), GYN (EXT)
Achillea ptarmica L.	Asteraceae	FLOW, LEAF	II 151	Ptarmica	MUSK (EXT)
Aconitum spp.	Ranunculaceae	SUBT	IV 080	Uno altro Aconito	POIS (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Acorus calamus L.	Acoraceae	SUBT	I 002	Acoro	ANTI (INT), GAST (INT), GYN (EXT), MUSK (INT), OPHT (EXT), OTH (INT), RESP (INT), URO (INT)
Adiantum capillus-veneris L.	Pteridaceae	HERB	IV 138	Adianto	ANTI (INT), DERM (EXT), GAST (INT), GYN (INT), OTH (INT), RESP (INT), URO (INT)
Aegilops neglecta Req. ex Bertol.	Poaceae	HERB	IV 141	Egilopa	DERM (EXT)
Aeonium arboreum Webb & Berthel.	Crassulaceae	LEAF	IV 091	Semprevivo maggiore	ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY), MUSK (EXT), NERV (EXT), OPHT (EXT), PARA (INT)
Agrimonia spp.	Rosaceae	HERB, SEED	IV 043	Eupatorio	ANTI (INT), DERM (EXT), GAST (INT)
Agrostemma githago L.	Caryophyllaceae	HERB, SEED	III 109	Lichnide salvatica	ANTI (INT), GAST (INT), REPE (EXT)
Ajuga chamaepitys L.	Lamiaceae	HERB	III 169, III 170	Chamepitio, Un'altro Chamepitio	ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY), MUSK (INT), URO (INT)
Alisma spp.	Alismataceae	HERB, SUBT	III 163	Alisma	ANTI (INT), DERM (EXT), GAST (INT), GYN (INT), MUSK (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Alkanna tinctoria (L.) Tausch	Boraginaceae	LEAF, SUBT	IV 025	Anchusa	DERM (EXT), GAST (INT), GYN (CLY), PARA (EXT), URO (INT)
Allium ampeloprasum L.	Amaryllidaceae	LEAF, SEED	II 138, II 139	Porro Capitato, Ampelopraso	ANTI (INT), DERM (EXT), FOOD (INT), GAST (INT), GYN (EXT), GYN (INT), LIBI (INT), OTO (EXT), RESP (INT), RHI (INT), URO (INT)
Allium cepa L.	Amaryllidaceae	SUBT	II 140	Cipolla capitata	CARD (CLY), DERM (EXT), FOOD (INT), GAST (INT), GYN (CLY), OPHT (EXT), OTH (EXT), OTO (EXT), RESP (EXT), URO (INT)
Allium sativum L.	Amaryllidaceae	LEAF, SUBT	II 141	Aglio Domestico	ANTI (INT), CARD (INT), DERM (EXT), FOOD (INT), GYN (EXT), GYN (FUMI), NERV (EXT), PARA (EXT), PARA (INT), RESP (INT), URO (INT)
Allium spp.	Amaryllidaceae	LEAF, SEED, SUBT	II 142	Scordopraso	CARD (CLY), DERM (EXT), FOOD (INT), GAST (INT), GYN (CLY), GYN (EXT), GYN (INT), LIBI (INT), OPHT (EXT), OTH (EXT), OTO (EXT), RESP (EXT), RESP (INT), RHI (INT), URO (INT)
Aloe spp.	Asphodelaceae	EXUD	III 023	Aloe	CARD (CLY), DERM (EXT), GAST (INT), MUSK (EXT), NERV (EXT), NERV (INT), OPHT (EXT), ORAL (EXT), RESP (EXT), RESP (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Althaea cannabina L.	Malvaceae	SUBT	III 160	Canape salvatico	DERM (EXT), MUSK (EXT), OTH (EXT)
Althaea officinalis L.	Malvaceae	LEAF, SEED, SUBT	III 157	Althea	ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY), GYN (EXT), GYN (INT), MUSK (EXT), MUSK (INT), NERV (EXT), NERV (INT), OTH (INT), REPE (EXT), URO (INT)
Amaranthus spp.	Amaranthaceae	LEAF	II 108	Blito	FOOD (INT), GAST (INT)
Ambrosia maritima L.	Asteraceae	HERB	III 123	Ambrosia	OTH (EXT)
Ammi spp.	Apiaceae	SEED	III 065	Ammi	ANTI (INT), DERM (EXT), GAST (INT), GYN (FUMI), GYN (INT), MUSK (EXT), URO (INT)
Amomum subulatum Roxb.	Zingiberaceae	FRU	I 014	Amomo	ANTI (INT), DERM (EXT), DERM (INT), GAST (INT), GYN (CLY), GYN (EXT), MUSK (EXT), NERV (INT), OPHT (EXT), URO (INT)
Anacyclus pyrethrum (L.) Lag.	Asteraceae	SUBT	III 080	Pirethro	MUSK (INT), NERV (EXT), NERV (INT)
Anagallis spp.	Primulaceae	HERB, SEED	II 169	Anagallide	ANTI (INT), DERM (EXT), GAST (INT), NERV (EXT), OPHT (EXT), OTH (EXT), RESP (EXT), URO (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Anagyris foetida L.	Fabaceae	LEAF, SEED, SUBT	III 161	Anagiri	DERM (EXT), GAST (INT), GYN (EXT), GYN (INT), NERV (INT), RESP (INT)
Anchusa spp.	Boraginaceae	HERB, SEED, SUBT	IV 130	Buglossa	DERM (EXT), FEV (INT), NERV (EXT)
Anemone spp.	Ranunculaceae	HERB, LEAF, SUBT	II 167	Anemone	DERM (EXT), GYN (CLY), GYN (INT), OPHT (EXT), OTH (EXT), PARA (EXT), RESP (EXT)
Anethum graveolens L.	Apiaceae	ASH, LEAF, SEED	III 062	Anetho	ANDR (INT), DERM (EXT), GAST (INT), GYN (EXT), GYN (INT), URO (INT)
Antirrhinum spp.	Plantaginaceae	FLOW	IV 135	Antirrhino	DERM (EXT), OTH (EXT)
Apium graveolens L.	Apiaceae	LEAF, SEED, SUBT	III 069	Apio	ANTI (INT), FOOD (INT), GAST (INT), GYN (INT), NERV (INT), OPHT (EXT), RESP (INT), URO (INT)
Apium nodiflorum (L.) Lag.	Apiaceae	LEAF, SEED, SUBT	III 070	Eleoselino	ANTI (INT), GAST (INT), GYN (INT), NERV (INT), OPHT (EXT), RESP (INT), URO (INT)
Aquilaria spp.	Thymelaeaceae	WOOD	I 021	Agallocho	GAST (INT), ORAL (EXT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Arctium spp.	Asteraceae	LEAF, SUBT	IV 109	Personata	DERM (EXT), MUSK (EXT), RESP (INT)
Arisarum vulgare O.Targ.Tozz.	Araceae	SUBT	II 158	Arisaro	DERM (EXT), OPHT (EXT), OTH (EXT)
Aristolochia spp.	Aristolochiaceae	SUBT	III 004	Aristolochia	ANTI (INT), DERM (EXT), FEV (INT), GAST (INT), GYN (CLY), GYN (INT), MUSK (INT), ORAL (EXT), RESP (INT)
Artemisia abrotanum L.	Asteraceae	SEED	III 026	Abrotano	ANTI (INT), DERM (EXT), FEV (EXT), GYN (INT), MUSK (INT), OPHT (EXT), OTH (INT), REPE (FUMI), RESP (INT), URO (INT)
Artemisia absinthium L.	Asteraceae	HERB	III 024	Assenzo	ANTI (INT), DERM (EXT), GAST (EXT), GAST (INT), GYN (CLY), MUSK (EXT), NERV (FUMI), OPHT (EXT), OTH (EXT), OTO (EXT), OTO (FUMI), PARA (EXT), REPE (EXT), REPE (FUMI), RESP (EXT), URO (EXT), URO (INT)
Artemisia arborescens (Vaill.) L.	Asteraceae	FLOW, HERB	III 121	Artemisia	GYN (CLY), GYN (EXT), GYN (INT), URO (INT)
Artemisia herba-alba L.	Asteraceae	HERB	III 025	Assenzo marino	GAST (INT), PARA (INT)
Artemisia spp.	Asteraceae	FLOW, HERB	III 122	Artemisia delle frondi sottili	GAST (EXT), MUSK (EXT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Arum spp.	Araceae	LEAF, SEED, SUBT	II 157	Aro	DERM (EXT), FOOD (INT), GYN (CLY), GYN (FUMI), GYN (INT), LIBI (INT), MUSK (EXT), OPHT (EXT), OTH (INT), OTO (EXT), RESP (INT), RHI (EXT), URO (INT)
Arundo donax spp.	Poaceae	ASH, LEAF, SUBT	I 095a	Canna	DERM (EXT), MUSK (EXT)
Asarum europaeum L.	Aristolochiaceae	SUBT	I 009	Asaro	GYN (INT), MUSK (INT), URO (INT)
Asparagus spp.	Asparagaceae	HERB, SEED, SUBT	II 114	Asparago	ANDR (INT), ANTI (INT), FOOD (INT), GAST (INT), GYN (INT), MUSK (INT), NERV (EXT), POIS (INT), URO (INT)
Asphodelus spp.	Asphodelaceae	ASH, FLOW, LEAF, SEED, SUBT	II 159	Asphodelo	ANDR (EXT), ANTI (INT), DERM (EXT), GAST (INT), GYN (INT), MUSK (INT), NERV (EXT), OPHT (EXT), OTH (EXT), OTH (INT), OTO (EXT), RESP (INT), URO (INT)
Asplenium adiantum-nigrum L.	Aspleniaceae	SUBT	IV 188	Driopteri	DERM (EXT)
Asplenium sagittatum (DC.) Bunge, A. J.	Aspleniaceae	LEAF	III 146	Hemionite	GAST (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Asplenium scolopendrium L.	Aspleniaceae	LEAF	III 115	Phillitide	ANTI (INT), GAST (INT), OTH (INT)
Asplenium trichomanes L.	Aspleniaceae	HERB	IV 139	Trichomane	ANTI (INT), DERM (EXT), GAST (INT), GYN (INT), OTH (INT), RESP (INT), URO (INT)
Aster amellus L.	Asteraceae	LEAF	IV 122	Aster Attico	DERM (EXT), GAST (INT), NERV (INT), OPHT (EXT), RESP (INT)
Astracantha gummifera (Labill.) Podlech	Fabaceae	EXUD	III 021	Tragacantha	OPHT (EXT), RESP (EXT), RESP (INT), URO (INT)
Athamanta cretensis L.	Apiaceae	SEED, SUBT	III 078a	Dauco	ANTI (INT), DERM (EXT), GAST (INT), GYN (INT), RESP (INT), URO (INT)
Atriplex halimus L.	Amaranthaceae	LEAF, SUBT	I 101	Alimo	FOOD (INT), GAST (INT), GYN (INT), OTH (INT)
Atriplex hortensis L.	Amaranthaceae	LEAF, SEED	II 110	Dell'Atriplice	FOOD (INT), GAST (INT)
Atropa belladonna L.	Solanaceae	SUBT	IV 076	Solatro furioso	NERV (INT), POIS (INT)
Aucklandia lappa DC.	Asteraceae	SUBT	I 015	Costo	ANTI (INT), DERM (EXT), FEV (INT), GYN (CLY), GYN (FUMI), GYN (INT), LIBI (INT), NERV (INT), PARA (INT), RESP (INT), URO (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Avena sativa L.	Poaceae	SEED	II 085	Vena	GAST (INT), RESP (INT)
Ballota nigra L.	Lamiaceae	LEAF	III 111	Ballote	DERM (EXT)
Ballota pseudodictamnus (L.) Benth.	Lamiaceae	HERB, SUBT	III 033	Dittamo falso	ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY), GYN (FUMI), GYN (INT), REPE (EXT)
Cytinus spp.	Cytinaceae	HERB	I 108	Hipocisto	GAST (CLY), GAST (INT), GYN (INT), RESP (INT)
Berula erecta (Huds.) Coville	Apiaceae	LEAF	II 116	Sio	GAST (INT), GYN (INT), URO (INT)
Beta vulgaris L.	Amaranthaceae	LEAF, SUBT	II 112	Bietola	DERM (EXT), OTO (EXT), PARA (EXT)
Bituminaria bituminosa (L.) C.H.Stirt.	Fabaceae	LEAF, SEED, SUBT	III 117	Trifoglio	ANTI (INT), DERM (EXT), FEV (INT), GYN (INT), NERV (INT), RESP (INT), URO (INT)
Bongardia chrysogonum (L.) Spach	Berberidaceae	SUBT	IV 058	Chrisogono	DERM (EXT)
Boswellia spp.	Burseraceae	ASH, BARK, EXUD	I 067, I 068	Incenso, Corteccia dello Incenso	DERM (EXT), GAST (INT), GYN (CLY), GYN (EXT), OPHT (EXT), OTO (EXT), POIS (INT), RESP (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Brassica oleracea L.	Brassicaceae	ASH, FLOW, HERB, LEAF, SEED, SUBT	II 111a	Brassica	ANTI (INT), DERM (EXT), DERM (INT), FOOD (INT), GAST (INT), GYN (CLY), GYN (EXT), GYN (INT), MUSK (EXT), NERV (INT), OPHT (INT), OTH (EXT), OTH (INT), PARA (EXT), PARA (INT), RESP (EXT), URO (INT)
Brassica rapa L.	Brassicaceae	HERB, SEED, SUBT	II 102, II 103	Rape, Napi	ANTI (INT), DERM (EXT), FOOD (INT), LIBI (INT), MUSK (EXT), NERV (INT), URO (INT)
Bryonia alba L.	Cucurbitaceae	HERB, LEAF, SUBT	IV 184	Vite nera	ANTI (INT), DERM (EXT), FOOD (INT), GAST (EXT), GAST (INT), GYN (CLY), GYN (EXT), GYN (INT), MUSK (EXT), NERV (INT), OTH (EXT), OTH (INT), PARA (EXT), RESP (EXT), URO (INT)
Bryonia cretica L.	Cucurbitaceae	FRU, HERB, LEAF, SEED, SUBT	IV 183	Vite bianca	ANTI (INT), DERM (EXT), FOOD (INT), GAST (EXT), GAST (INT), GYN (CLY), GYN (EXT), GYN (INT), MUSK (EXT), NERV (INT), OTH (EXT), OTH (INT), PARA (EXT), RESP (EXT), URO (INT)
Bupleurum fruticosum L.	Apiaceae	SEED	III 056	Seseli Ethiopico	FEV (INT), GAST (INT), GYN (INT), NERV (INT), OTH (INT), RESP (INT), URO (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Cachrys spp.	Apiaceae	HERB, SEED, SUBT	III 081, III 082	Rosmarino, Cachri	ANTI (INT), DERM (EXT), DERM (INT), GAST (INT), GYN (INT), MUSK (INT), NERV (INT), OPHT (EXT), OTH (INT), RESP (INT), URO (INT)
Calystegia soldanella (L.) Roem. & Schult.	Convolvulaceae	HERB	II 111b	Brassica marina	GAST (INT)
Cannabis sativa L.	Cannabaceae	LEAF, SEED	III 159	Canape domestico	ANDR (INT), GYN (INT), OTO (EXT)
Capparis spinosa L.	Capparaceae	FLOW, LEAF, SUBT	II 164	Capparo	DERM (EXT), FOOD (INT), GAST (INT), GYN (INT), MUSK (INT), NERV (EXT), NERV (INT), ORAL (EXT), OTH (INT), PARA (EXT), RESP (INT), URO (INT)
Capsella spp.	Brassicaceae	SEED	II 145	Thlaspi	GAST (INT), GYN (INT), MUSK (CLY), OTH (INT)
Cardopatium corymbosum (L.) Pers.	Asteraceae	SUBT	III 009	Chameleone nero	DERM (EXT), NERV (EXT), ORAL (EXT), PARA (EXT)
Carlina gummifera (L.) Less.	Asteraceae	SUBT	III 008	Chameleone bianco	ANTI (INT), PARA (INT), POIS (INT), URO (INT)
Carthamus lanatus L.	Asteraceae	FLOW, LEAF, SEED	III 101	Atrattile	ANTI (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Carthamus tinctorius L.	Asteraceae	SEED	IV 189	Cnico	GAST (INT)
Carum carvi L.	Apiaceae	SEED, SUBT	III 061	Caro	ANTI (INT), FOOD (INT), GAST (INT), URO (INT)
Castanea sativa Mill.	Fagaceae	FRU, SEED	I 123	Castagne	ANTI (INT), DERM (EXT), OTH (EXT), URO (INT)
Celtis australis L.	Cannabaceae	FRU, WOOD	I 135	Loto albero	DERM (EXT), FOOD (INT), GAST (CLY), GAST (INT), GYN (CLY), GYN (INT)
Centaurea spp.	Asteraceae	SUBT	III 006	Centaurea maggiore	DERM (EXT), FEV (INT), GAST (INT), GYN (CLY), GYN (INT), MUSK (INT), OTH (INT), RESP (EXT), RESP (INT)
Centaurium erythraea Rafn.	Gentianaceae	HERB	III 007	Centaurea minore	DERM (EXT), GAST (INT), GYN (CLY), MUSK (CLY), NERV (INT), OPHT (EXT)
Ceratonia siliqua L.	Fabaceae	FRU	I 131	Silique	URO (INT)
Cerinthe major L.	Boraginaceae	LEAF	II 177	Telephio	DERM (EXT)
Ceterach officinarum Willd.	Aspleniaceae	LEAF	III 145	Aspleno	GAST (INT), GYN (EXT), URO (INT)
Drimia maritima (L.) Stearn	Asparagaceae	SEED, SUBT	II 162	Scilla	DERM (EXT), GAST (FUMI), GAST (INT), REPE (EXT), RESP (INT), URO (FUMI), URO (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Chelidonium majus L.	Papaveraceae	HERB, SUBT	II 171	Chelidonia	DERM (EXT), GAST (INT), NERV (EXT), OPHT (EXT)
Chondrilla juncea L.	Asteraceae	EXUD, HERB, SUBT	II 122	Chondrilla	ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY)
Cicer arietinum L.; *Pisum sativum* L.	Fabaceae	SEED	II 095	Ceci	ANDR (EXT), DERM (EXT), FOOD (INT), GAST (INT), GYN (INT), PARA (EXT), URO (INT)
Cichorium intybus L.	Asteraceae	LEAF, SUBT	II 121	Endivia	DERM (EXT), FOOD (INT), GAST (EXT), GAST (INT), MUSK (EXT), OPHT (EXT)
Cinnamomum spp.	Lauraceae	BARK	I 012	Cassia	ANTI (INT), DERM (EXT), GYN (EXT), GYN (FUMI), OPHT (INT), URO (INT)
Cinnamomum spp.	Lauraceae	BARK	I 013	Cinnamomo	ANTI (INT), DERM (EXT), GYN (CLY), GYN (INT), RESP (INT), URO (INT)
Cistus ladanifer L.	Cistaceae	EXUD	I 109	Ladano	DERM (EXT), GAST (INT), GYN (CLY), GYN (FUMI), NERV (INT), OTO (EXT), RESP (INT), URO (INT)
Cistus spp.	Cistaceae	FLOW	I 107	Cisto	DERM (EXT), GAST (INT)
Citrullus colocynthis (L.) Schrad.	Cucurbitaceae	FRU	IV 178	Colocinthida	GAST (CLY), GAST (INT), GYN (CLY), MUSK (CLY), NERV (CLY), NERV (EXT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Citrus medica L.	Rutaceae	FRU, SEED	I 132g	Mele di Media	ANTI (INT), FOOD (INT), GYN (INT)
Clematis spp.	Ranunculaceae	HERB, SEED, SUBT	IV 182	Vite salvatica	DERM (EXT), FOOD (INT), GAST (INT), URO (INT)
Clinopodium acinos (L.) Kuntze	Lamiaceae	HERB	III 045	Acino	DERM (EXT), GAST (INT), GYN (INT)
Clinopodium nepeta (L.) Kuntze	Lamiaceae	LEAF	III 038	Calamintha	ANTI (INT), DERM (EXT), DERM (INT), FEV (INT), GAST (INT), GYN (CLY), GYN (INT), MUSK (EXT), OTH (INT), PARA (EXT), PARA (INT), REPE (EXT), REPE (FUMI), RESP (INT), URO (INT)
Clinopodium vulgare L.	Lamiaceae	HERB	III 103	Clinopodio	ANTI (INT), DERM (INT), GAST (INT), GYN (INT), MUSK (INT), OTH (INT), URO (INT)
Colchicum spp.	Colchicaceae	SUBT	IV 086	Colchio	POIS (INT)
Commiphora spp.	Burseraceae	EXUD, SEED, WOOD	I 018	Balsamo	ANTI (INT), DERM (EXT), FEV (EXT), GAST (EXT), GAST (INT), GYN (CLY), GYN (EXT), MUSK (EXT), MUSK (INT), NERV (INT), OPHT (INT), OTH (INT), RESP (INT), URO (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Commiphora spp.	Burseraceae	EXUD	I 064	Mirrha	DERM (EXT), FEV (INT), GAST (INT), GYN (CLY), MUSK (EXT), MUSK (INT), NERV (INT), OPHT (EXT), ORAL (EXT), OTO (EXT), PARA (INT), RESP (EXT), RESP (INT)
Conium maculatum L.	Apiaceae	HERB, SEED	IV 081	Cicuta	ANDR (EXT), DERM (EXT), GYN (EXT), LIBI (EXT), NERV (EXT), OPHT (EXT), POIS (INT)
Convolvulus arvensis L.	Convolvulaceae	LEAF	IV 041	Helsine	GAST (INT)
Convolvulus scammonia L.	Convolvulaceae	EXUD, SUBT	IV 172	Scammonea	DERM (EXT), GAST (INT), GYN (CLY), MUSK (EXT), NERV (EXT), PARA (EXT)
Coriandrum sativum L.	Apiaceae	LEAF, SEED	III 066	Coriandro	ANDR (EXT), ANDR (INT), DERM (EXT), PARA (INT)
Coris monspeliensis L.	Primulaceae	SUBT	IV 010	Simphitio petreo	DERM (EXT), GAST (EXT), GAST (INT), GYN (INT), OTH (INT), RESP (INT), URO (INT)
Cornus mas L.	Cornaceae	FRU, LEAF	I 136	Corniolo	DERM (EXT), FOOD (INT), GAST (INT)
Coronilla scorpioides (L.) Koch	Fabaceae	HERB	IV 194	Scorpioide	DERM (EXT)
Corylus avellana L.	Betulaceae	SEED	I 143	Avellane	DERM (EXT), RESP (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Crataegus azarolus L.	Rosaceae	FRU	I 134b	Epimelida	FOOD (INT), GAST (INT)
Crataegus spp.	Rosaceae	FRU, SUBT	I 103	Oxiacantha	DERM (EXT), GAST (INT), GYN (EXT), GYN (INT)
Cressa cretica L.	Convolvulaceae	SUBT	III 147	Anthillide	DERM (EXT), GYN (CLY), NERV (INT), URO (INT)
Crithmum maritimum L.	Apiaceae	LEAF, SEED, SUBT	II 118	Crithmo	FOOD (INT), GAST (INT), GYN (INT), URO (INT)
Crocus sativus L.	Iridaceae	FLOW, SUBT	I 025, I 026	Croco, Crocomagma	DERM (EXT), FOOD (INT), GAST (CLY), GYN (CLY), GYN (EXT), OPHT (EXT), OTH (INT), POIS (INT), URO (INT)
Cucumis melo L.	Cucurbitaceae	FRU, SEED, SUBT	II 124b	Pepone	DERM (EXT), FOOD (INT), GAST (INT), OPHT (EXT), OTH (EXT), URO (INT)
Cucumis sativus L.	Cucurbitaceae	FRU, LEAF, SEED	II 124a	Cocomero domestico	DERM (EXT), GAST (INT), NERV (FUMI), URO (INT)
Cuminum cyminum L.	Apiaceae	SEED	III 063	Cimino domestico	ANDR (EXT), ANTI (INT), DERM (EXT), GAST (CLY), GAST (EXT), GYN (CLY), RESP (INT), RHI (EXT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Cupressus sempervirens L.	Cupressaceae	FRU, LEAF	I 083	Cipresso	DERM (EXT), DERM (INT), GAST (EXT), GAST (INT), OPHT (EXT), REPE (FUMI), RESP (INT), RHI (EXT), URO (INT)
Cuscuta spp.	Convolvulaceae	HERB	IV 179	Epithimo	GAST (INT), NERV (INT), OTH (INT)
Cyclamen spp.	Primulaceae	SUBT	II 153	Ciclamino	ANTI (INT), DERM (EXT), GAST (CLY), GAST (EXT), GAST (INT), GYN (CLY), GYN (EXT), GYN (INT), LIBI (INT), MUSK (EXT), OPHT (EXT), OTH (EXT), URO (INT)
Cydonia oblonga Mill.	Rosaceae	FLOW, FRU	I 132a	Cotogne	DERM (EXT), DERM (INT), GAST (EXT), GAST (INT), GYN (EXT), GYN (INT), OPHT (EXT), OTH (INT), RESP (INT), URO (INT)
Cymbopogon schoenanthus (L.) Spreng.	Poaceae	FLOW, SUBT	I 016	Giunco odorato	ANTI (INT), CARD (INT), GAST (INT), GYN (EXT), GYN (INT), MUSK (INT), RESP (INT), URO (INT)
Cynanchum acutum L.	Apocynaceae	LEAF	IV 083	Apocino	POIS (INT)
Cynara scolymus L.; *Cynara cardunculus* L.	Asteraceae	HERB, SUBT	III 014	Cardo	DERM (EXT), FOOD (INT), URO (INT)
Cynodon dactylon (L.) Pers.	Poaceae	SUBT	IV 032	Gramigna	DERM (EXT), GAST (INT), URO (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Cyperus papyrus L.	Cyperaceae	ASH, HERB, SUBT	I 096	Papiro	DERM (EXT), FOOD (INT)
Cyperus rotundus L.	Cyperaceae	SUBT	I 004	Cipero	ANTI (INT), GYN (FUMI), ORAL (EXT), URO (INT)
Danae racemosa (L.) Moench	Asparagaceae	SUBT	IV 046	Radice Idea	GAST (INT), GYN (INT)
Daphne gnidium L.	Thymelaeaceae	LEAF, SEED	IV 174	Thimelea	GAST (INT), GYN (CLY), OTH (INT)
Daphne laureola L.	Thymelaeaceae	FRU, LEAF	IV 150	Daphnoide	GAST (INT), GYN (INT), RESP (INT), RHI (INT)
Daphne spp.	Thymelaeaceae	LEAF	IV 173	Chamelea	DERM (EXT), GAST (INT)
Daucus carota L.	Apiaceae	HERB, LEAF, SEED, SUBT	III 054, II 126	Pastinaca, Gingidio	ANTI (INT), DERM (EXT), FOOD (INT), GYN (CLY), GYN (INT), LIBI (INT), MUSK (INT), REPE (INT), URO (INT)
Delphinium spp.	Ranunculaceae	HERB, SEED	III 079	Delphinio	ANTI (INT), REPE (EXT)
Delphinium staphisagria L.	Ranunculaceae	SEED	IV 157	Staphis agria	DERM (EXT), GAST (INT), NERV (EXT), ORAL (EXT), PARA (EXT), RESP (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Diospyros spp.	Ebenaceae	WOOD	I 110	Ebeno	DERM (EXT), OPHT (EXT), OPHT (INT)
Dipsacus spp.	Asteraceae	SUBT	III 011	Dissaco	DERM (EXT), FEV (EXT)
Dittrichia spp.	Asteraceae	FLOW, HERB, LEAF	III 130	Coniza	DERM (EXT), GAST (INT), GYN (CLY), GYN (EXT), GYN (INT), NERV (EXT), OTH (EXT), POIS (EXT), POIS (FUMI), REPE (EXT), REPE (FUMI), URO (INT)
Dracunculus vulgaris Schott.	Araceae	FLOW, LEAF, SEED, SUBT	II 155, II 156	Dragontea maggiore, Dragontea minore	DERM (EXT), FOOD (INT), GYN (CLY), GYN (FUMI), GYN (INT), LIBI (INT), OPHT (EXT), OTH (INT), OTO (EXT), RESP (INT), RHI (EXT), URO (INT)
Dryopteris filix-mas (L.) Schott	Dryopteridaceae	SUBT	IV 185	Felce	DERM (EXT), GAST (INT), PARA (INT)
Dysphania botrys (L.) Mosyakin & Clemants	Amaranthaceae	HERB	III 124	Botri	RESP (INT)
Ecballium elaterium (L.) A.Rich.	Cucurbitaceae	FRU, LEAF, SUBT	IV 156	Cocomero salvatico	DERM (EXT), GAST (EXT), GAST (INT), GYN (CLY), MUSK (EXT), NERV (EXT), OTH (INT), OTO (EXT), PARA (EXT), RESP (EXT), RESP (INT), URO (INT)
Echinophora tenuifolia L.	Apiaceae	FLOW, SEED	III 051	Panace Asclepio	DERM (EXT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Echium angustifolium Mill.	Boraginaceae	LEAF, SUBT	IV 026	Seconda Anchusa	ANTI (INT), DERM (EXT), POIS (EXT)
Echium spp.	Boraginaceae	LEAF, SEED, SUBT	IV 029	Echio	ANTI (INT), GYN (INT), MUSK (INT), REPE (INT)
Elettaria cardamomum (L.) Maton	Zingiberaceae	FRU	I 005	Cardamomo	ANTI (INT), GAST (INT), GYN (FUMI), MUSK (INT), NERV (INT), OTH (INT), PARA (EXT), PARA (INT), RESP (INT), URO (INT)
Ephedra spp.	Ephedraceae	FRU	IV 053	Trago	GAST (INT), GYN (INT)
Equisetum spp.	Equisetaceae	HERB, SUBT	IV 048	Coda di cavallo	DERM (EXT), GAST (INT), OTH (INT), RESP (INT), RHI (EXT), URO (INT)
Equisetum spp.	Equisetaceae	HERB, SUBT	IV 049	Una altra Coda di cavallo	DERM (EXT), GAST (INT), OTH (INT), RESP (INT), RHI (EXT), URO (INT)
Erica spp.	Ericaceae	FLOW, LEAF	I 098	Erica	DERM (EXT)
Eruca vesicaria (L.) Cav.	Brassicaceae	LEAF, SEED	II 129	Ruchetta	FOOD (INT), GAST (INT), LIBI (INT), URO (INT)
Eryngium maritimum L.	Apiaceae	LEAF, SUBT	III 022	Eringio montano	ANTI (INT), DERM (EXT), FOOD (INT), GAST (INT), GYN (INT), MUSK (INT), NERV (INT), URO (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Euphorbia acanthothamnos Heldr. & Sart. ex Boiss.	Euphorbiaceae	EXUD, HERB, SUBT	IV 163	Hippophae	GAST (INT)
Euphorbia apios L.	Euphorbiaceae	HERB, SUBT	IV 177	Apios	GAST (INT)
Euphorbia resinifera O.Berg	Euphorbiaceae	EXUD	III 090	Euphorbio	DERM (EXT), MUSK (EXT), MUSK (INT), OPHT (EXT)
Euphorbia chamaesyce L.	Euphorbiaceae	EXUD, HERB	IV 171	Chamesice	DERM (EXT), GAST (INT), GYN (CLY), OPHT (EXT)
Euphorbia lathyris L.	Euphorbiaceae	EXUD, HERB, SEED	IV 168	Lathiri	GAST (INT)
Euphorbia spp.	Euphorbiaceae	EXUD, LEAF, SEED, SUBT	IV 166	Tithimali	DERM (EXT), GAST (INT), NERV (EXT), POIS (EXT), POIS (INT)
Euphorbia peplis L.	Euphorbiaceae	SEED	IV 170	Peplio	GAST (INT)
Euphorbia peplus L.	Euphorbiaceae	SEED	IV 169	Peplo	GAST (INT)
Euphorbia pithyusa L.	Euphorbiaceae	EXUD, HERB, SUBT	IV 167	Pitiusa	GAST (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Fagus sylvatica L.	Fagaceae	BARK, FRU, LEAF, SEED	I 122b	Faggio	ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY), OTH (EXT), RESP (INT), URO (INT)
Ferula communis L.	Apiaceae	HERB, SEED	III 085	Ferola	ANTI (INT), GAST (INT), RESP (INT), RHI (EXT)
Ferula spp.	Apiaceae	EXUD	III 091	Galbano	ANTI (INT), DERM (EXT), GYN (CLY), GYN (FUMI), GYN (INT), MUSK (EXT), NERV (EXT), NERV (FUMI), OTH (EXT), POIS (EXT), REPE (FUMI), RESP (EXT), URO (INT)
Ferula spp.	Apiaceae	EXUD	III 089	Sagapeno	ANTI (INT), FEV (INT), GAST (INT), GYN (FUMI), GYN (INT), MUSK (INT), NERV (INT), OPHT (EXT), OTH (INT), RESP (INT)
Ferula spp.	Apiaceae	EXUD	III 092	Ammoniaco	DERM (EXT), GAST (EXT), GAST (INT), GYN (INT), MUSK (EXT), MUSK (INT), NERV (EXT), NERV (INT), OPHT (INT), OTH (EXT), OTH (INT), RESP (EXT), RESP (INT), URO (INT)
Ficaria verna Huds.	Ranunculaceae	HERB, SUBT	II 172	Chelidonia minore	DERM (EXT), NERV (EXT), OTH (EXT), PARA (EXT), RESP (EXT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Ficus carica L.	Moraceae	ASH, EXUD, FRU, LEAF	I 146	Fichi	ANTI (INT), CARD (INT), DERM (EXT), FOOD (EXT), FOOD (INT), GAST (CLY), GAST (INT), GYN (CLY), GYN (EXT), GYN (INT), MUSK (EXT), NERV (EXT), NERV (INT), ORAL (EXT), OTH (INT), OTO (EXT), PARA (EXT), RESP (EXT), RESP (INT), URO (EXT), URO (INT)
Ficus sycomorus L.	Moraceae	EXUD, FRU	I 145	Fico d'Egitto	DERM (EXT), FEV (INT), FOOD (INT), GAST (INT)
Foeniculum vulgare Mill.	Apiaceae	LEAF, SEED, SUBT	III 076, III 077	Finocchio, Finocchio salvatico	ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY), GYN (INT), OPHT (EXT), URO (INT)
Fraxinus spp.	Oleaceae	ASH, LEAF	I 089	Frassino	ANTI (INT), PARA (EXT)
Fumaria officinalis L.	Papaveraceae	HERB	IV 112	Fumaria	DERM (EXT), OPHT (INT), URO (INT)
Gagea graeca (L.) Irmsch.	Liliaceae	FLOW, LEAF, SEED	III 116	Phalangio	ANTI (INT), GAST (INT)
Galatella linosyris (L.) Rchb.	Asteraceae	SUBT	IV 057	Chrisocome	GAST (INT), GYN (INT), RESP (INT)
Galium aparine L.	Rubiaceae	HERB, SEED	III 098	Aparine	ANTI (INT), DERM (EXT), OTO (EXT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Galium verum L.	Rubiaceae	FLOW, SUBT	IV 098	Gallio	DERM (EXT), LIBI (INT), NERV (EXT)
Gentiana lutea L.	Gentianaceae	SUBT	III 003	Gentiana maggiore	ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY), OPHT (EXT), OTH (INT)
Genus species I 011	-	LEAF	I 011	Malabathro	ANTI (INT), GAST (INT), GYN (INT), OPHT (EXT), URO (INT)
Genus species I 017	-	SUBT	I 017	Calamo odorato	GYN (CLY), GYN (EXT), GYN (INT), RESP (FUMI), URO (INT)
Genus species I 019	-	WOOD	I 019	Aspalatho	DERM (EXT), GYN (CLY), ORAL (EXT), RESP (INT), RHI (EXT), URO (INT)
Genus species I 022	-	BARK	I 022	Narcaphtho	GYN (FUMI)
Genus species I 023	-	EXUD	I 023	Cancamo	GAST (INT), GYN (INT), NERV (EXT), NERV (INT), OPHT (EXT), OPHT (INT), ORAL (EXT), RESP (INT)
Genus species I 066	Burseraceae	EXUD	I 066	Bdellio	ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY), GYN (FUMI), MUSK (EXT), MUSK (INT), OTH (EXT), RESP (INT), URO (INT)
Genus species I 091-2	-	BARK	I 091-2	Macero	GAST (INT), RESP (INT)
Genus species I 099	-	FRU	I 099	Acacalide	OPHT (EXT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Genus species I 147	-	FRU, LEAF	I 147	Perseo	DERM (EXT), FOOD (INT)
Genus species I 148	Brassicaceae	SUBT	I 148	Iberide	MUSK (EXT)
Genus species II 099	Fabaceae	SEED	II 099	Fagivoli	GAST (INT)
Genus species II 132	-	HERB	II 132	Barba di becco	FOOD (INT)
Genus species II 135	Fabaceae	FRU	II 135	Smilace de gli horti	FOOD (INT), URO (INT)
Genus species II 161	-	SUBT	II 161	Bulbo che fa vomitare	GAST (INT), URO (INT)
Genus species II 174	-	SUBT	II 174	Othonna	DERM (EXT)
Genus species III 010	Asteraceae	SEED, SUBT	III 010	Crocodilio	GAST (INT), RHI (INT), URO (INT)
Genus species III 012	Asteraceae	SEED, SUBT	III 012	Spinca bianca	ANTI (INT), DERM (EXT), GAST (INT), MUSK (INT), NERV (EXT), REPE (EXT), RESP (INT), URO (INT)
Genus species III 013	Asteraceae	SUBT	III 013	Spina Arabica	GAST (INT), GYN (CLY), RESP (INT)
Genus species III 015	-	SUBT	III 015	Poterio	MUSK (EXT)
Genus species III 020	Asteraceae	SUBT	III 020	Leucacantha	MUSK (INT), NERV (EXT), OTH (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Genus species III 030	Lamiaceae	HERB	III 030	Tragorigano	ANTI (INT), DERM (EXT), GAST (INT), GYN (INT), OTH (INT), RESP (EXT), RESP (INT), URO (INT)
Genus species III 034	Lamiaceae	HERB, SUBT	III 034	Dittamo di Candia	ANTI (INT), DERM (EXT), DERM (INT), GAST (INT), GYN (CLY), GYN (FUMI), GYN (INT), REPE (EXT)
Genus species III 046	-	LEAF, SUBT	III 046	Bacchara	ANTI (INT), DERM (EXT), GYN (CLY), GYN (EXT), GYN (INT), MUSK (INT), NERV (EXT), NERV (FUMI), OPHT (EXT), OTH (INT), RESP (INT), URO (INT)
Genus species III 049	-	SUBT	III 049	Moli	GYN (CLY)
Genus species III 052	-	HERB, SUBT	III 052	Panace Chironio	ANTI (INT), DERM (EXT)
Genus species III 057	Apiaceae	SEED	III 057	Seseli del Peleponneso	FEV (INT), GAST (INT), GYN (INT), NERV (INT), OTH (INT), RESP (INT), URO (INT)
Genus species III 067	Asteraceae	HERB, SUBT	III 067	Hieracio maggiore	DERM (EXT), GAST (INT), OTH (EXT)
Genus species III 068	Asteraceae	HERB, SUBT	III 068	Hieracio minore	DERM (EXT), GAST (INT), OTH (EXT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Genus species III 071	Apiaceae	SEED, SUBT	III 071	Oreoselino	ANTI (INT), GYN (INT), URO (INT)
Genus species III 088	Apiaceae	EXUD, LEAF, SUBT	III 088	Laserpitio	ANTI (INT), DERM (EXT), FEV (INT), FOOD (INT), GAST (INT), GYN (INT), MUSK (EXT), MUSK (INT), NERV (EXT), NERV (INT), OPHT (EXT), ORAL (INT), OTH (EXT), OTH (INT), RESP (EXT), RESP (INT), RHI (EXT), URO (INT)
Genus species III 093	-	EXUD	III 093	Sarcocolla	DERM (EXT), OPHT (EXT)
Genus species III 099	-	HERB, SEED	III 099	Alisso	DERM (EXT), GAST (INT), OTH (EXT), OTH (INT)
Genus species III 102	Lamiaceae	SEED	III 102	Policnemone	DERM (EXT), OTH (INT), URO (INT)
Genus species III 107	-	SEED	III 107	Leuca	ANTI (INT), DERM (EXT)
Genus species III 128	-	SEED, SUBT	III 128	Circea	GYN (INT)
Genus species III 129	-	HERB, SEED, SUBT	III 129	Enanthe	GYN (INT), URO (INT)
Genus species III 131	Liliaceae	LEAF, SUBT	III 131	Hemerocalle	DERM (EXT), GYN (CLY), GYN (EXT), GYN (INT), OPHT (EXT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Genus species III 133	-	SEED	III 133	Crateogono	GYN (INT)
Genus species III 135	Orchidaceae	SUBT	III 135	Testicolo di cane	ANDR (INT), GYN (INT), LIBI (INT)
Genus species III 136	Orchidaceae	SUBT	III 136	Altro testicolo	DERM (EXT), GAST (INT), ORAL (EXT), OTH (EXT)
Genus species III 137	-	SUBT	III 137	Satirio	LIBI (INT), MUSK (INT)
Genus species III 138	-	SEED, SUBT	III 138	Satirio erithronio	LIBI (EXT), LIBI (INT)
Genus species III 141	Boraginaceae	LEAF	III 141	Onosma	GYN (INT)
Genus species III 144	-	FRU, HERB, SEED	III 144	Androsace	MUSK (EXT), URO (INT)
Genus species IV 001	Lamiaceae	HERB	IV 001	Betonica	ANTI (INT), DERM (EXT), GAST (INT), GYN (INT), MUSK (INT), NERV (INT), OTH (INT), RESP (INT), URO (INT)
Genus species IV 002	-	HERB	IV 002	Britanica	DERM (EXT)
Genus species IV 008	-	LEAF, SEED	IV 008	Una altra Clematide	FOOD (INT), GAST (INT), PARA (EXT)
Genus species IV 009	-	SUBT	IV 009	Polemonia	ANTI (INT), DERM (EXT), GAST (INT), MUSK (INT), NERV (EXT), URO (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Genus species IV 012	-	HERB	IV 012	Holostio	OTH (INT)
Genus species IV 014	-	HERB, SUBT	IV 014	Climeno	DERM (EXT), GAST (INT), GYN (INT), RESP (INT), RHI (EXT)
Genus species IV 017	-	HERB	IV 017	Sassifragia	FEV (INT), GAST (INT), URO (INT)
Genus species IV 020	-	SEED	IV 020	Medio	GYN (INT)
Genus species IV 021	-	LEAF, SUBT	IV 021	Epimedio	GYN (EXT), GYN (INT)
Genus species IV 027	Boraginaceae	SEED, SUBT	IV 027	Terza Anchusa	PARA (INT), POIS (EXT)
Genus species IV 028	-	SUBT	IV 028	Licopside	DERM (EXT)
Genus species IV 031	-	SEED	IV 031	Erino	OPHT (EXT), OTO (EXT)
Genus species IV 033	-	HERB	IV 033	Gramigna cannaria	POIS (INT)
Genus species IV 034	-	HERB, SUBT	IV 034	Gramigna di Parnaso	OPHT (EXT)
Genus species IV 035	Lamiaceae	LEAF	IV 035	Siderite	DERM (EXT)
Genus species IV 051	-	LEAF, SEED	IV 051	Tragio	DERM (EXT), GYN (INT), URO (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Genus species IV 052	-	SUBT	IV 052	Uno altro Tragio	GAST (INT)
Genus species IV 056	-	HERB	IV 056	Paronichia	DERM (EXT)
Genus species IV 062	-	LEAF	IV 062	verbenaca	DERM (EXT), GYN (EXT)
Genus species IV 064	Fabaceae	SUBT	IV 064	Astragalo	DERM (EXT), GAST (INT), URO (INT)
Genus species IV 077	-	SEED, SUBT	IV 077	Doricnio	LIBI (INT), NERV (INT), POIS (INT)
Genus species IV 079	-	SUBT	IV 079	Aconito	OPHT (EXT), POIS (INT)
Genus species IV 087	-	LEAF, SUBT	IV 087	Ephemero	DERM (EXT), NERV (EXT)
Genus species IV 089	-	LEAF	IV 089	Alsine	OPHT (EXT), OTO (EXT)
Genus species IV 093	Crassulaceae	LEAF	IV 093	Uno altro Semprevivo	DERM (EXT)
Genus species IV 095	-	HERB	IV 095	Uno altro Umbilico di Venere	DERM (EXT), GAST (INT), GYN (CLY), MUSK (EXT), OPHT (EXT), PARA (INT)
Genus species IV 108	-	SUBT	IV 108	Arctio	DERM (EXT), MUSK (INT), NERV (EXT), URO (INT)
Genus species IV 111	-	HERB	IV 111	Epipactide	ANTI (INT), GAST (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Genus species IV 119	-	SEED	IV 119	Miagro	DERM (EXT)
Genus species IV 120	-	SUBT	IV 120	Onagra	DERM (EXT)
Genus species IV 121	Asteraceae	SUBT	IV 121	Cirsio	CARD (EXT)
Genus species IV 123	-	SEED	IV 123	Isopiro	GAST (INT), RESP (INT)
Genus species IV 125	-	SEED, SUBT	IV 125	Cacalia	DERM (EXT), RESP (INT)
Genus species IV 126	-	HERB, SEED, SUBT	IV 126	Bunio	GAST (INT), GYN (INT), URO (INT)
Genus species IV 127	-	HERB	IV 127	Bunio falso	DERM (EXT), GAST (INT), MUSK (INT), URO (INT)
Genus species IV 128	-	LEAF	IV 128	Chamecisso	GAST (INT), MUSK (INT)
Genus species IV 129	-	HERB	IV 129	Chameleuca	MUSK (INT)
Genus species IV 131	Boraginaceae	LEAF	IV 131	Cinoglossa	DERM (EXT), GAST (INT)
Genus species IV 132	-	SUBT	IV 132	Phiteuma	LIBI (INT)
Genus species IV 133	-	SUBT	IV 133	Leontopodio	DERM (EXT), LIBI (EXT)
Genus species IV 136	-	SEED	IV 136	Catanance	LIBI (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Genus species IV 142	-	HERB, SUBT	IV 142	Bromo	RHI (EXT)
Genus species IV 143	-	HERB	IV 143	Glauco	GYN (INT)
Genus species IV 155	-	SEED	IV 155	Sesamoide minore	DERM (EXT), GAST (INT)
Genus species IV 164	-	EXUD, HERB, SUBT	IV 164	Hippophesto	NERV (INT), OTH (INT), RESP (INT)
Genus species IV 176	-	LEAF, SEED, SUBT	IV 176	Picnocomo	DERM (EXT), GAST (INT)
Genus species IV 181	-	HERB	IV 181	Empetro	GAST (INT)
Genus species IV 191	-	HERB	IV 191	Cinocrambe	GAST (INT), OTH (INT)
Geranium tuberosum L.	Geraniaceae	SUBT	III 125	Geranio	GYN (INT)
Gladiolus italicus Mill.	Iridaceae	SUBT	IV 022	Xiphio	DERM (EXT), GAST (INT), GYN (INT), LIBI (INT)
Glaucium corniculatum (L.) Curtis	Papaveraceae	HERB	III 094	Glaucio	OPHT (EXT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Glaucium flavum Crantz	Papaveraceae	FLOW, LEAF, SEED, SUBT	IV 068	Papavero cornuto	DERM (EXT), GAST (INT), MUSK (INT), OTH (EXT), URO (INT)
Glebionis coronaria (L.) Cass. ex Spach	Asteraceae	FLOW, HERB	III 150, IV 060	Buphthalmo, Chrisanthemo	DERM (EXT), FOOD (INT), GAST (INT)
Globularia alypum L.	Plantaginaceae	SEED	IV 180	Alipo	GAST (INT), OTH (INT)
Glycyrrhiza spp.	Fabaceae	SUBT	III 005	Glicirrhiza	DERM (EXT), GAST (EXT), GAST (INT), OPHT (EXT), RESP (INT), URO (INT)
Hedera helix L.	Araliaceae	FLOW, FRU, HERB, LEAF, SUBT	II 170	Hedera	ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY), GYN (INT), NERV (EXT), NERV (INT), OTO (EXT), PARA (EXT)
Helichrysum spp.	Asteraceae	FLOW	IV 059	Helichrisio	ANTI (INT), GYN (INT), MUSK (INT), OTH (INT), REPE (EXT), RESP (INT), URO (INT)
Heliotropium spp.	Boraginaceae	HERB, SEED	IV 192, IV 193	Heliotropio maggiore, Heliotropio minore	DERM (EXT), FEV (INT), GAST (INT), GYN (CLY), GYN (EXT), MUSK (EXT), OTH (EXT), PARA (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Helleborus spp.	Ranunculaceae	HERB	IV 153	Elleboro nero	DERM (EXT), GAST (INT), GYN (CLY), MUSK (INT), NERV (EXT), NERV (INT), OTH (INT), OTO (EXT), PARA (EXT), URO (EXT)
Heracleum spp.	Apiaceae	FLOW, SEED, SUBT	III 084	Sphondiliio	DERM (EXT), GAST (INT), GYN (INT), NERV (EXT), NERV (FUMI), NERV (INT), RESP (INT)
Hippuris vulgaris L.	Plantaginaceae	HERB	IV 005	Poligono	ANTI (INT), DERM (EXT), FEV (INT), GAST (EXT), GAST (INT), GYN (CLY), OTH (EXT), OTH (INT), OTO (EXT), RESP (EXT), RESP (INT), URO (INT)
Hirschfeldia incana (L.) Lagr.-Foss.	Brassicaceae	HERB	II 107	Lampsana	FOOD (INT), GAST (INT)
Hordeum spp.	Poaceae	SEED	II 078	Orzo	DERM (EXT), DERM (INT), FOOD (INT), GAST (EXT), GAST (INT), GYN (INT), MUSK (INT), ORAL (INT), PARA (EXT), URO (INT)
Hyacinthus orientalis L.	Asparagaceae	SEED, SUBT	IV 065	Hiacintho	ANDR (EXT), ANTI (INT), GAST (INT), URO (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Hyoscyamus spp.	Solanaceae	HERB, SEED, SUBT	IV 071	Hiosciamo	ANDR (EXT), DERM (EXT), FEV (INT), GAST (CLY), GYN (CLY), GYN (EXT), GYN (INT), MUSK (INT), NERV (EXT), NERV (INT), OPHT (EXT), OTH (INT), OTO (INT), RESP (INT)
Hypecoum procumbens L.	Papaveraceae	HERB	IV 070	Hipecoo	DERM (EXT), GAST (INT), MUSK (EXT), NERV (CLY), NERV (EXT), NERV (INT), OPHT (EXT), OTO (EXT), RESP (INT)
Hypericum spp.	Hypericaceae	SEED	III 168	Coriandro	ANTI (INT), FEV (EXT), GYN (INT), MUSK (EXT), MUSK (INT), URO (INT)
Hypericum spp.	Hypericaceae	HERB, SEED	III 167	Androsemo	DERM (EXT), GAST (INT), MUSK (INT)
Hypericum spp.	Hypericaceae	SEED	III 166	Asciro	DERM (EXT), MUSK (INT)
Hypericum spp.	Hypericaceae	LEAF, SEED	III 165	Hiperico	DERM (EXT), FEV (INT), GYN (CLY), MUSK (INT), URO (INT)
Hyphaene thebaica (L.) Mart.	Arecaceae	FRU, SEED	I 126b	Dattoli Thebaici	DERM (EXT), FEV (INT), FOOD (INT), OPHT (EXT)
Hyssopus officinalis L.	Lamiaceae	HERB	III 027-1	Hissopo	GAST (EXT), GAST (INT), MUSK (EXT), NERV (EXT), ORAL (EXT), OTH (EXT), OTO (FUMI), PARA (INT), RESP (EXT), RESP (INT), URO (EXT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Inula helenium L.	Asteraceae	LEAF, SUBT	I 027	Helenio	ANTI (INT), FOOD (INT), GAST (INT), GYN (INT), MUSK (EXT), OTH (INT), RESP (INT), URO (INT)
Iris foetidissima L.	Iridaceae	SEED, SUBT	IV 024	Xiride	DERM (EXT), GAST (INT), MUSK (EXT), MUSK (INT), OTH (EXT), OTH (INT), URO (INT)
Iris spp.	Iridaceae	SUBT	I 001	Iride	ANDR (INT), ANTI (INT), DERM (EXT), FEV (INT), GAST (INT), GYN (CLY), GYN (INT), MUSK (CLY), MUSK (EXT), NERV (CLY), NERV (EXT), NERV (INT), OPHT (INT), RESP (INT)
Isatis tinctoria L.	Brassicaceae	LEAF	II 175, II 176	Isatide	DERM (EXT), GAST (EXT), GAST (INT)
Juglans regia L.	Juglandaceae	ASH, OIL, SEED	I 032c, I 142	Olio delle Noci, Noci	ANTI (INT), DERM (EXT), FOOD (INT), GAST (EXT), GAST (INT), GYN (CLY), GYN (EXT), MUSK (EXT), OTO (EXT), PARA (INT)
Juncus spp.	Juncaceae	LEAF, SEED	IV 054	Giunco	DERM (EXT), GAST (INT), GYN (INT), NERV (INT), URO (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Juniperus excelsa M.Bieb.	Cupressaceae	EXUD, FRU	I 086	Cedro	ANDR (EXT), ANTI (INT), DERM (EXT), GYN (CLY), GYN (EXT), GYN (INT), NERV (EXT), OPHT (EXT), OTH (EXT), OTH (INT), OTO (EXT), PARA (CLY), PARA (EXT), REPE (EXT), RESP (EXT), RESP (INT), URO (INT)
Juniperus spp.	Cupressaceae	BARK, FRU, LEAF	I 084	Ginepro	ANTI (INT), GAST (INT), GYN (INT), OTH (INT), PARA (EXT), REPE (FUMI), RESP (INT), URO (INT)
Juniperus sabina L.	Cupressaceae	LEAF	I 085	Sabina	DERM (EXT), GYN (CLY), GYN (FUMI), OTH (EXT), URO (INT)
Kickxia elatine (L.) Dunmort	Scrophulariaceae	LEAF	IV 042	Elatine	GAST (INT), OPHT (EXT)
Lactuca sativa L.	Asteraceae	LEAF, SEED	II 125a	Lattuca domestica	DERM (EXT), FOOD (INT), GAST (INT), GYN (INT), LIBI (INT), NERV (INT), OTH (EXT)
Lactuca serriola L.	Asteraceae	LEAF, SEED	II 125b	Lattuca salvatica	ANTI (INT), DERM (EXT), GYN (INT), LIBI (INT), NERV (INT), OPHT (INT), URO (INT)
Lagenaria siceraria (Molina) Standl.	Cucurbitaceae	FRU	II 123	Zucca	DERM (EXT), FOOD (INT), GAST (INT), MUSK (EXT), OPHT (EXT), OTH (EXT), OTO (EXT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Lagoecia cuminoides L.	Apiaceae	SEED	III 064	Cimino salvatico	ANDR (EXT), ANTI (INT), GAST (INT), MUSK (EXT), URO (INT)
Laurus nobilis L.	Lauraceae	FRU, LEAF, SUBT	I 087	Lauro	ANTI (INT), DERM (EXT), GAST (INT), GYN (EXT), GYN (INT), NERV (INT), OTH (EXT), OTO (EXT), RESP (INT), URO (EXT), URO (INT)
Lavandula stoechas L.	Lamiaceae	HERB	III 027-2	Stecha	ANTI (INT), OTH (INT), RESP (INT)
Lawsonia inermis L.	Oleaceae	FLOW, LEAF	I 105a	Ligustro	DERM (EXT), MUSK (EXT), NERV (EXT), ORAL (EXT), OTH (EXT)
Lemna minor L.	Araceae	HERB	IV 090	Lente de I paludi	DERM (EXT), GAST (INT), MUSK (EXT)
Lens culinaris Medik.	Fabaceae	SEED	II 098	Lenticchie	DERM (EXT), FOOD (INT), GAST (INT), GYN (EXT), MUSK (EXT), OPHT (EXT)
Leontice leontopetalum L.	Berberidaceae	SUBT	III 104	Leontopetalo	ANTI (INT), MUSK (CLY)
Leopoldia comosa (L.) Parl.	Asparagaceae	SUBT	II 160	Bulbo che si mangia	DERM (EXT), DERM (INT), FOOD (INT), GAST (INT), LIBI (INT), MUSK (EXT), ORAL (EXT), OTH (EXT), OTH (INT), OTO (EXT), RESP (EXT), URO (EXT)
Lepidium draba L.	Brassicaceae	SEED	II 146	Arabide	FOOD (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Lepidium sativum L.	Brassicaceae	HERB, LEAF, SEED	II 144, II 165	Nasturtio, Lepidio	ANTI (INT), DERM (EXT), DERM (INT), GAST (EXT), GAST (INT), GYN (INT), LIBI (INT), MUSK (EXT), NERV (EXT), PARA (INT), REPE (FUMI), RESP (INT)
Levisticum officinale W.D.J.Koch	Apiaceae	SEED, SUBT	III 053	Ligustico	ANTI (INT), FOOD (INT), GAST (INT), GYN (CLY), URO (INT)
Ligustrum vulgare L.	Oleaceae	FLOW, LEAF	I 105b	Ligustro	DERM (EXT), MUSK (EXT), NERV (EXT), ORAL (EXT), OTH (EXT)
Lilium candidum L.	Liliaceae	FLOW, LEAF, SEED, SUBT	III 110	Giglio	ANDR (EXT), ANTI (INT), DERM (EXT), GYN (CLY), GYN (INT), MUSK (EXT), PARA (EXT)
Limonium spp.	Plumbaginaceae	SEED, SUBT	IV 018, IV 137	Limonio, Tripolio	ANTI (INT), GAST (INT), GYN (INT), URO (INT)
Linum usitatissimum L.	Linaceae	SEED	II 094	Lino	DERM (EXT), GAST (CLY), GYN (CLY), GYN (EXT), LIBI (INT), RESP (INT)
Lithospermum officinale L.	Boraginaceae	SEED	III 152	Lithospermo	URO (INT)
Lolium spp.	Poaceae	HERB	IV 045	Phenice	DERM (EXT), GAST (INT), GYN (INT), URO (INT)
Lolium temulentum L.	Poaceae	SEED	II 091	Loglio	DERM (EXT), GYN (CLY), PARA (EXT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Lonicera spp.	Caprifoliaceae	LEAF, SEED	IV 015	Periclimeno	FEV (EXT), GAST (INT), GYN (INT), NERV (INT), RESP (INT), URO (INT)
Lonicera spp.	Caprifoliaceae	SEED	II 154	altro Ciclamino	GAST (INT), GYN (INT), RESP (INT)
Loranthus europaeus Jacq.	Loranthaceae	FRU	III 097	Vischio	DERM (EXT), GAST (EXT)
Lupinus spp.	Fabaceae	SEED, SUBT	II 101	Lupini	DERM (EXT), GAST (INT), GYN (CLY), MUSK (EXT), OTH (EXT), PARA (EXT), PARA (INT), URO (INT)
Lysimachia vulgaris L.	Primulaceae	HERB	IV 003	Lisimachia	DERM (EXT), GAST (CLY), GAST (INT), GYN (CLY), POIS (EXT), REPE (EXT), RESP (INT), RHI (EXT)
Malus domestica Borkh.	Rosaceae	FRU	I 132b, I 132c	Melimele, Mele Epirotiche	GAST (INT), PARA (INT), URO (INT)
Malva spp.	Malvaceae	SUBT	III 158	Alcea	GAST (INT), OTH (INT)
Malva sylvestris L.	Malvaceae	LEAF, SEED, SUBT	II 109	Malva	ANTI (INT), DERM (EXT), FOOD (INT), GAST (CLY), GAST (INT), GYN (CLY), GYN (EXT), GYN (INT), REPE (EXT), URO (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Mandragora spp.	Solanaceae	FRU, LEAF, SUBT	IV 078	Mandragora	ANTI (INT), DERM (EXT), GAST (CLY), GAST (INT), GYN (CLY), GYN (INT), LIBI (INT), MUSK (EXT), NERV (CLY), NERV (FUMI), NERV (INT), OPHT (EXT), POIS (INT)
Marrubium vulgare L.	Lamiaceae	LEAF, SEED	III 113	Marrobio	ANTI (INT), DERM (EXT), GAST (EXT), GYN (INT), MUSK (INT), OPHT (EXT), OTO (EXT), RESP (INT)
Matricaria camomilla L.; *Chamaemelum nobile* (L.) All.	Asteraceae	FLOW, HERB, SUBT	III 148	Anthemide	FEV (CLY), GAST (INT), GYN (EXT), GYN (INT), OPHT (EXT), ORAL (EXT), OTH (INT), URO (EXT), URO (INT)
Matthiola incana (L.) R.Br.	Brassicaceae	HERB, SEED, SUBT	III 132	Leucoio	DERM (EXT), GAST (EXT), GYN (CLY), GYN (EXT), GYN (INT), MUSK (INT), ORAL (EXT)
Medicago arborea L.	Fabaceae	LEAF	IV 115	Citiso	DERM (EXT), URO (INT)
Medicago sativa L.	Fabaceae	SEED	II 136	Medica	FOOD (INT)
Melilotus spp.	Fabaceae	HERB	III 043	Meliloto	ANDR (EXT), DERM (EXT), GAST (INT), GYN (CLY), NERV (EXT), OPHT (EXT), OTH (EXT), OTO (EXT)
Melilotus spp.	Fabaceae	HERB	IV 113	Loto domestico	OPHT (EXT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Melissa officinalis L.	Lamiaceae	LEAF	III 112	Melissophillio	ANTI (INT), DERM (EXT), GAST (CLY), GAST (INT), GYN (EXT), MUSK (EXT), NERV (EXT), RESP (EXT)
Mentha spp.	Lamiaceae	HERB, SEED	II 117a	Sisembro	DERM (EXT), GAST (INT), NERV (EXT), URO (INT)
Mentha pulegium L.	Lamiaceae	HERB	III 031	Pulegio	ANTI (INT), DERM (EXT), GAST (EXT), GAST (INT), GYN (EXT), GYN (INT), MUSK (EXT), MUSK (INT), NERV (EXT), ORAL (EXT), OTH (EXT), OTH (INT), RESP (INT)
Mentha x *piperita* L.	Lamiaceae	HERB	III 036	Mentha	DERM (EXT), DERM (INT), FOOD (INT), GAST (INT), GYN (CLY), GYN (EXT), LIBI (INT), NERV (EXT), ORAL (EXT), OTH (INT), OTO (EXT), PARA (INT)
Mercurialis spp.	Euphorbiaceae	HERB, SEED	III 134, IV 190	Phillo, Mercorella	GAST (INT), GYN (CLY), GYN (INT)
Mespilus germanica L.	Rosaceae	FRU	I 134a	Nespolo	FOOD (INT)
Meum athamanticum Jacq.	Apiaceae	SUBT	I 003	Meo	GAST (INT), GYN (EXT), GYN (INT), MUSK (EXT), RESP (EXT), URO (EXT), URO (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Moringa oleifera Lam.	Moringaceae	OIL, SEED	IV 161, I 032a	Ghianda unguentaria, Olio Balanino	DERM (EXT), GAST (INT), MUSK (EXT), OTO (EXT), PARA (EXT)
Morus alba L.; *Morus nigra* L.	Moraceae	BARK, EXUD, FRU, LEAF	I 144	Moro	ANTI (INT), DERM (EXT), FOOD (INT), GAST (INT), NERV (EXT), PARA (INT), RESP (EXT), RESP (INT)
Myriophyllum spp.	Haloragaceae	HERB	IV 117	Miriophillo	DERM (EXT), MUSK (INT)
Myrrhis odorata (L.) Scop.	Apiaceae	SUBT	IV 118	Mirrhide	ANTI (INT), FEV (INT), FOOD (INT), GYN (INT), RESP (INT)
Myrtus communis L.	Myrtaceae	FRU, LEAF	I 129	Mirto	ANDR (EXT), ANTI (INT), DERM (EXT), GAST (EXT), GAST (INT), GYN (EXT), MUSK (EXT), OPHT (EXT), OTH (EXT), OTO (EXT), RESP (INT), URO (INT)
Narcissus poeticus L.	Amaryllidaceae	SUBT	IV 162	Narcisso	DERM (EXT), GAST (INT), MUSK (EXT)
Nardostachys jatamansi (D.Don) DC.	Valerianaceae	SUBT	I 006	Nardo	ANTI (INT), GAST (INT), GYN (EXT), GYN (INT), OPHT (EXT), URO (INT)
Nasturtium officinale R.Br.	Brassicaceae	LEAF	II 117b	Cardamino	DERM (EXT), FOOD (INT), URO (INT)
Nelumbo nucifera Gaertn.	Nelumbonaceae	SEED, SUBT	II 097, IV 116	Fava d'Egitto, Loto d'Egitto	FOOD (INT), GAST (EXT), OTO (EXT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Nerium oleander L.	Apocynaceae	FLOW, LEAF	IV 084	Nerio	ANTI (INT), POIS (INT)
Nigella sativa L.	Ranunculaceae	SEED	III 087	Melanthio	ANTI (INT), DERM (EXT), GYN (INT), NERV (EXT), NERV (INT), OPHT (EXT), PARA (EXT), POIS (INT), REPE (FUMI), RESP (EXT), RESP (FUMI), URO (INT)
Nuphar lutea (L.) Sm.	Nymphaeaceae	SEED, SUBT	III 143	Un'altra Nimphea	GYN (INT)
Nymphaea alba L.	Nymphaeaceae	SEED, SUBT	III 142	Nimphea	DERM (EXT), GAST (EXT), GAST (INT), LIBI (INT), URO (EXT)
Ocimum basilicum L.	Lamiaceae	LEAF, SEED	II 130	Basilico	DERM (EXT), FOOD (INT), GAST (INT), GYN (INT), OPHT (EXT), OTH (INT), RESP (EXT), URO (INT)
Olea europaea L.	Oleaceae	ASH, EXUD, FRU, LEAF, OIL, SEED	I 028, I 117, I 118, I 119, I 120, I 121	Olio Ophacino, Olivo salvatico, Olive, Olio delle olive salvatiche, Olivo d'Ethiopia, Morca dell'olio	ANTI (INT), DERM (CLY), DERM (EXT), FEV (INT), GAST (EXT), GAST (INT), GYN (CLY), GYN (EXT), GYN (INT), MUSK (EXT), NERV (EXT), NERV (INT), OPHT (EXT), ORAL (EXT), OTH (CLY), OTH (EXT), PARA (EXT), PARA (INT), URO (EXT), URO (INT)
Onobrychis caput-galli (L.) Lam.	Fabaceae	HERB	III 164	Onobrichi	DERM (EXT), URO (EXT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Ononis spinosa L.	Fabaceae	HERB, SUBT	III 019	Anonide	DERM (EXT), FOOD (INT), NERV (EXT), URO (INT)
Onopordum spp.	Asteraceae	LEAF, SUBT	III 016	Ancanthio	MUSK (INT)
Opopanax spp.	Apiaceae	EXUD, SEED	III 050	Panace Heracleo	ANTI (INT), DERM (EXT), FEV (INT), GAST (INT), GYN (CLY), GYN (INT), MUSK (EXT), MUSK (INT), NERV (EXT), NERV (INT), OPHT (EXT), OTH (INT), RESP (INT), URO (INT)
Origanum dictamnus L.	Lamiaceae	HERB, SUBT	III 032	Dittamo	ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY), GYN (FUMI), GYN (INT), REPE (EXT)
Origanum majorana L.	Lamiaceae	HERB	III 042	Maiorana	DERM (EXT), GAST (INT), GYN (CLY), MUSK (EXT), NERV (EXT), OPHT (EXT), URO (INT)
Origanum sipyleum L.	Lamiaceae	HERB	III 044	Maro	DERM (EXT)
Origanum vulgare L.	Lamiaceae	HERB	III 029	Origano	ANTI (INT), DERM (EXT), GAST (EXT), GAST (INT), GYN (INT), ORAL (EXT), OTH (EXT), OTH (INT), OTO (EXT), PARA (EXT), REPE (EXT), RESP (EXT), RESP (INT), URO (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Ornithogalum umbellatum L.	Asparagaceae	SUBT	II 133	Ornithogalo	FOOD (INT)
Orobanche spp.	Orobanchaceae	HERB	II 131	Orobanche	FOOD (INT)
Oryza sativa L.	Poaceae	SEED	II 086	Riso	FOOD (INT), GAST (INT)
Osyris alba L.	Santalaceae	HERB	IV 145	Osiride	GAST (INT)
Otanthus maritimus (L.) Hoffmanns. & Link	Asteraceae	HERB	III 126	Gnaphalio	GAST (INT)
Paeonia spp.	Paeoniaceae	SEED, SUBT	III 151	Peonia	GAST (INT), GYN (INT), NERV (INT), URO (INT)
Paliurus spina-christi Mill.	Rhamnaceae	HERB, LEAF	I 100	Rhamno	DERM (EXT), OTH (EXT)
Pancratium maritimum L.	Amaryllidaceae	SEED, SUBT	II 163	Pancratio	DERM (EXT), GAST (FUMI), GAST (INT), REPE (EXT), RESP (INT), URO (FUMI), URO (INT)
Panicum miliaceum L.	Poaceae	SEED	II 088	Miglio	FOOD (INT), GAST (EXT), GAST (INT), NERV (EXT), URO (INT)
Papaver argemone L.	Papaveraceae	HERB	II 168	Argemone	OPHT (EXT), OTH (EXT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Papaver rhoeas L.	Papaveraceae	FRU, LEAF, SEED	IV 066	Papavero salvatico	FOOD (INT), GAST (INT), NERV (EXT), NERV (INT), OTH (EXT)
Papaver somniferum L.	Papaveraceae	EXUD, FRU, LEAF, SEED	IV 067	Papavero domestico	DERM (EXT), FOOD (INT), GAST (INT), GYN (INT), MUSK (EXT), NERV (CLY), NERV (EXT), NERV (INT), OPHT (EXT), OTH (EXT), OTO (EXT), RESP (INT)
Parietaria spp.	Urticaceae	HERB	IV 088	Helsine	DERM (EXT), MUSK (EXT), OTH (EXT), OTO (EXT), RESP (EXT)
Pastinaca sativa L.	Apiaceae	HERB, SEED, SUBT	III 075	Elaphobosco	ANTI (INT), FOOD (INT)
Peganum harmala L.	Nitrariaceae	SEED	III 048	Ruta salvatica	OPHT (EXT)
Persicaria hydropiper (L.) Delarbre	Polygonaceae	LEAF, SEED	II 150	Hidropepe	DERM (EXT), FOOD (INT), MUSK (EXT)
Petasites spp.	Asteraceae	HERB	IV 110	Petasite	DERM (EXT)
Petroselinum crispum (Mill.) Fuss	Apiaceae	SEED	III 072	Petroselino	GAST (INT), GYN (INT), MUSK (INT), URO (INT)
Peucedanum cervaria (L.) Cusson ex Lapeyr.	Apiaceae	SEED	III 078b	Dauco	ANTI (INT), DERM (EXT), GAST (INT), GYN (INT), RESP (INT), URO (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Peucedanum officinale L.	Apiaceae	EXUD, SUBT	III 086	Peucedano	DERM (EXT), GAST (INT), GYN (EXT), GYN (FUMI), GYN (INT), MUSK (EXT), NERV (EXT), NERV (FUMI), OTO (EXT), REPE (FUMI), RESP (INT), URO (INT)
Phalaris spp.	Poaceae	HERB, SEED	III 153	Phalaride	URO (INT)
Phillyrea spp.	Oleaceae	LEAF	I 106	Phillirea	GYN (INT), ORAL (EXT), URO (INT)
Phoenix dactylifera L.	Arecaceae	FLOW, FRU, LEAF, WOOD	I 126a, I 127	Palma & dattoli, Corteccia de I frutti della palma	CARD (INT), DERM (EXT), FOOD (INT), GAST (INT), GYN (INT), MUSK (EXT), OTH (INT), PARA (EXT), RESP (INT), URO (INT)
Phragmites spp.	Poaceae	ASH, LEAF, SUBT	I 095b	Phragmitide	DERM (EXT), MUSK (EXT)
Physalis alkekengi L.	Solanaceae	FRU, LEAF	IV 074	Solatro Halicacabo	DERM (EXT), GAST (INT), GYN (CLY), NERV (EXT), OPHT (EXT), OTH (EXT), OTO (EXT), URO (INT)
Pimpinella anisum L.	Apiaceae	SEED	III 060	Aniso	ANTI (INT), GAST (INT), GYN (INT), LIBI (INT), NERV (FUMI), NERV (INT), OTO (EXT), URO (INT)
Pimpinella saxifraga L.	Apiaceae	HERB	II 128	Caucalide	FOOD (INT), URO (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Pinus spp.	Pinaceae	ASH, BARK, LEAF, SEED	I 071	Pezzo & Pino	DERM (EXT), FOOD (INT), GAST (INT), GYN (FUMI), NERV (CLY), NERV (EXT), OPHT (EXT), OTH (INT), RESP (INT), URO (INT)
Piper spp.	Piperaceae	SEED	II 148	Pepe	ANTI (INT), DERM (EXT), FEV (INT), FOOD (INT), GAST (INT), GYN (CLY), GYN (INT), NERV (INT), OPHT (EXT), OPHT (INT), RESP (EXT), RESP (INT), URO (INT)
Pistacia lentiscus L.	Anacardiaceae	BARK, EXUD, FRU, HERB, LEAF, SUBT	I 072	Lentisco	DERM (EXT), GAST (INT), GYN (CLY), GYN (INT), MUSK (EXT), ORAL (EXT), RESP (INT), URO (EXT)
Pistacia terebinthus L.	Anacardiaceae	BARK, EXUD, FRU, LEAF, OIL	I 073	Terebintho	ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY), GYN (INT), LIBI (INT), MUSK (EXT), NERV (EXT), ORAL (EXT), OTO (EXT), PARA (EXT), RESP (INT), URO (EXT), URO (INT)
Pistacia vera L.	Anacardiaceae	SEED	I 141	Pistacchi	ANTI (INT), GAST (INT)
Pistia stratiotes L.	Araceae	HERB	IV 104	Stratiote acquatico	DERM (EXT), URO (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Plantago afra L.	Plantaginaceae	SEED	IV 072	Psillio	DERM (EXT), GAST (EXT), MUSK (EXT), NERV (EXT), OTO (EXT), PARA (EXT), REPE (EXT)
Plantago coronopus L.	Plantaginaceae	HERB, SUBT	II 119	Coronopo	FOOD (INT), GAST (INT)
Plantago spp. (excl. *Plantago afra* L.)	Plantaginaceae	LEAF, SEED, SUBT	II 115	Piantagine	DERM (EXT), FEV (INT), GAST (CLY), GAST (INT), GYN (CLY), NERV (EXT), NERV (INT), OPHT (EXT), ORAL (EXT), OTH (EXT), OTO (EXT), RESP (INT), URO (INT)
Platanus orientalis L.	Platanaceae	BARK, FRU, LEAF	I 088	Platano	ANTI (INT), DERM (EXT), NERV (EXT), OPHT (EXT)
Polygala venulosa Sm.	Polygalaceae	HERB	IV 144	Poligala	GYN (INT)
Polygonatum verticillatum (L.) All.	Asparagaceae	SUBT	IV 006	Poligonato	DERM (EXT)
Polygonum aviculare L.	Polygonaceae	HERB	IV 004	Poligono maschio	ANTI (INT), DERM (EXT), FEV (INT), GAST (EXT), GAST (INT), GYN (CLY), OTH (EXT), OTH (INT), OTO (EXT), RESP (EXT), RESP (INT), URO (INT)
Polypodium spp.	Polypodiaceae	SUBT	IV 187	Filicola	DERM (EXT), GAST (INT), MUSK (EXT), OTH (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Polystichum lonchitis (L.) Roth	Dryopteridaceae	LEAF	III 156	Un'altra Lonchite	DERM (EXT), GAST (INT)
Populus alba L.	Salicaceae	BARK, LEAF	I 090	Popolo bianco	GYN (INT), MUSK (INT), OPHT (EXT), OTO (EXT), URO (INT)
Populus nigra L.	Salicaceae	EXUD, LEAF, SEED	I 091-1	Popolo nero	GAST (INT), MUSK (EXT), NERV (INT)
Portulaca oleracea L.	Portulacaceae	HERB	II 113	Portulaca	ANTI (INT), CARD (CLY), DERM (EXT), FEV (INT), FOOD (INT), GAST (CLY), GAST (INT), GYN (CLY), LIBI (INT), NERV (EXT), OPHT (EXT), OPHT (INT), ORAL (EXT), OTH (EXT), OTH (INT), PARA (INT), RESP (INT), URO (EXT), URO (INT)
Potamogeton natans L.	Potamogetonaceae	LEAF	IV 103	Potamogeto	DERM (EXT)
Potentilla spp.	Rosaceae	HERB, SUBT	IV 044	Cinquefoglio	ANTI (INT), DERM (EXT), FEV (INT), GAST (INT), MUSK (INT), NERV (EXT), NERV (INT), OTH (EXT), OTH (INT), PARA (EXT), RESP (EXT), RESP (INT)
Prunus armeniaca L.	Rosaceae	FRU	I 132f	Mele Armeniache	GAST (INT)
Prunus avium (L.) L.; *Prunus cerasus* L.	Rosaceae	EXUD, FRU	I 130	Ciregie	GAST (INT), RESP (INT), URO (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Prunus domestica L.; *Prunus spinosa* L.	Rosaceae	EXUD, FRU, LEAF	I 138	Pruno	DERM (EXT), FOOD (INT), GAST (INT), ORAL (EXT), RESP (EXT), URO (INT)
Prunus dulcis L.	Rosaceae	EXUD, FRU, OIL, SEED, SUBT	I 031, I 140	Olio delle Mandorle, Mandorle	DERM (EXT), DERM (INT), FOOD (INT), GAST (INT), GYN (CLY), NERV (EXT), NERV (INT), OPHT (EXT), OTO (EXT), POIS (INT), RESP (INT), URO (INT)
Prunus persica (L.) Batsch	Rosaceae	FRU	I 132e	Mele Persiche	FOOD (INT), GAST (INT)
Pteridium aquilinum (L.) Kuhn	Dennstaedtiaceae	LEAF, SUBT	IV 186	Felce femina	DERM (EXT), GAST (INT), GYN (INT), OTH (EXT), PARA (EXT), PARA (INT)
Punica granatum L.	Punicaceae	FLOW, FRU, SEED, SUBT	I 128	Melagrano	DERM (EXT), FOOD (INT), GAST (EXT), GAST (INT), GYN (EXT), OPHT (INT), ORAL (EXT), OTO (EXT), PARA (INT), RESP (INT), RHI (EXT), URO (INT)
Pyrus spp.	Rosaceae	ASH, FRU	I 133	Pere	ANTI (INT), GAST (INT)
Quercus ilex L.	Fagaceae	BARK, FRU, LEAF, SEED	I 122c	Elice	ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY), OTH (EXT), RESP (INT), URO (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Quercus spp.	Fagaceae	BARK, FRU, LEAF, SEED	I 122a	Quercia	ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY), OTH (EXT), RESP (INT), URO (INT)
Ranunculus spp.	Ranunculaceae	HERB	II 166	Ranuncolo	DERM (EXT), NERV (EXT), PARA (EXT)
Raphanus raphanistrum L. (incl. *Raphanus sativus* L.)	Brassicaceae	LEAF, SEED, SUBT	II 104	Raphano	ANTI (INT), DERM (EXT), FOOD (INT), GAST (EXT), GAST (INT), GYN (INT), MUSK (EXT), RESP (EXT), RESP (INT), URO (EXT), URO (INT)
Reseda spp.	Resedaceae	SEED	IV 154	Sesamoide maggiore	GAST (INT), OTH (INT)
Rhamnus spp.	Rhamnaceae	FRU, HERB, SUBT	I 113	Licio	ANTI (INT), DERM (EXT), GAST (CLY), GAST (INT), GYN (CLY), OPHT (EXT), ORAL (EXT), OTO (EXT), PARA (EXT), RESP (INT)
Rheum spp.	Polygonaceae	SUBT	III 002	Rhapontico	ANTI (INT), DERM (INT), FEV (INT), GAST (INT), GYN (INT), MUSK (INT), NERV (INT), OTH (INT), RESP (INT), URO (INT)
Rhus coriaria L.	Anacardiaceae	EXUD, FRU, LEAF	I 125	Rhu	CARD (CLY), DERM (EXT), FOOD (INT), GAST (CLY), GAST (EXT), GAST (INT), GYN (CLY), MUSK (EXT), NERV (EXT), ORAL (EXT), OTH (EXT), OTO (EXT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Ricinus communis L.	Euphorbiaceae	LEAF, OIL, SEED	IV 165, I 030	Ricino, Olio Ricino	DERM (EXT), GAST (INT), GYN (CLY), GYN (EXT), OPHT (EXT), OTO (EXT), PARA (EXT), URO (INT)
Rosa spp.	Rosaceae	FRU	I 104	Rovo canino	GAST (INT)
Rosa spp.	Rosaceae	FLOW, LEAF	I 111	Rose	DERM (EXT), GAST (EXT), GAST (INT), GYN (CLY), GYN (EXT), NERV (EXT), OPHT (EXT), ORAL (EXT), OTH (EXT), OTO (EXT), RESP (INT)
Rosmarinus officinalis L.	Lamiaceae	HERB	III 083	Rosmarino coronario	GAST (INT), NERV (INT)
Rubia spp.	Rubiaceae	FRU, HERB, SUBT	III 154	Erithrodano	ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY), MUSK (INT), NERV (INT), URO (INT)
Rubus sectio *Rubus*	Rosaceae	FLOW, FRU, HERB, LEAF	IV 039	Rovo	ANTI (INT), CARD (INT), DERM (EXT), GAST (INT), GYN (INT), OPHT (EXT), ORAL (EXT), ORAL (INT)
Rubus idaeus L.	Rosaceae	FLOW, FRU, HERB, LEAF	IV 040	Rovo Ideo	ANTI (INT), DERM (EXT), GAST (INT), GYN (INT), OPHT (EXT), ORAL (EXT), ORAL (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Rumex spp.	Polygonaceae	LEAF, SEED, SUBT	II 106	Rombice	ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY), GYN (INT), NERV (EXT), OTO (EXT), PARA (EXT), URO (INT)
Ruscus aculeatus L.	Asparagaceae	FRU, HERB, SUBT	IV 148	Rusco	GAST (INT), GYN (INT), NERV (INT), URO (INT)
Ruscus hypoglossum L.	Asparagaceae	HERB, SUBT	IV 134	Hippoglosso	NERV (EXT), OTH (EXT)
Ruscus hypophyllum L.	Asparagaceae	LEAF	IV 151	Chamedaphne	GAST (INT), GYN (CLY), GYN (INT), NERV (EXT), URO (INT)
Ruta spp.	Rutaceae	HERB, SEED, SUBT	III 047	Ruta	ANDR (EXT), ANTI (INT), DERM (CLY), DERM (EXT), FEV (INT), GAST (CLY), GAST (INT), GYN (CLY), GYN (EXT), GYN (INT), MUSK (EXT), MUSK (INT), NERV (EXT), NERV (INT), OPHT (EXT), OPHT (INT), OTH (INT), OTO (EXT), PARA (INT), POIS (INT), RESP (INT), RHI (EXT), URO (EXT), URO (INT)
Salix spp.	Salicaceae	BARK, LEAF, SEED	I 116	Salice	DERM (EXT), GYN (INT), MUSK (EXT), OPHT (EXT), OTH (INT), OTO (EXT), RESP (INT)
Salvia aethiopis L.	Lamiaceae	SUBT	IV 107	Ethiopide	MUSK (INT), RESP (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Salvia spp.	Lamiaceae	LEAF	III 035	Salvia	ANDR (EXT), ANTI (INT), DERM (EXT), GYN (INT), URO (INT)
Salvia viridis L.	Lamiaceae	HERB, SEED	III 139	Hormino	DERM (EXT), DERM (INT), LIBI (INT), OPHT (EXT)
Sambucus spp.	Adoxaceae	FRU, LEAF, SUBT	IV 175	Sambuco	ANTI (INT), DERM (EXT), GAST (INT), GYN (EXT), GYN (INT), MUSK (EXT), OTH (EXT), URO (INT)
Sanguisorba spp.	Rosaceae	LEAF	IV 036	Una altra Siderite	DERM (EXT)
Saponaria ocymoides L.	Caryophyllaceae	SEED	IV 030	Ocimoide	ANTI (INT), MUSK (INT)
Saponaria officinalis L.	Caryophyllaceae	SUBT	II 152	Radicetta	DERM (EXT), GAST (INT), GYN (CLY), OPHT (EXT), ORAL (EXT), PARA (EXT), RESP (INT), URO (INT)
Sarcopoterium spinosum (L.) Spach	Rosaceae	LEAF, SEED	IV 013	Stebe	GAST (CLY), OPHT (EXT), OTO (EXT)
Satureja thymbra L.	Lamiaceae	HERB	III 040	Satureia	DERM (EXT), GAST (INT), GYN (INT), MUSK (EXT), OPHT (INT), OTH (EXT), PARA (INT), RESP (EXT), RESP (INT), URO (INT)
Scandix pecten-veneris L.	Apiaceae	HERB	II 127	Scandice	FOOD (INT), GAST (INT), URO (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Scirpoides holoschoenus (L.) Soják	Cyperaceae	HERB, SEED	IV 055	Lichene	DERM (EXT), GAST (INT), GYN (INT), NERV (INT), URO (INT)
Scrophularia spp.	Scrophulariaceae	FLOW	IV 037	Terza Siderite	DERM (EXT)
Scrophularia peregrina L.	Scrophulariaceae	HERB, SEED	IV 097	Galiopsi	DERM (EXT)
Securigera securidaca (L.) Degen & Dorfl.	Fabaceae	SEED	III 140	Hedisaro	ANTI (INT), GAST (INT), GYN (CLY)
Sedum amplexicaule DC.	Crassulaceae	LEAF	IV 092	Semprevivo minore	ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY), MUSK (EXT), NERV (EXT), OPHT (EXT), PARA (INT)
Sedum cepaea L.	Crassulaceae	LEAF	III 162	Cepea	URO (INT)
Sedum roseum (L.) Scop.	Crassulaceae	SUBT	IV 047	Radice Rhodia	NERV (EXT)
Senecio vulgaris L.	Asteraceae	HERB	IV 099	Senecio	ANDR (EXT), DERM (EXT), GAST (INT), MUSK (EXT), POIS (INT)
Serapias spp.	Orchidaceae	SUBT	III 155	Lonchite	URO (INT)
Sesamum indicum L.	Pedaliaceae	HERB, OIL, SEED	II 090, I 032b	Sesamo, Olio di Sisamo	DERM (EXT), GAST (EXT), MUSK (EXT), NERV (EXT), OPHT (EXT), OTH (EXT), OTO (EXT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Seseli tortuosum L.	Apiaceae	SEED, SUBT	III 055	Seseli Massiliense	FEV (INT), GAST (INT), GYN (INT), NERV (INT), OTH (INT), RESP (INT), URO (INT)
Setaria italica (L.) P. Beauv.; *Sorghum* spp.	Poaceae	SEED	II 089	Panico	FOOD (INT), GAST (EXT), GAST (INT), NERV (EXT), URO (INT)
Silene coronaria (Desr.) Clairv. ex Rchb.	Caryophyllaceae	SEED	III 108	Lichnide	ANTI (INT)
Silene vulgaris (Moench) Garcke	Caryophyllaceae	SEED	IV 069	Papavero spumeo	GAST (INT), NERV (INT)
Silybum marianum (L.) Gaertn.	Asteraceae	HERB, SUBT	IV 160	Silibro	FOOD (INT), GAST (INT)
Sinapis alba L.; *Brassica nigra* (L.) K.Koch	Brassicaceae	SEED	II 143	Senape	DERM (EXT), FEV (INT), GAST (INT), GYN (INT), MUSK (EXT), MUSK (INT), NERV (EXT), NERV (INT), OPHT (EXT), ORAL (EXT), OTO (EXT), PARA (EXT), RESP (EXT), RESP (INT)
Sison amomum L.	Apiaceae	SEED	III 059	Sisone	FOOD (INT), GAST (INT), GYN (INT), URO (INT)
Sisymbrium irio L.	Brassicaceae	SEED	II 147	Irione	ANDR (EXT), ANTI (INT), DERM (EXT), GAST (INT), GYN (EXT), MUSK (INT), RESP (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Sium sisarum L.	Apiaceae	SUBT	II 105	Sisaro	GAST (INT), URO (INT)
Smilax aspera L.	Smilacaceae	FRU, LEAF	IV 146	Smilace aspra	ANTI (INT)
Smyrnium olusatrum L.	Apiaceae	LEAF, SEED, SUBT	III 073	Hipposelino	FOOD (INT), GYN (INT), URO (INT)
Smyrnium perfoliatum L.	Apiaceae	LEAF, SEED, SUBT	III 074	Smirnio	ANTI (INT), DERM (EXT), FEV (INT), GAST (INT), GYN (CLY), GYN (INT), MUSK (INT), OTH (EXT), RESP (INT), URO (INT)
Solanum americanum Mill.	Solanaceae	LEAF	IV 073	Solatro hortolana	DERM (EXT), FOOD (INT), GYN (CLY), NERV (EXT), OPHT (EXT), OTH (EXT), OTO (EXT)
Sonchus spp.	Asteraceae	LEAF, SUBT	II 120	Soncho	DERM (CLY), DERM (EXT), FOOD (INT), GAST (EXT), GAST (INT), GYN (CLY), GYN (INT)
Sorbus domestica L.	Rosaceae	FRU	I 137	Sorbe	FOOD (INT), GAST (INT)
Sparganium spp.	Typhaceae	SEED, SUBT	IV 023	Sparganio	ANTI (INT)
Spartium junceum L.	Fabaceae	FLOW, HERB, SEED	IV 159	Spartio	GAST (INT), MUSK (CLY), MUSK (INT), RESP (INT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Stachys spp.	Lamiaceae	LEAF	III 114	Stachi	GYN (INT)
Streptopus amplexifolius (L.) DC.	Asparagaceae	SUBT	IV 149	Lauro Alessandrino	GYN (INT), URO (INT)
Styrax officinalis L.	Styracaceae	EXUD	I 065	Stirace	GYN (CLY), GYN (INT), NERV (EXT), RESP (INT)
Symphytum officinale L	Boraginaceae	SUBT	IV 011	Uno altro Simphito	DERM (EXT), OTH (EXT), OTH (INT), RESP (INT)
Tamarix spp.	Tamaricaceae	ASH, BARK, FRU, HERB, WOOD	I 097	Mirice	ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY), GYN (EXT), GYN (INT), NERV (EXT), OPHT (EXT), ORAL (EXT), PARA (EXT), RESP (INT)
Tanacetum parthenium (L.) Sch.Bip.	Asteraceae	FLOW, HERB	III 149	Parthenio	DERM (EXT), GAST (INT), GYN (EXT), NERV (INT), OTH (EXT), RESP (INT)
Taxus baccata L.	Taxaceae	HERB	IV 082	Smilace	POIS (EXT)
Teucrium chamaedrys L.	Lamiaceae	HERB	III 106	Trissagine	DERM (EXT), GAST (INT), GYN (INT), MUSK (INT), OPHT (EXT), RESP (INT), URO (INT)
Teucrium flavum L.	Lamiaceae	HERB	III 105	Teucrio	DERM (EXT), GAST (EXT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Teucrium polium L.	Lamiaceae	HERB	III 118	Polio	ANTI (INT), DERM (EXT), GAST (INT), GYN (INT), REPE (EXT), REPE (FUMI), URO (INT)
Teucrium scordium L.	Lamiaceae	HERB	III 119	Scordio	ANTI (INT), DERM (EXT), DERM (INT), GAST (INT), GYN (CLY), MUSK (INT), OTH (INT), RESP (INT), URO (INT)
Thalictrum spp.	Ranunculaceae	LEAF	IV 100	Thalittro	DERM (EXT)
Thapsia garganica L.	Apiaceae	EXUD, HERB, SUBT	IV 158	Thapsia	DERM (EXT), GAST (INT), MUSK (EXT), MUSK (INT), OTH (EXT), OTH (INT), PARA (EXT), RESP (EXT), RESP (INT)
Thymbra capitata (L.) Cav.	Lamiaceae	HERB	III 039	Thimo	DERM (EXT), FOOD (INT), GAST (INT), GYN (INT), MUSK (EXT), OPHT (INT), OTH (EXT), PARA (INT), RESP (EXT), RESP (INT), URO (INT)
Thymus spp.	Lamiaceae	HERB	III 041	Serpillo	DERM (EXT), GAST (INT), GYN (INT), NERV (EXT), OTH (INT), URO (INT)
Tordylium spp.	Apiaceae	HERB, SEED, SUBT	III 058	Tordilio	GYN (INT), RESP (EXT), URO (INT)
Trapa natans L.	Lythraceae	FRU, HERB	IV 016a	Tribolo acquatico	FOOD (INT), OPHT (EXT), ORAL (EXT), OTH (EXT), OTH (INT), PARA (EXT), URO (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Tribulus terrestris L.	Zygophyllaceae	FRU, HERB	IV 016b	Tribolo terrestre	ANTI (INT), DERM (EXT), OPHT (EXT), ORAL (EXT), OTH (EXT), PARA (EXT), URO (INT)
Trifolium spp.	Fabaceae	HERB	IV 019	Lagopo	GAST (INT), OTH (EXT)
Trigonella esculenta Willd.	Fabaceae	SEED	IV 114	Loto salvatico	DERM (EXT), URO (INT)
Trigonella foenum-graecum L.	Fabaceae	SEED	II 093	Fien Greco	DERM (EXT), GAST (EXT), GAST (INT), GYN (CLY), GYN (EXT)
Triticum spp. (incl. *T. aestivum* L.)	Poaceae	SEED	II 077, II 092	Grano, Amilo	DERM (EXT), FOOD (INT), GAST (EXT), GAST (INT), GYN (EXT), MUSK (EXT), OPHT (EXT), ORAL (EXT), ORAL (INT), OTH (EXT), PARA (EXT), RESP (EXT), RESP (INT)
Triticum spp. (incl. T. dicoccon (Schrank.) Schübl. and *T. monococcum* L.)	Poaceae	SEED	II 080, II 081, II 082, II 084, II 087	Zea, Crimno, Olira, Trago, Halica	DERM (EXT), FOOD (INT), GAST (CLY), GAST (INT), PARA (EXT)
Tussilago farfara L.	Asteraceae	LEAF, SUBT	III 120	Tossilagine	DERM (EXT), GYN (INT), OTH (EXT), RESP (FUMI)
Typha spp.	Typhaceae	SEED	III 127	Tipha	DERM (EXT)

Taxon [1]	Family [2]	Part [3]	Book Chapter	Vernacular Name	Use [4,5,6]
Ulmus spp.	Ulmaceae	BARK, LEAF, SUBT	I 093	Olmo	DERM (EXT), FOOD (INT), MUSK (EXT), PARA (EXT), RESP (INT)
Umbilicus spp.	Crassulaceae	LEAF, SUBT	IV 094	Ombilico di Venere	DERM (EXT), GAST (EXT), GYN (EXT), LIBI (INT), OTH (EXT), URO (INT)
Urtica spp.	Urticaceae	HERB, SEED	IV 096	Ortica	DERM (EXT), GAST (EXT), GAST (INT), GYN (CLY), GYN (INT), LIBI (INT), MUSK (EXT), ORAL (EXT), OTH (INT), RESP (INT), RHI (EXT), URO (INT)
Valeriana celtica L.	Valerianaceae	HERB, SUBT	I 007	Nardo Celtico	ANTI (INT), GAST (INT), URO (INT)
Valeriana spp.	Valerianaceae	SUBT	I 010	Phu	ANTI (INT), GYN (INT), MUSK (INT), URO (INT)
Valeriana tuberosa L.	Valerianaceae	HERB, SUBT	I 008	Nardo Montano	ANTI (INT), GAST (INT), URO (INT)
Veratrum album L.	Melanthiaceae	SUBT	IV 152	Elleboro bianco	GAST (INT), GYN (CLY), OPHT (EXT), POIS (EXT)
Verbascum spp.	Scrophulariaceae	LEAF, SUBT	IV 106	Verbasco	DERM (EXT), GAST (INT), NERV (EXT), OPHT (EXT), OTH (INT), REPE (EXT), RESP (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Verbena spp.	Verbenaceae	HERB, LEAF, SUBT	IV 063	Herba sacra	ANTI (INT), DERM (EXT), FEV (INT), GAST (INT), OTH (EXT), RESP (EXT)
Vicia cracca L.	Fabaceae	SEED	II 137	Apaca	GAST (INT)
Vicia ervilia (L.) Willd.	Fabaceae	SEED	II 100	Ervo	DERM (EXT), FOOD (INT), GAST (INT), GYN (EXT), RESP (INT), URO (INT)
Vicia faba L.	Fabaceae	SEED	II 096	Fave	ANDR (EXT), DERM (EXT), FOOD (INT), GAST (INT), GYN (INT), MUSK (EXT), OPHT (EXT), RESP (INT)
Vinca spp.	Apocynaceae	HERB	IV 007	Clematide	ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY), NERV (EXT)
Vincetoxicum hirundinaria Medik.	Apocynaceae	LEAF, SUBT	III 100	Asclepiade	ANTI (INT), GAST (INT), GYN (EXT)
Viola spp.	Violaceae	LEAF	IV 124	Viole porporee	DERM (EXT), GAST (EXT), OPHT (EXT)
Vitex agnus-castus L.	Lamiaceae	LEAF, SEED	I 115	Vitice	ANDR (EXT), ANDR (INT), ANTI (INT), DERM (EXT), GAST (INT), GYN (CLY), GYN (EXT), GYN (FUMI), GYN (INT), MUSK (EXT), NERV (EXT), NERV (INT), OTH (EXT), REPE (EXT), REPE (FUMI), URO (INT)

Taxon [1]	**Family** [2]	**Part** [3]	**Book Chapter**	**Vernacular Name**	**Use** [4,5,6]
Vitis spp.	Vitaceae	ASH, EXUD, FRU, HERB, LEAF, SEED	V 001, V 003, V 004, V 005, V 006	Vite vinifera, Uva, Uva Passa, Enanthe, Omphacio	ANDR (EXT), DERM (EXT), FEV (INT), GAST (CLY), GAST (EXT), GAST (INT), GYN (CLY), GYN (EXT), GYN (INT), MUSK (EXT), NERV (EXT), OPHT (EXT), OPHT (INT), ORAL (EXT), ORAL (INT), OTH (EXT), OTO (EXT), PARA (EXT), RESP (EXT), RESP (INT), URO (INT)
Withania somnifera (L.) Dunal	Solanaceae	FRU, SEED, SUBT	IV 075	Solatro sonnifero	NERV (EXT), NERV (INT), OPHT (EXT), URO (INT)
Xanthium strumarium L.	Asteraceae	FRU	IV 140	Xanthio	DERM (EXT)
Zingiber officinale Roscoe.	Zingiberaceae	LEAF, SUBT	II 149	Gengevo	ANTI (INT), FOOD (INT), GAST (INT), OPHT (INT)
Ziziphus jujuba Mill.	Rhamnaceae	FRU, LEAF, SUBT	I 102	Paliuro	ANTI (INT), DERM (EXT), RESP (INT), URO (INT)

Supplementary material of Chapter 3

Table 7-2 Contemporary plant uses in Campania compared to recommendations in Dioscorides' *DMM* (*ex* Matthioli, 1568) and Galen's *DSMF*.

CAMPANIAN DATABASE	GAS	DER	NER	SKM	GYN	RES	FEV	UR0	EAR	EYE	NOS
Adiantum capillus-veneris L.	1	2	0	0	4	5	0	0	0	0	0
Allium cepa L.	3	7	0	0	1	4	0	4	0	0	0
Anagallis arvensis L. s.l.	0	1	0	0	0	2	0	0	0	0	0
Anemone sp.	0	2	2	1	0	0	0	0	0	0	0
Apium sp.	0	0	0	0	0	1	0	2	0	0	0
Artemisia sp.	2	0	1	1	0	0	0	0	0	0	0
Arum sp.	0	0	0	2	0	0	0	0	0	0	0
Arundo sp.	1	1	0	0	0	1	0	1	0	0	0
Asparagus sp.	2	0	0	0	0	0	0	6	0	0	0
Asphodelus sp.	0	1	0	1	0	0	0	0	0	0	0
Avena sp.	0	1	1	0	0	1	0	0	0	0	0
Brassica sp.	3	3	0	2	0	2	1	0	0	0	0
Calamintha nepeta (L.) Savi s.l.	4	2	2	1	0	4	0	0	0	0	0
Centaurium erythraea Rafn. s.l.	2	1	1	0	0	0	3	0	0	0	0
Ceratonia siliqua L.	2	1	0	0	0	3	0	0	0	0	0
Ceterach officinarum Willd. s.l.	1	0	0	0	1	4	0	1	0	0	0
Cichorium intybus L. s.l.	4	2	1	1	0	0	1	1	0	0	0
Convolvulus arvensis L.	1	1	0	1	0	0	0	0	0	0	0
Crataegus sp.	1	0	3	1	0	2	1	0	0	0	0

Cyclamen sp.	1	0	0	0	0	0	0	0	0	0	0
Cydonia oblonga Mill.	0	1	0	0	0	1	1	0	0	0	0
Cynara cardunculus L. & *scolymus* L. s.l	5	0	0	0	0	0	0	1	0	0	0
Cynodon dactylon (L.) Pers.	5	0	1	1	0	4	1	7	0	0	0
Daucus carota L. s.l.	1	2	0	0	0	3	0	2	0	0	0
Ecballium elaterium (L.) A. Rich.	2	0	0	0	0	0	0	0	0	0	0
Equisetum sp.	0	3	0	0	0	0	0	1	0	0	0
Ficus carica L.	1	7	0	0	0	7	0	1	0	0	0
Foeniculum vulgare Mill.	6	1	1	0	1	3	0	1	0	0	0
Fumaria sp.	3	3	0	0	0	0	0	0	0	0	0
Hedera helix L. s.l.	0	4	2	2	1	3	0	0	0	0	0
Helichrysum italicum (Roth) G. Don s.l.	0	0	0	0	0	2	0	0	0	0	0
Helleborus sp.	0	0	1	1	2	0	0	0	0	0	0
Hordeum vulgare L.	0	1	0	0	0	4	0	2	0	0	0
Hypericum perforatum L. & *perfoliatum* L.	1	8	1	1	0	1	0	0	0	0	0
Juglans regia L.	5	3	1	1	0	3	0	1	0	0	0
Lactuca sp.	5	6	6	1	2	1	0	1	0	1	0
Laurus nobilis L.	10	2	3	4	1	6	2	1	1	0	0
Lavatera sp. & *Althaea* sp.	3	3	0	0	0	3	0	0	0	0	0
Linum usitatissimum L.	3	6	1	1	0	5	0	0	0	1	0
Lonicera sp.	0	1	0	0	0	0	0	1	0	0	0
Malva sp.	7	8	3	1	3	8	1	1	0	0	0
Marrubium vulgare L.	1	0	0	0	1	1	1	0	0	0	0
Matricaria chamomilla L. & *Tanacetum* sp.	8	5	8	5	3	3	0	1	1	1	0
Mentha pulegium L.	1	0	0	1	0	2	0	0	0	0	0
Mentha sp.	9	4	4	2	1	4	0	0	0	0	0
Morus sp.	1	0	0	0	0	2	0	1	0	0	0
Muscari sp.	0	0	1	0	0	0	0	2	0	0	0
Myrtus communis L.	2	2	0	2	1	1	0	1	0	1	0
Nasturtium officinale R. Br.	1	0	0	0	0	0	0	1	0	0	0

Ocimum basilicum L.	5	1	1	0	0	2	0	1	0	0	0
Olea europaea L.	4	6	0	3	1	2	1	1	1	0	0
Origanum vulgare L. s.l. & *majorana* L.	4	2	3	1	1	6	0	0	0	0	0
Papaver rhoeas L.	0	2	10	0	0	4	0	0	0	0	0
Papaver somniferum L.	0	0	2	0	0	0	0	0	0	0	0
Parietaria sp.	6	7	0	4	1	3	0	5	0	0	0
Petroselinum crispum (Mill.) Fuss	3	2	1	1	5	0	0	1	0	0	0
Pinus sp.	0	2	0	0	0	0	0	1	0	0	0
Pistacia lensticus L.	0	1	1	1	0	1	0	0	0	0	0
Pistacia terebinthus L.	0	1	0	0	0	1	0	0	0	0	0
Plantago sp. (*P. psyllium* not included)	2	9	0	2	0	3	0	3	0	1	0
Polygonum aviculare L. s.l.	4	0	0	1	0	1	0	2	0	0	0
Prunus cerasus L. & *avium* L.	1	0	0	1	0	3	0	3	0	0	0
Prunus dulcis (Mill.) D.A. Webb	3	0	0	0	0	2	0	0	0	0	0
Prunus persica (L.) Batsch	1	0	0	0	0	0	0	0	0	0	0
Punica granatum L.	4	0	1	1	1	0	1	1	0	0	0
Ranunculus sp.	0	1	1	1	0	0	0	0	0	0	0
Ricinus communis L.	2	1	0	0	0	0	0	0	0	0	0
Rosa sp.	2	4	0	0	0	1	0	1	0	1	0
Rosmarinus officinalis L.	5	1	2	2	1	4	0	0	0	0	0
Rubus sp. *(R. idaeus* not included)	4	7	0	0	1	5	0	2	0	0	0
Rumex sp.	2	4	0	0	0	0	0	0	0	0	0
Ruscus sp.	1	1	0	0	0	0	0	6	0	0	0
Ruta sp.	5	4	4	7	3	0	0	0	1	1	0
Sambucus nigra L.	7	6	2	3	0	6	1	3	1	1	0
Senecio sp.	0	0	0	1	2	0	0	1	0	0	0
Solanum nigrum L.	0	2	1	1	0	0	0	0	0	0	0
Sonchus sp.	1	2	0	0	0	1	0	1	0	0	0
Tamus communis L. (now: *Dioscorea communis* (L.) Caddick & Wilkin.)	0	0	0	2	0	0	0	0	0	0	0

Thymus sp.	3	2	0	1	0	4	0	1	0	1	0
Trigonella foenum-graecum L.	0	0	0	0	1	1	0	0	0	0	0
Triticum sp.	1	2	2	0	1	1	0	0	0	0	0
Tussilago farfara L.	0	2	1	0	0	4	0	0	0	0	0
Ulmus sp.	0	4	0	0	0	1	1	0	0	0	0
Umbilicus sp.	0	3	0	0	0	0	0	0	0	0	0
Urtica sp.	2	8	1	8	0	2	0	3	0	0	0
Verbascum sp.	0	2	1	0	0	4	0	0	0	0	0
Verbena officinalis L.	2	1	1	1	0	1	2	0	0	0	0
TOTAL	**182**	**185**	**79**	**76**	**40**	**159**	**18**	**77**	**5**	**9**	**0**

Red = Dioscorides and Galen recommend the use; Yellow: Only Dioscorides makes the recommendation; Orange: Only Galen makes the recommendation. Numbers in cells correspond to the number of studies citing a plant taxon-use category-pair.

Table 7-3 Contemporary plant uses in Sardinia compared to recommendations in Dioscorides' *DMM* (*ex* Matthioli, 1568) and Galen's *DSMF*.

SARDINIAN DATABASE	GAS	DER	NER	SKM	GYN	RES	FEV	UR0	EAR	EYE	NOS
Adiantum capillus-veneris L.	1	5	4	0	5	5	0	3	0	1	0
Allium cepa L.	2	4	1	1	0	5	0	4	2	0	0
Anagallis arvensis L. s.l.	0	1	1	0	0	1	0	0	0	0	0
Anemone sp.	1	0	0	0	1	0	0	1	0	0	0
Apium sp.	4	1	0	2	0	1	1	2	0	0	0
Artemisia sp.	11	2	3	3	1	6	1	1	0	1	0
Arum sp.	0	6	0	2	0	1	0	1	0	0	0
Arundo sp.	0	7	0	0	2	0	0	2	1	0	0
Asparagus sp.	0	0	2	2	0	1	0	7	0	0	0
Asphodelus sp.	0	12	0	1	0	4	1	2	0	0	0
Avena sp.	2	1	0	0	0	0	0	2	0	0	0
Brassica sp.	1	4	1	1	0	1	0	0	0	0	0
Calamintha nepeta (L.) Savi s.l.	1	0	0	0	0	0	0	0	0	0	0
Centaurium erythraea Rafn. s.l.	4	4	0	0	1	0	7	0	0	0	0
Ceratonia siliqua L.	4	0	0	0	0	1	0	0	0	0	0
Ceterach officinarum Willd. s.l.	3	1	0	0	0	0	1	3	0	0	0
Cichorium intybus L. s.l.	9	0	0	2	0	0	2	3	0	0	0
Convolvulus arvensis L.	3	1	0	0	0	0	0	0	0	0	0

Crataegus sp.	4	2	9	1	2	0	2	3	0	0	0
Cyclamen sp.	1	1	0	0	1	0	0	0	0	0	0
Cydonia oblonga Mill.	3	1	1	0	0	2	0	0	0	0	0
Cynara cardunculus L. & *scolymus* L. s.l	4	0	0	0	0	0	0	0	0	0	0
Cynodon dactylon (L.) Pers.	6	1	0	1	0	3	1	8	0	0	0
Daucus carota L. s.l.	4	2	2	0	2	1	0	3	0	0	0
Ecballium elaterium (L.) A. Rich.	3	0	1	0	0	0	0	0	0	0	0
Equisetum sp.	2	6	0	3	0	2	0	7	0	0	1
Ficus carica L.	4	8	1	1	0	4	0	0	0	0	0
Foeniculum vulgare Mill.	10	0	0	1	3	2	0	3	0	1	0
Fumaria sp.	5	3	1	0	0	2	0	1	0	0	0
Hedera helix L. s.l.	1	6	3	3	0	5	0	0	0	0	0
Helichrysum italicum (Roth) G. Don s.l.	1	3	2	3	0	4	0	0	0	0	0
Helleborus sp.	0	1	1	0	0	0	0	0	0	0	0
Hordeum vulgare L.	4	1	0	0	0	3	0	0	0	1	0
Hypericum perforatum L. & *perfoliatum* L.	3	9	2	4	1	2	0	2	0	0	0
Juglans regia L.	1	2	1	0	0	0	0	0	0	0	0
Lactuca sp.	0	1	0	0	0	0	0	0	0	0	0
Laurus nobilis L.	16	2	1	6	1	7	0	1	0	0	0
Lavatera sp. & *Althaea* sp.	3	5	0	1	0	6	0	0	0	2	0
Linum usitatissimum L.	5	3	1	1	1	8	0	0	1	0	0
Lonicera sp.	3	1	0	3	1	1	0	1	0	0	0
Malva sp.	19	18	3	0	2	12	1	7	0	3	0
Marrubium vulgare L.	10	2	3	5	3	8	5	0	0	0	0
Matricaria chamomilla L. & *Tanacetum* sp.	8	4	5	3	2	2	1	0	0	5	0
Mentha pulegium L.	4	2	1	1	0	0	0	1	0	0	
Mentha sp.	11	5	3	2	1	2	1	0	0	0	
Morus sp.	1	0	0	0	0	0	0	0	0	0	0
Muscari sp.	0	0	0	0	0	0	0	1	0	0	0
Myrtus communis L.	9	7	1	0	0	7	0	2	0	0	0

Nasturtium officinale R. Br.	7	3	2	0	1	4	1	4	0	0	0
Ocimum basilicum L.	5	1	3	0	0	3	0	0	1	0	0
Olea europaea L.	8	9	0	2	0	0	5	1	4	0	0
Origanum vulgare L. s.l. & *majorana* L.	3	0	1	0	0	0	0	0	0	0	0
Papaver rhoeas L.	1	0	9	1	0	5	0	0	0	0	0
Papaver somniferum L.	1	0	1	0	0	1	0	0	0	0	0
Parietaria sp.	12	8	6	1	0	4	2	13	1	0	0
Petroselinum crispum (Mill.) Fuss	8	2	3	0	2	1	0	5	1	1	0
Pinus sp.	0	1	0	0	0	1	0	0	0	0	0
Pistacia lensticus L.	6	11	2	3	0	4	0	0	0	0	0
Pistacia terebinthus L.	1	2	2	0	0	3	0	1	0	0	0
Plantago sp. (*P. psyllium* not included)	6	6	0	2	1	2	0	4	0	1	0
Polygonum aviculare L. s.l.	1	1	0	0	0	0	1	0	0	0	0
Prunus cerasus L. & *avium* L.	3	0	0	1	0	2	0	3	0	0	0
Prunus dulcis (Mill.) D.A. Webb	3	2	0	0	0	2	0	0	0	0	0
Prunus persica (L.) Batsch	1	0	0	0	0	0	0	0	0	0	0
Punica granatum L.	3	0	0	0	0	0	0	0	0	0	0
Ranunculus sp.	0	2	0	2	0	1	0	0	0	0	0
Ricinus communis L.	2	0	0	0	0	0	0	0	0	0	0
Rosa sp.	5	0	0	0	1	2	0	1	0	2	0
Rosmarinus officinalis L.	11	5	4	3	0	7	0	3	0	0	0
Rubus sp. (*R. idaeus* not included)	10	8	1	0	1	1	0	2	0	1	0
Rumex sp.	3	6	0	1	0	1	2	5	0	0	0
Ruscus sp.	2	4	2	4	0	0	0	5	0	0	0
Ruta sp.	8	1	1	2	1	1	1	0	1	5	0
Sambucus nigra L.	4	6	4	4	0	4	0	0	0	8	0
Senecio sp.	1	0	0	0	3	0	0	1	0	0	0
Solanum nigrum L.	0	5	5	3	0	2	0	0	0	0	0
Sonchus sp.	2	4	0	1	0	0	0	2	0	0	0
Tamus communis L. (now: *Dioscorea*	0	1	1	5	0	0	0	0	0	0	0

communis (L.) Caddick & Wilkin.)											
Thymus sp.	6	3	4	1	0	7	1	1	0	0	0
Trigonella foenum-graecum L.	0	0	0	0	0	1	0	0	0	0	0
Triticum sp.	2	5	2	3	0	2	0	0	0	0	0
Tussilago farfara L.	0	1	0	1	0	1	0	0	0	0	0
Ulmus sp.	0	1	0	1	0	0	0	0	0	0	0
Umbilicus sp.	2	10	1	0	0	1	0	2	0	0	0
Urtica sp.	10	16	4	6	2	3	1	8	1	0	2
Verbascum sp.	3	3	0	0	0	3	0	0	0	0	0
Verbena officinalis L.	1	1	2	0	0	0	2	0	0	0	0
TOTAL	**332**	**273**	**114**	**100**	**42**	**178**	**40**	**132**	**13**	**32**	**3**

Red = Dioscorides and Galen recommend the use; Yellow: Only Dioscorides makes the recommendation; Orange: Only Galen makes the recommendation. Numbers in cells correspond to the number of studies citing a plant taxon-use category-pair.

Table 7-4 Contemporary plant uses in Sicily compared to recommendations in Dioscorides' *DMM* (*ex* Matthioli, 1568) and Galen's *DSMF*.

SICILIAN DATABASE	GAS	DER	NER	SKM	GYN	RES	FEV	URO	EAR	EYE	NOS
Adiantum capillus-veneris L.	2	3	0	1	9	3	0	0	0	0	0
Allium cepa L.	2	2	1	1	0	3	0	4	0	0	1
Anagallis arvensis L. s.l.	0	1	0	0	0	2	0	0	0	1	0
Anemone sp.	0	0	1	0	0	0	0	0	0	0	0
Apium sp.	3	1	0	2	0	3	0	7	0	0	0
Artemisia sp.	10	8	0	0	1	2	4	1	0	2	0
Arum sp.	0	2	0	1	0	0	0	0	0	0	0
Arundo sp.	0	8	1	1	0	0	1	2	0	0	0
Asparagus sp.	3	0	0	1	0	1	0	6	0	0	0
Asphodelus sp.	0	12	0	1	0	0	0	0	0	0	0
Avena sp.	2	2	0	1	0	1	0	2	0	0	0
Brassica sp.	3	1	0	2	2	4	0	1	0	0	0
Calamintha nepeta (L.) Savi s.l.	5	6	3	3	1	1	0	1	0	0	0
Centaurium erythraea Rafn. s.l.	1	0	0	0	0	0	2	0	0	0	0
Ceratonia siliqua L.	3	0	0	0	0	8	0	1	0	0	0
Ceterach officinarum Willd. s.l.	0	1	1	0	0	1	0	11	0	0	0
Cichorium intybus L. s.l.	13	0	0	0	0	0	0	5	0	0	0

Convolvulus arvensis L.	3	2	0	2	0	0	0	0	0	0	0
Crataegus sp.	2	1	1	0	0	0	2	1	0	0	0
Cyclamen sp.	1	3	0	1	1	0	0	0	0	0	0
Cydonia oblonga Mill.	4	3	1	0	0	0	0	0	0	0	0
Cynara cardunculus L. & *scolymus* L. s.l	5	1	0	0	0	1	0	1	0	0	0
Cynodon dactylon (L.) Pers.	7	2	0	0	1	1	0	17	0	0	0
Daucus carota L. s.l.	3	2	0	0	1	1	0	2	0	1	0
Ecballium elaterium (L.) A. Rich.	3	3	2	2	1	0	2	0	0	0	0
Equisetum sp.	2	2	0	0	0	1	0	9	0	0	2
Ficus carica L.	2	7	0	0	1	7	0	0	0	0	0
Foeniculum vulgare Mill.	11	2	0	0	3	3	0	4	0	1	0
Fumaria sp.	1	1	1	0	1	0	0	2	0	0	0
Hedera helix L. s.l.	1	8	1	2	1	2	0	0	0	0	0
Helichrysum italicum (Roth) G. Don s.l.	1	1	0	0	0	1	0	0	0	0	0
Helleborus sp.	0	1	1	0	0	0	0	0	0	0	0
Hordeum vulgare L.	3	1	0	0	0	2	0	1	0	0	0
Hypericum perforatum L. & *perfoliatum* L.	1	11	1	3	0	2	0	1	0	0	0
Juglans regia L.	1	2	0	0	0	0	0	0	0	0	0
Lactuca sp.	2	4	4	1	0	0	0	1	0	0	0
Laurus nobilis L.	18	2	2	3	2	4	1	1	0	0	0
Lavatera sp. & *Althaea* sp.	2	1	0	0	0	0	0	1	0	0	0
Linum usitatissimum L.	2	4	1	0	0	2	0	0	0	0	0
Lonicera sp.	0	0	1	0	0	1	0	0	0	0	0
Malva sp.	14	10	2	0	0	4	0	6	0	2	0
Marrubium vulgare L.	1	1	1	2	0	4	1	0	0	0	0
Matricaria chamomilla L. & *Tanacetum* sp.	3	1	3	1	2	0	0	0	0	2	0
Mentha pulegium L.	4	2	2	0	1	3	0	0	0	1	0
Mentha sp.	5	2	3	1	1	3	1	0	0	0	0
Morus sp.	2	1	0	0	0	2	1	1	0	0	0

Muscari sp.	1	2	0	0	0	0	0	2	0	0	0
Myrtus communis L.	1	5	2	0	1	1	0	1	0	0	0
Nasturtium officinale R. Br.	3	0	0	0	2	2	0	2	0	0	0
Ocimum basilicum L.	1	2	1	0	1	1	0	0	0	0	0
Olea europaea L.	1	2	1	1	0	1	1	0	0	0	0
Origanum vulgare L. s.l. & *majorana* L.	3	1	3	4	1	7	0	1	0	0	0
Papaver rhoeas L.	1	0	11	0	0	3	1	0	0	0	0
Papaver somniferum L.	0	0	2	0	0	0	0	0	0	0	0
Parietaria sp.	9	11	2	5	0	2	1	13	0	1	0
Petroselinum crispum (Mill.) Fuss	3	1	1	0	1	0	0	4	1	0	1
Pinus sp.	0	2	1	0	0	2	0	1	0	0	0
Pistacia lensticus L.	0	2	1	0	0	2	2	0	0	0	0
Pistacia terebinthus L.	1	1	0	2	0	0	0	0	0	0	0
Plantago sp. (*P. psyllium* not included)	2	5	0	1	0	0	0	1	0	1	0
Polygonum aviculare L. s.l.	1	4	0	0	0	0	0	7	0	0	0
Prunus cerasus L. & *avium* L.	2	0	0	1	0	0	0	1	0	0	0
Prunus dulcis (Mill.) D.A. Webb	2	1	0	0	0	1	0	0	0	0	0
Prunus persica (L.) Batsch	2	1	1	0	0	0	0	1	0	0	0
Punica granatum L.	4	1	0	0	1	2	0	1	0	0	0
Ranunculus sp.	0	3	0	2	0	0	0	0	0	0	0
Ricinus communis L.	3	1	1	1	1	0	0	0	0	0	0
Rosa sp.	1	1	0	0	0	1	0	1	0	2	0
Rosmarinus officinalis L.	6	0	3	3	1	2	0	0	0	0	0
Rubus sp. (*R. idaeus* not included)	5	13	0	0	0	0	0	1	0	0	0
Rumex sp.	1	3	2	0	0	0	0	0	0	0	0
Ruscus sp.	1	2	0	0	0	0	0	2	0	0	0
Ruta sp.	15	2	2	8	4	1	0	1	0	0	0
Sambucus nigra L.	2	4	2	7	0	3	1	2	1	0	0
Senecio sp.	3	1	0	0	1	1	0	0	0	0	0
Solanum nigrum L.	0	5	2	2	0	0	0	1	0	0	0

Sonchus sp.	5	1	2	1	0	0	0	1	0	0	0
Tamus communis L. (now: *Dioscorea communis* (L.) Caddick & Wilkin.)	0	0	0	3	0	0	0	1	0	0	0
Thymus sp.	3	2	0	1	1	5	0	0	0	0	0
Trigonella foenum-graecum L.	1	1	1	0	0	0	0	1	0	0	0
Triticum sp.	1	3	0	0	0	0	0	0	0	0	0
Tussilago farfara L.	0	5	0	0	0	4	1	0	0	0	0
Ulmus sp.	0	3	0	3	0	0	0	0	0	0	0
Umbilicus sp.	0	10	1	0	0	0	0	0	0	0	0
Urtica sp.	7	12	0	3	1	1	0	1	0	0	1
Verbascum sp.	0	11	1	0	0	1	0	1	0	0	0
Verbena officinalis L.	3	4	3	6	1	2	4	0	0	0	0
TOTAL	**245**	**256**	**80**	**86**	**46**	**118**	**26**	**137**	**2**	**14**	**5**

Red = Dioscorides and Galen recommend the use; Yellow: Only Dioscorides makes the recommendation; Orange: Only Galen makes the recommendation. Numbers in cells correspond to the number of studies citing a plant taxon-use category-pair.

Table 7-5 List of plant species treated as ethnotaxa and considered in the analysis.

Nr.	Taxon	Family
1	*Adiantum capillus-veneris* L.	Adiantaceae
2	*Allium cepa* L.	Amaryllidaceae
3	*Anagallis arvensis* L. s.l.	Primulaceae
4	*Anemone* spp. (*A. coronaria* L., *A. hortensis* L., *A. nemorosa* L.)	Ranunculaceae
5	*Apium graveolens* L. & *A. nodiflorum* (L.) Lag.	Apiaceae
6	*Artemisia* spp. (*A. alba* Turra, *A. abrotanum* L., *A. arborescens* (Vaill.) L.)	Asteraceae
7	*Arum* spp. (*A. italicum* Mill., *A. maculatum* L., *A. pictum* L.f.)	Araceae
8	*Arundo donax* L. & *A. plinii* Turra	Poaceae
9	*Asparagus* spp. (*A. acutifolius* L., *A. albus* L., *A. officinalis* L.)	Asparagaceae
10	*Asphodelus* spp. (*A. albus* Mill., *A. cerasiferus* J. Gay, *A. fistulosus* L., *A. macrocarpus* Parl., *A. microcarpus* Salzm. & Viv., *A. ramosus* L.)	Xanthorrhoeaceae
11	*Avena* spp. (*A. barbata* Pott ex Link, *A. fatua* L., *A. sativa* L.)	Poaceae
12	*Brassica* spp. (*B. oleracea* L., *B. napus* L., *B. rapa* L.)	Brassicaceae
13	*Calamintha nepeta* (L.) Savi s.l.	Lamiaceae
14	*Centaurium erythraea* Rafn. s.l.	Gentianaceae
15	*Ceratonia siliqua* L.	Fabaceae
16	*Ceterach officinarum* Willd. s.l.	Aspleniaceae
17	*Cichorium intybus* L. s.l.	Asteraceae
18	*Convolvulus arvensis* L.	Convolvulaceae
19	*Crataegus monogyna* Jacq. & *C. laevigata* (Poir.) DC.	Rosaceae
20	*Cyclamen hederifolium* Aiton & *C. repandum* Sm	Primulaceae
21	*Cydonia oblonga* Mill.	Rosaceae
22	*Cynara cardunculus* L. & *C. scolymus* L. s.l	Asteraceae
23	*Cynodon dactylon* (L.) Pers.	Poaceae

24	*Daucus carota* L. s.l.	Apiaceae
25	*Ecballium elaterium* (L.) A. Rich.	Cucurbitaceae
26	*Equisetum* spp. (*E. arvense* L., *E. giganteum* L., *E. telmateia* Ehrh., *E. ramosissimum* Desf.)	Equisetaceae
27	*Ficus carica* L.	Moraceae
28	*Foeniculum vulgare* Mill.	Apiaceae
29	*Fumaria* spp. (*F. agraria* Lag., *F. capreolata* L., *F. officinalis* L., *F. parviflora* Lam.)	Papaveraceae
30	*Hedera helix* L. s.l.	Araliaceae
31	*Helichrysum italicum* (Roth) G. Don s.l.	Asteraceae
32	*Helleborus* spp. (*H. bocconei* Ten., *H. foetidus* L., *H. lividus* Aiton ex Curtis)	Ranunculaceae
33	*Hordeum vulgare* L.	Poaceae
34	*Hypericum perforatum* L. & *H. perfoliatum* L.	Hypericaceae
35	*Juglans regia* L.	Juglandaceae
36	*Lactuca* spp. (*L. sativa* L., *L. serriola* L., *L. viminea* (L.) J.Presl & C.Presl, *L. virosa* Habl.)	Asteraceae
37	*Laurus nobilis* L.	Lauraceae
38	*Lavatera* spp. (*L. cretica* L., *L. olbia* L., *L. trimestris* L.) & *Althaea officinalis* L.	Malvaceae
39	*Linum usitatissimum* L.	Linaceae
40	*Lonicera implexa* Aiton	Caprifoliaceae
41	*Malva* spp. (*M. neglecta* Wallr., *M. nicaeensis* All., *M. parviflora* L., *M. sylvestris* L.)	Malvaceae
42	*Marrubium vulgare* L.	Lamiaceae
43	*Matricaria chamomilla* L., *Tanacetum parthenium* (L.) Sch.Bip. & *T. vulgare* L.	Asteraceae
44	*Mentha pulegium* L.	Lamiaceae
45	*Mentha* spp. (*M. aquatica* L., *M.* × *piperita* L., *M. spicata* L., *M. suaveolens* Ehrh.)	Lamiaceae
46	*Morus alba* L. & *M. nigra* L.	Moraceae
47	*Muscari racemosum* Mill. & *Leopoldia comosa* (L.) Parl.	Asparagaceae
48	*Myrtus communis* L.	Myrtaceae
49	*Nasturtium officinale* R. Br.	Brassicaceae
50	*Ocimum basilicum* L.	Lamiaceae
51	*Olea europaea* L.	Oleaceae

52	*Origanum vulgare* L. s.l. & *O. majorana* L.	Lamiaceae
53	*Papaver rhoeas* L.	Papaveraceae
54	*Papaver somniferum* L.	Papaveraceae
55	*Parietaria* spp. (*P. judaica* L., *P. lusitanica* L., *P. officinalis* L.)	Urticaceae
56	*Petroselinum crispum* (Mill.) Fuss	Apiaceae
57	*Pinus halepensis* Mill. & *P. pinea* L.	Pinaceae
58	*Pistacia lensticus* L.	Anacardiaceae
59	*Pistacia terebinthus* L.	Anacardiaceae
60	*Plantago* spp. (*P. coronopus* L., *P. lagopus* L., *P. lanceolata* L., *P. major* L., *P. serraria* L.)	Plantaginaceae
61	*Polygonum aviculare* L. s.l.	Polygonaceae
62	*Prunus cerasus* L. & *P. avium* L.	Rosaceae
63	*Prunus dulcis* (Mill.) D.A. Webb	Rosaceae
64	*Prunus persica* (L.) Batsch	Rosaceae
65	*Punica granatum* L.	Lythraceae
66	*Ranunculus* spp. (*R. arvensis* L., *R. bulbosus* L., *R. paludosus* Poir., *R. muricatus* L., *R. millefolius* Banks & Sol., *R. sardous* Crantz, *R. sceleratus* L.) & *Ficaria verna* Huds.	Ranunculaceae
67	*Ricinus communis* L.	Euphorbiaceae
68	*Rosa* spp. (*R. canina* L., *R. sempervirens* L., *R. serafini* Viv.)	Rosaceae
69	*Rosmarinus officinalis* L.	Lamiaceae
70	*Rubus* spp.	Rosaceae
71	*Rumex* spp. (*R. acetosa* L., *R. acetosella* L., *R. bucephalophorus* L., *R. conglomeratus* Murray, *R. crispus* L., *R. obtusifolius* L., *R. pulcher* L., *R. sanguineus* L., *thyrsoides* Desf.)	Polygonaceae
72	*Ruscus aculeatus* L. & *R. hypoglossum* L.	Asparagaceae
73	*Ruta chalaepensis* L. & *R. graveolens* L.	Rutaceae
74	*Sambucus nigra* L.	Adoxaceae
75	*Senecio* spp. (*S. delphinifolius* Rchb., *S. lycopifolius* Desf., *S. vulgaris* L.) & *Jacobaea candida* (C.Presl) B.Nord. & Greuter	Asteraceae
76	*Solanum nigrum* L.	Solanaceae

77	*Sonchus* spp. (*S. asper* (L.) Hill, *S. oleraceus* (L.) L., *S. tenerrimus* L.)	Solanaceae
78	*Tamus communis* L. (now: *Dioscorea communis* (L.) Caddick & Wilkin.)	Dioscoreaceae
79	*Thymus herba-barona* Loisel., *T. vulgaris* L. & *Thymbra capitata* (L.) Cav.	Lamiaceae
80	*Trigonella foenum-graecum* L.	Fabaceae
81	*Triticum aestivum* L. & *T. durum* Desf.	Poaceae
82	*Tussilago farfara* L.	Asteraceae
83	*Ulmus glabra* Huds. & *U. minor* Mill.	Ulmaceae
84	*Umbilicus horizontalis* (Guss.) DC. & *U. rupestris* (Salisb.) Dandy	Crassulaceae
85	*Urtica* spp. (*U. atrovirens* Req. ex Loisel., *U. dioica* L., *U. membranacea* Poir. ex Savigny, *U. pilulifera* L., *U. urens* L.)	Urticaceae
86	*Verbascum* spp. (*V. creticum* (L.f.) Cav., *V. densiflorum* Bertol., *V. pulverulentum* Vill., *V. sinuatum* L., *V. thapsus* L.)	Scrophulariaceae
87	*Verbena officinalis* L.	Verbenaceae

Table 7-6 ANOVA table of Probit regression.

Supplementary table 5. ANOVA table of Probit regression

	Df	Deviance	Resid.	Df Resid. Dev	Pr(>Chi)
NULL			2870	41.772	
plant	86	5.3002	2784	36.472	< 2e-16 ***
Use	10	11.0159	2774	25.456	< 2e-16 ***
joint.rec	1	1.3826	2773	24.073	< 2e-16 ***
Geo	2	2.4393	2771	21.634	< 2e-16 ***
joint.rec:geo	2	0.0790	2769	21.555	0.00626 **

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Supplementary material of Chapter 5

Table 7-7 Symptom- and organ defined categories of use (54) employed for the classification of the medicinal plant knowledge in *De Materia Medica* (*ex* Matthioli, 1568).

Abbreviation	**Description**
ANDR	Andrology (incl. male fertility)
ANTI	Antidotes (systemically applied)
CARD	Cardiovascular problems (hemorrhoids)
FEVE	Fever (incl. malaria)
FOOD	Food (spices, staples)
G-DI	Diarrheal conditions (diarrhea, dysentery)
G-FU	Gastric function (purging, vomiting, digestion, flatulence, heartburn, appetite)
G-LS	Liver, spleen, jaundice
G-OT	Other gastrointestinal ailments (anal prolapse, hiccup, hematemesis, ruptures, hernia)
G-PA	Gastrointestinal pain
G-PL	Purgatives, laxatives
GY-B	Abortives (abortion, afterbirth, induce contractions)
GY-I	Induce vaginal discharge (menstrual and other fluxes)
GY-O	Other gynecological conditions (lactation, breast inflammation)
GY-S	Staunch vaginal discharge (staunch menstrual and other fluxes)
GY-U	Uterine conditions
LIBI	Libido regulators (aphrodisiacs, anaphrodisiacs)
M-BJ	Bones and joints (fractures, splinters, joints)
M-MT	Muscles and tendons (cramps, spasms, thoracic pain, lower back pain)
N-EP	Epilepsy
N-HT	Headache, toothache
N-PS	Psychiatric disorders (psychiatry, hypnotics, soporifics, psychosis, stimulants)
N-SC	Sciatica
N-VA	Various neurological ailments (syncope, tremor, vertigo, paralysis, general ailments, numbness)
O-AN	Angina
O-BR	Bruises
O-GO	Gout
O-HM	Humoral management
O-PI	Unspecific pain & inflammation
O-RS	*Rotti e spasimati* (i.e. "the ruptured and spastic"; unidentified illness)
O-SC	Scrofula
O-UL	Unspecified ulcers
O-VA	Various uses (e.g. veterinary, magic)
OPHT	Ophthalmology
PARA	Parasites (e.g. lice, scabies, tapeworms)
POIS	Poison (hunting, fish poisons, toxins)

R-CO	Cough (cough, bloody cough)
R-DR	Difficult respiration (e.g. dyspnea, breathing difficulties, asthma)
R-EX	Expectoration (expectorants, trachea, catarrhs)
R-OT	Other respiratory complaints (tuberculosis, pneumonia, unspecific chest complaints, lost voice, lung defects)
REPE	Repellents (e.g. against insects, snakes)
RORO	Otorhinolaryngology (e.g. dentistry, sinusitis, epistaxis, polyps)
S-CO	Cosmetics (e.g. hair, nails, face, skin, armpit odor)
S-EX	Skin excrescences (e.g. tumors, warts, calli)
S-IF	Skin infections (erysipelas, impetigo, abscesses, furuncle, carbuncle, pustules, gangrene)
S-IJ	Injuries (wounds, fissures, abrasions, splinters, burns, sunburns)
S-IN	Dermatitis (pruritus, skin inflammations, blisters, boils, eruptions)
S-OT	Other skin conditions (nails, paronychia, chilblain, vitiligo, eschars, scars, indurations, fistula, swellings)
S-SB	Snakebites (topically applied antidotes)
U-CA	Urinary calculus
U-DI	Diuresis
U-ED	Edema
U-OT	Other urinary ailments (kidney, bladder)
U-PU	Problematic urination

Figure 7-3 Sites of botanical fieldwork

Table 7-8 List of collected herbal drugs described in *De Materia Medica* (*ex* Matthioli, 1568).

[1] Generic and subgeneric taxon names follow The Plant List 1.1 (2013 and references therein). [2] The differentiated plant parts/products are (10): BARK: barks; FLOW: flowers; FRU: fruits; HERB: herbs; LEAF: leaves; OIL: oils; EXUD: exudates; SEED: seeds; SUBT: subterranean parts and WOOD: wood.

Taxon in Matthioli (1568)[1]	Collected species	Collected part(s)[2]	Specimen number(s)
Acacia spp.	Acacia senegal (L.) Willd.	EXUD	
Acanthus mollis L.	Acanthus mollis L.	SUBT	POS-122
Achillea ageratum L.	Achillea ageratum L.	HERB	POS-291
Achillea millefolium L.	Achillea millefolium L.	FLOW, HERB	POS-995
Achillea ptarmica L.	Achillea ptarmica L.	FLOW, LEAF	POS-996
Aconitum spp.	Aconitum napellus L.	SUBT	POS-452
Acorus calamus L.	Acorus calamus L.	SUBT	
Adiantum capillus-veneris L.	Adiantum capillus-veneris L.	HERB	POS-132
Aegilops neglecta Req. ex Bertol.	Aegilops neglecta Req. ex Bertol.	HERB	POS-912
Aeonium arboreum Webb & Berthel.	Aeonium arboreum Webb & Berthel.	LEAF	POS-600
Agrimonia spp.	Agrimonia eupatoria L.	HERB, SEED	
Agrostemma githago L.	Agrostemma githago L.	HERB, SEED	POS-934, POS-951
Ajuga chamaepitys L.	Ajuga chamaepitys L.	HERB	POS-292
Alisma spp.	Alisma plantago-aquatica L.	HERB, SUBT	POS-91, POS-991
Alkanna tinctoria (L.) Tausch	Alkanna tinctoria (L.) Tausch	LEAF, SUBT	POS-646
Allium ampeloprasum L.	Allium ampeloprasum L.	LEAF, SEED	
Allium cepa L.	Allium cepa L.	SUBT	
Allium sativum L.	Allium sativum L.	LEAF, SUBT	
Aloe spp.	Aloe sp.	EXUD	
Althaea officinalis L.	Althaea officinalis L.	LEAF, SEED, SUBT	POS-340
Ambrosia maritima L.	Ambrosia maritima L.	HERB	
Ammi spp.	Ammi visnaga (L.) Lam.	SEED	
Amomum subulatum Roxb.	Amomum subulatum Roxb.	FRU	
Anacyclus pyrethrum (L.) Lag.	Anacyclus pyrethrum (L.) Lag.	SUBT	

Taxon in Matthioli (1568)[1]	Collected species	Collected part(s)[2]	Specimen number(s)
Anagallis spp.	Anagallis arvensis L.	HERB, SEED	
Anagyris foetida L.	Anagyris foetida L.	LEAF, SEED, SUBT	POS-21
Anchusa spp.	Anchusa azurea Mill.	HERB, SEED, SUBT	POS-293
Anemone spp.	Anemone coronaria L.	HERB, LEAF, SUBT	POS-590
Anethum graveolens L.	Anethum graveolens L.	LEAF, SEED	
Antirrhinum spp.	Antirrhinum majus L.	FLOW	POS-70
Apium graveolens L.	Apium graveolens L.	LEAF, SEED, SUBT	
Apium nodiflorum (L.) Lag.	Apium nodiflorum (L.) Lag.	LEAF, SEED, SUBT	POS-941
Aquilaria spp.	Aquilaria sp.	WOOD	
Arctium spp.	Arctium lappa L.	LEAF, SUBT	POS-119
Arisarum vulgare O.Targ.Tozz.	Arisarum vulgare O.Targ.Tozz.	SUBT	
Aristolochia spp.	Aristolochia rotunda ssp. insularis (E.Nardi & Arrigoni) Gamisans	SUBT	POS-608
Artemisia abrotanum L.	Artemisia abrotanum L.	SEED	
Artemisia absinthium L.	Artemisia absinthium L.	HERB	
Artemisia arborescens (Vaill.) L.	Artemisia arborescens (Vaill.) L.	FLOW, HERB	POS-666
Artemisia herba-alba L.	Artemisia herba-alba L.	HERB	
Arum spp.	Arum maculatum L.	LEAF, SEED, SUBT	
Ulmus spp.	Arundo donax L.	LEAF, SUBT	
Asarum europaeum L.	Asarum europaeum L.	SUBT	
Asparagus spp.	Asparagus sp.	HERB, SEED, SUBT	POS-136
Asphodelus spp.	Asphodelus ramosus L.	FLOW, LEAF, SEED, SUBT	POS-597
Asplenium sagittatum (DC.) Bunge, A. J.	Asplenium sagittatum (DC.) Bunge, A. J.	LEAF	POS-963
Asplenium scolopendrium L.	Asplenium scolopendrium L.	LEAF	POS-310

Taxon in Matthioli (1568)[1]	**Collected species**	**Collected part(s)[2]**	**Specimen number(s)**
Asplenium trichomanes L.	Asplenium trichomanes L.	HERB	
Aster amellus L.	Aster amellus L.	LEAF	POS-994
Astracantha gummifera (Labill.) Podlech	Astracantha gummifera (Labill.) Podlech	EXUD	
Athamanta cretensis L.	Athamanta cretensis L.	SEED, SUBT	POS-453
Atriplex halimus L.	Atriplex halimus L.	LEAF, SUBT	POS-74
Atriplex hortensis L.	Atriplex hortensis L.	LEAF, SEED	
Atropa belladonna L.	Atropa belladonna L.	SUBT	
Aucklandia lappa DC.	Aucklandia lappa DC.	SUBT	
Avena sativa L.	Avena sativa L.	SEED	
Ballota nigra L.	Ballota nigra L.	LEAF	
Ballota pseudodictamnus (L.) Benth.	Ballota pseudodictamnus (L.) Benth.	HERB, SUBT	
Berula erecta (Huds.) Coville	Berula erecta (Huds.) Coville	LEAF	POS-918
Beta vulgaris L.	Beta vulgaris L.	LEAF, SUBT	POS-50
Bituminaria bituminosa (L.) C.H.Stirt.	Bituminaria bituminosa (L.) C.H.Stirt.	LEAF, SEED, SUBT	POS-5
Bongardia chrysogonum (L.) Spach	Bongardia chrysogonum (L.) Spach	SUBT	POS-652
Boswellia spp.	Boswellia sp.	BARK, EXUD	
Brassica oleracea L.	Brassica oleracea L.	FLOW, HERB, LEAF, SEED, SUBT	
Brassica rapa L.	Brassica rapa L.	HERB, SEED, SUBT	
Bryonia cretica L.	Bryonia cretica L.	FRU, HERB, LEAF, SEED, SUBT	POS-289
Bupleurum fruticosum L.	Bupleurum fruticosum L.	SEED	POS-393, POS-979
Cachrys spp.	Cachrys libanotis L.	HERB, SEED, SUBT	POS-283
Calystegia soldanella (L.) Roem. & Schult.	Calystegia soldanella (L.) Roem. & Schult.	HERB	POS-506, POS-925
Cannabis sativa L.	Cannabis sativa L.	LEAF, SEED	

Taxon in Matthioli (1568)[1]	**Collected species**	**Collected part(s)[2]**	**Specimen number(s)**
Capparis spinosa L.	Capparis spinosa L.	FLOW, LEAF, SUBT	POS-196
Capsella spp.	Capsella bursa-pastoris (L.) Medik.	SEED	
Carlina gummifera (L.) Less.	Carlina gummifera (L.) Less.	SUBT	
Carthamus lanatus L.	Carthamus lanatus L.	FLOW, LEAF, SEED	POS-226, POS-940
Carthamus tinctorius L.	Carthamus tinctorius L.	SEED	
Carum carvi L.	Carum carvi L.	SEED	
Castanea sativa Mill.	Castanea sativa Mill.	FRU, SEED	
Celtis australis L.	Celtis australis L.	FRU, WOOD	POS-862
Centaurium erythraea Rafn.	Centaurium erythraea Rafn.	HERB	POS-156
Ceratonia siliqua L.	Ceratonia siliqua L.	FRU	
Cerinthe major L.	Cerinthe major L.	LEAF	POS-15
Ceterach officinarum Willd.	Ceterach officinarum Willd.	LEAF	POS-113
Chelidonium majus L.	Chelidonium majus L.	HERB, SUBT	
Chondrilla juncea L.	Chondrilla juncea L.	HERB, SUBT	POS-375
Cicer arietinum; Pisum sativum	Cicer arietinum L.	SEED	
Cichorium intybus L.	Cichorium intybus L.	LEAF, SUBT	
Cinnamomum spp.	Cinnamomum cassia (L.) J.Presl	BARK	
Cinnamomum spp.	Cinnamomum verum J.Presl	BARK	
Cistus ladanifer L.	Cistus ladanifer L.	EXUD	POS-294
Cistus spp.	Cistus salviifolius L.	FLOW	POS-636
Citrullus colocynthis (L.) Schrad.	Citrullus colocynthis (L.) Schrad.	FRU	
Citrus medica L.	Citrus medica L.	FRU, SEED	
Clematis spp.	Clematis vitalba L.	HERB, SEED, SUBT	POS-309
Clinopodium nepeta (L.) Kuntze	Clinopodium nepeta (L.) Kuntze	LEAF	
Clinopodium vulgare L.	Clinopodium vulgare L.	HERB	POS-937
Colchicum spp.	Colchicum autumnale L.	SUBT	

Taxon in Matthioli (1568)[1]	Collected species	Collected part(s)[2]	Specimen number(s)
Commiphora spp.	Commiphora gileadensis (L.) C.Chr.	EXUD, SEED, WOOD	
Commiphora spp.	Commiphora myrrha (Nees) Engl.	EXUD	
Conium maculatum L.	Conium maculatum L.	HERB, SEED	POS-120
Convolvulus arvensis L.	Convolvulus arvensis L.	LEAF	
Convolvulus scammonia L.	Convolvulus scammonia L.	EXUD, SUBT	POS-890
Coriandrum sativum L.	Coriandrum sativum L.	LEAF, SEED	
Coris monspeliensis L.	Coris monspeliensis L.	SUBT	POS-284
Cornus mas L.	Cornus mas L.	FRU, LEAF	
Coronilla scorpioides (L.) Koch	Coronilla scorpioides (L.) Koch	HERB	POS-878
Corylus avellana L.	Corylus avellana L.	SEED	
Crataegus azarolus L.	Crataegus azarolus L.	FRU	
Crataegus spp.	Crataegus sp.	FRU	
Cressa cretica L.	Cressa cretica L.	SUBT	POS-404
Crithmum maritimum L.	Crithmum maritimum L.	LEAF, SEED, SUBT	POS-771
Crocus sativus L.	Crocus sativus L.	FLOW, SUBT	
Cucumis melo L.	Cucumis melo L.	FRU, SEED, SUBT	
Cucumis sativus L.	Cucumis sativus L.	FRU, LEAF, SEED	
Cuminum cyminum L.	Cuminum cyminum L.	SEED	
Cupressus sempervirens L.	Cupressus sempervirens L.	FRU, LEAF	POS-173
Cuscuta spp.	Cuscuta sp.	HERB	POS-286
Cyclamen spp.	Cyclamen repandum Sm.	SUBT	POS-63
Cydonia oblonga Mill.	Cydonia oblonga Mill.	FLOW, FRU	
Cynanchum acutum L.	Cynanchum acutum L.	LEAF	POS-976
Cynara scolymus; Cynara cardunculus	Cynara scolymus L.	HERB, SUBT	
Cynodon dactylon (L.) Pers.	Cynodon dactylon (L.) Pers.	SUBT	
Cyperus papyrus L.	Cyperus papyrus L.	HERB	POS-267
Cyperus rotundus L.	Cyperus rotundus L.	SUBT	

Taxon in Matthioli (1568)[1]	Collected species	Collected part(s)[2]	Specimen number(s)
Cytinus spp.	Cytinus hypocistis (L.) L.	HERB	POS-49
Danae racemosa (L.) Moench	Danae racemosa (L.) Moench	SUBT	
Daphne gnidium L.	Daphne gnidium L.	LEAF, SEED	POS-59
Daphne laureola L.	Daphne laureola L.	FRU, LEAF	POS-463, POS-964
Daphne spp.	Daphne oleoides Schreb.	LEAF	POS-220
Daucus carota L.	Daucus carota L.	HERB, LEAF, SEED, SUBT	POS-336
Delphinium staphisagria L.	Delphinium staphisagria L.	SEED	
Diospyros spp.	Diospyros ebenum J.Koenig ex Retz.	WOOD	
Dipsacus spp.	Dipsacus fullonum L.	SUBT	POS-459
Dittrichia spp.	Dittrichia viscosa (L.) Greuter	FLOW, HERB, LEAF	POS-437
Dracunculus vulgaris Schott.	Dracunculus vulgaris Schott.	FLOW, LEAF, SEED, SUBT	
Drimia maritima (L.) Stearn	Drimia maritima (L.) Stearn	SEED, SUBT	
Dryopteris filix-mas (L.) Schott	Dryopteris filix-mas (L.) Schott	SUBT	POS-314
Dysphania botrys (L.) Mosyakin & Clemants	Dysphania botrys (L.) Mosyakin & Clemants	HERB	POS-781
Ecballium elaterium (L.) A.Rich.	Ecballium elaterium (L.) A.Rich.	FRU, LEAF, SUBT	POS-287
Echinophora tenuifolia L.	Echinophora tenuifolia L.	FLOW, SEED	POS-504
Echium angustifolium Mill.	Echium angustifolium Mill.	LEAF, SUBT	
Echium spp.	Echium italicum L.	SEED, SUBT	POS-121
Elettaria cardamomum (L.) Maton	Elettaria cardamomum (L.) Maton	FRU	
Ephedra spp.	Ephedra distachya L.	FRU	
Equisetum spp.	Equisetum fluviatile L.	HERB	
Equisetum spp.	Equisetum telmateia Ehrh.	HERB, SUBT	POS-627
Erica spp.	Erica scoparia L.	FLOW, LEAF	POS-56
Eruca vesicaria (L.) Cav.	Eruca vesicaria (L.) Cav.	LEAF, SEED	POS-604
Eryngium maritimum L.	Eryngium maritimum L.	LEAF, SUBT	POS-58

Taxon in Matthioli (1568)[1]	**Collected species**	**Collected part(s)**[2]	**Specimen number(s)**
Euphorbia acanthothamnos Heldr. & Sart. ex Boiss.	Euphorbia acanthothamnos Heldr. & Sart. ex Boiss.	HERB, SUBT	POS-886
Euphorbia apios L.	Euphorbia apios L.	SUBT	POS-899
Euphorbia lathyris L.	Euphorbia lathyris L.	HERB, SEED	POS-583
Euphorbia spp.	Euphorbia paralias L.	LEAF, SEED, SUBT	POS-276
Euphorbia pithyusa L.	Euphorbia pithyusa L.	HERB, SUBT	POS-204, POS-881
Euphorbia resinifera	Euphorbia sp.	EXUD	
Fagus sylvatica L.	Fagus sylvatica L.	BARK, FRU, LEAF, SEED	
Ferula communis L.	Ferula communis L.	HERB, SEED	
Ferula spp.	Ferula gummosa Boiss.	EXUD	
Ferula spp.	Ferula persica Willd.	EXUD	
Ferula spp.	Ferula tingitana L.	EXUD	
Ficaria verna Huds.	Ficaria verna Huds.	HERB, SUBT	
Ficus carica L.	Ficus carica L.	EXUD, FRU, LEAF	
Ficus sycomorus L.	Ficus sycomorus L.	FRU	
Foeniculum vulgare Mill.	Foeniculum vulgare Mill.	LEAF, SEED, SUBT	POS-137, POS-335
Fraxinus spp.	Fraxinus ornus L.	LEAF	
Fumaria officinalis L.	Fumaria officinalis L.	HERB	POS-210
Galium aparine L.	Galium aparine L.	HERB, SEED	
Galium verum L.	Galium verum L.	FLOW, SUBT	POS-319, POS-956
Gentiana lutea L.	Gentiana lutea L.	SUBT	
Gladiolus italicus Mill.	Gladiolus italicus Mill.	SUBT	POS-635
Glaucium corniculatum (L.) Curtis	Glaucium corniculatum (L.) Curtis	HERB	POS-288
Glaucium flavum Crantz	Glaucium flavum Crantz	FLOW, LEAF, SEED, SUBT	
Glebionis coronaria (L.) Cass. ex Spach	Glebionis coronaria (L.) Cass. ex Spach	FLOW, HERB	POS-16
Globularia alypum L.	Globularia alypum L.	SEED	POS-125

Taxon in Matthioli (1568)[1]	Collected species	Collected part(s)[2]	Specimen number(s)
Glycyrrhiza spp.	Glycyrrhiza glabra L.	SUBT	POS-290
Hedera helix L.	Hedera helix L.	FLOW, FRU, HERB, LEAF, SUBT	
Helichrysum spp.	Helichrysum italicum (Roth) G.Don	FLOW	POS-337
Heliotropium spp.	Heliotropium europaeum L.	HERB, SEED	POS-395
Helleborus spp.	Helleborus lividus Aiton	HERB	POS-946
Heracleum spp.	Heracleum sphondylium L.	FLOW, SEED, SUBT	
Hippuris vulgaris L.	Hippuris vulgaris L.	HERB	
Hirschfeldia incana (L.) Lagr.-Foss.	Hirschfeldia incana (L.) Lagr.-Foss.	HERB	POS-127
Hordeum spp.	Hordeum vulgare L.	SEED	
Hyacinthus orientalis L.	Hyacinthus orientalis L.	SUBT	
Hyoscyamus spp.	Hyoscyamus albus L.	HERB, SEED, SUBT	
Hypecoum procumbens L.	Hypecoum procumbens L.	HERB	POS-603
Hypericum spp.	Hypericum perfoliatum L.	HERB, SEED	POS-938
Hypericum spp.	Hypericum perforatum L.	SEED	
Hyphaene thebaica (L.) Mart.	Hyphaene thebaica (L.) Mart.	FRU, SEED	
Hyssopus officinalis L.	Hyssopus officinalis L.	HERB	
Inula helenium L.	Inula helenium L.	LEAF, SUBT	
Iris foetidissima L.	Iris foetidissima L.	SEED, SUBT	POS-928
Iris spp.	Iris x germanica L.	SUBT	
Isatis tinctoria L.	Isatis tinctoria L.	LEAF	POS-85
Juglans regia L.	Juglans regia L.	OIL, SEED	
Juncus spp.	Juncus acutus L.	LEAF, SEED	POS-273
Juniperus excelsa M.Bieb.	Juniperus excelsa M.Bieb.	EXUD, FRU	
Juniperus spp.	Juniperus oxycedrus L.	BARK, FRU, LEAF	POS-133
Juniperus sabina L.	Juniperus sabina L.	LEAF	
Lactuca sativa L.	Lactuca sativa L.	LEAF, SEED	
Lactuca serriola L.	Lactuca serriola L.	LEAF, SEED	POS-400

Taxon in Matthioli (1568)[1]	Collected species	Collected part(s)[2]	Specimen number(s)
Lagenaria siceraria (Molina) Standl.	Lagenaria siceraria (Molina) Standl.	FRU	
Lagoecia cuminoides L.	Lagoecia cuminoides L.	SEED	POS-887
Laurus nobilis L.	Laurus nobilis L.	FRU, LEAF, SUBT	POS-970
Lavandula stoechas L.	Lavandula stoechas L.	HERB	POS-55
Lawsonia inermis L.	Lawsonia inermis L.	LEAF	
Lemna minor L.	Lemna minor L.	HERB	POS-414
Lens culinaris Medik.	Lens culinaris Medik.	SEED	
Leontice leontopetalum L.	Leontice leontopetalum L.	SUBT	
Leopoldia comosa (L.) Parl.	Leopoldia comosa (L.) Parl.	SUBT	POS-219
Lepidium sativum L.	Lepidium sativum L.	HERB, LEAF, SEED	
Levisticum officinale W.D.J.Koch	Levisticum officinale W.D.J.Koch	SEED, SUBT	
Ligustrum vulgare L.	Ligustrum vulgare L.	FLOW, LEAF	POS-334, POS-957
Lilium candidum L.	Lilium candidum L.	LEAF, SUBT	POS-884
Limonium spp.	Limonium sp.	SUBT	POS-51, POS-282
Linum usitatissimum L.	Linum usitatissimum L.	SEED	
Lithospermum officinale L.	Lithospermum officinale L.	SEED	
Lolium spp.	Lolium perenne L.	HERB	
Lolium temulentum L.	Lolium temulentum L.	SEED	
Lonicera spp.	Lonicera implexa Aiton	LEAF, SEED	POS-885
Lupinus spp.	Lupinus angustifolius Guss.	SEED, SUBT	
Lysimachia vulgaris L.	Lysimachia vulgaris L.	HERB	POS-302
Malus domestica Borkh.	Malus domestica Borkh.	FRU	
Malva spp.	Malva alcea L.	SUBT	POS-958
Malva sylvestris L.	Malva sylvestris L.	LEAF, SEED, SUBT	POS-211
Mandragora spp.	Mandragora officinalis Mill.	FRU, LEAF, SUBT	
Marrubium vulgare L.	Marrubium vulgare L.	LEAF, SEED	POS-123

Taxon in Matthioli (1568)[1]	**Collected species**	**Collected part(s)**[2]	**Specimen number(s)**
Matricaria chamomilla; Chamaemelum nobile	Matricaria chamomilla L.	FLOW, HERB, SUBT	
Matthiola incana (L.) R.Br.	Matthiola incana (L.) R.Br.	HERB, SEED, SUBT	
Medicago arborea L.	Medicago arborea L.	LEAF	POS-268, POS-898
Medicago sativa L.	Medicago sativa L.	SEED	
Melilotus spp.	Melilotus officinalis (L.) Pall.	HERB	
Melilotus spp.	Melilotus sulcatus (L.) All.	HERB	
Melissa officinalis L.	Melissa officinalis L.	LEAF	
Mentha spp.	Mentha aquatica L.	HERB, SEED	POS-217, POS-406
Mentha piperita L	Mentha piperita L	HERB	
Mentha pulegium L.	Mentha pulegium L.	HERB	
Mercurialis spp.	Mercurialis annua L.	HERB, SEED	POS-11
Mespilus germanica L.	Mespilus germanica L.	FRU	
Meum athamanticum Jacq.	Meum athamanticum Jacq.	SUBT	POS-305
Moringa oleifera Lam.	Moringa oleifera Lam.	OIL, SEED	
Morus alba; Morus nigra	Morus alba L.	BARK, EXUD, FRU, LEAF	POS-939
Myriophyllum spp.	Myriophyllum sp.	HERB	POS-919
Myrtus communis L.	Myrtus communis L.	FRU, LEAF	POS-166
Nardostachys jatamansi (D.Don) DC.	Nardostachys jatamansi (D.Don) DC.	SUBT	
Nasturtium officinale R.Br.	Nasturtium officinale R.Br.	LEAF	POS-238
Nelumbo nucifera Gaertn.	Nelumbo nucifera Gaertn.	SEED, SUBT	
Nerium oleander L.	Nerium oleander L.	FLOW, LEAF	POS-997
Nigella sativa L.	Nigella sativa L.	SEED	
Nuphar lutea (L.) Sm.	Nuphar lutea (L.) Sm.	SEED, SUBT	
Nymphaea alba L.	Nymphaea alba L.	SUBT	
Ocimum basilicum L.	Ocimum basilicum L.	LEAF, SEED	
Olea europaea L.	Olea europaea L.	FRU, LEAF, OIL, SEED	

Taxon in Matthioli (1568)[1]	Collected species	Collected part(s)[2]	Specimen number(s)
Onobrychis caput-galli (L.) Lam.	Onobrychis caput-galli (L.) Lam.	HERB	POS-894
Ononis spinosa L.	Ononis spinosa L.	SUBT	POS-296
Onopordum spp.	Onopordum illyricum L.	LEAF, SUBT	POS-943
Opopanax spp.	Opopanax chironius (L.) W.D.J. Koch	EXUD, SEED	POS-348
Origanum dictamnus L.	Origanum dictamnus L.	HERB, SUBT	POS-396, POS-888
Origanum majorana L.	Origanum majorana L.	HERB	
Origanum sipyleum L.	Origanum sipyleum L.	HERB	POS-891
Origanum vulgare L.	Origanum vulgare L.	HERB	
Orobanche spp.	Orobanche sp.	HERB	
Oryza sativa L.	Oryza sativa L.	SEED	
Osyris alba L.	Osyris alba L.	HERB	POS-4
Otanthus maritimus (L.) Hoffmanns. & Link	Otanthus maritimus (L.) Hoffmanns. & Link	HERB	POS-148
Paeonia spp.	Paeonia mascula (L.) Mill.	SEED, SUBT	POS-642
Paliurus spina-christi Mill.	Paliurus spina-christi Mill.	HERB, LEAF	
Pancratium maritimum L.	Pancratium maritimum L.	SEED, SUBT	
Panicum miliaceum L.	Panicum miliaceum L.	SEED	
Papaver rhoeas L.	Papaver rhoeas L.	FRU, LEAF, SEED	
Papaver somniferum L.	Papaver somniferum L.	EXUD, FRU, LEAF, SEED	POS-163
Parietaria spp.	Parietaria judaica L.	HERB	POS-60
Pastinaca sativa L.	Pastinaca sativa L.	HERB, SEED, SUBT	
Peganum harmala L.	Peganum harmala L.	SEED	
Persicaria hydropiper (L.) Delarbre	Persicaria hydropiper (L.) Delarbre	LEAF, SEED	POS-821
Petasites spp.	Petasites hybridus (L.) G.Gaertn., B.Mey. & Scherb.	HERB	
Petroselinum crispum (Mill.) Fuss	Petroselinum crispum (Mill.) Fuss	SEED	
Peucedanum officinale L.	Peucedanum officinale L.	EXUD, SUBT	POS-462

Taxon in Matthioli (1568)[1]	Collected species	Collected part(s)[2]	Specimen number(s)
Phillyrea spp.	Phillyrea angustfolia L.	LEAF	
Phoenix dactylifera L.	Phoenix dactylifera L.	FLOW, FRU, LEAF	
Phragmites spp.	Phragmites australis (Cav.) Trin. ex Steud.	LEAF, SUBT	
Physalis alkekengi L.	Physalis alkekengi L.	FRU, LEAF	POS-817
Pimpinella anisum L.	Pimpinella anisum L.	SEED	
Pimpinella saxifraga L.	Pimpinella saxifraga L.	HERB	
Pinus spp.	Pinus pinea L.	BARK, LEAF, SEED	
Piper spp.	Piper nigrum L.	SEED	
Pistacia lentiscus L.	Pistacia lentiscus L.	BARK, EXUD, FRU, HERB, LEAF, SUBT	POS-19, POS-648
Pistacia terebinthus L.	Pistacia terebinthus L.	BARK, EXUD, FRU, LEAF	POS-370, POS-896
Pistacia vera L.	Pistacia vera L.	SEED	
Pistia stratiotes L.	Pistia stratiotes L.	HERB	POS-674
Plantago afra L.	Plantago afra L.	SEED	POS-175
Plantago coronopus L.	Plantago coronopus L.	HERB, SUBT	POS-931
Plantago spp. (excl. Plantago afra)	Plantago media L.	LEAF, SEED, SUBT	
Platanus orientalis L.	Platanus orientalis L.	BARK, FRU, LEAF	
Polygala venulosa Sm.	Polygala venulosa Sm.	HERB	POS-889
Polygonatum verticillatum (L.) All.	Polygonatum verticillatum (L.) All.	SUBT	
Polygonum aviculare L.	Polygonum aviculare L.	HERB	
Polypodium spp.	Polypodium vulgare L.	SUBT	POS-67
Polystichum lonchitis (L.) Roth	Polystichum lonchitis (L.) Roth	LEAF	
Populus alba L.	Populus alba L.	BARK, LEAF	
Populus nigra L.	Populus nigra L.	LEAF, SEED	POS-933
Portulaca oleracea L.	Portulaca oleracea L.	HERB	
Potamogeton natans L.	Potamogeton natans L.	LEAF	

Taxon in Matthioli (1568)[1]	**Collected species**	**Collected part(s)**[2]	**Specimen number(s)**
Potentilla spp.	Potentilla reptans L.	HERB, SUBT	POS-659
Prunus armeniaca L.	Prunus armeniaca L.	FRU	
Prunus avium; Prunus cerasus	Prunus avium (L.) L.	EXUD, FRU	
Prunus domestica; Prunus spinosa	Prunus domestica L.	EXUD, FRU, LEAF	
Prunus dulcis L.	Prunus dulcis L.	EXUD, FRU, OIL, SEED, SUBT	
Prunus persica (L.) Batsch	Prunus persica (L.) Batsch	FRU	
Pteridium aquilinum (L.) Kuhn	Pteridium aquilinum (L.) Kuhn	LEAF, SUBT	POS-106
Punica granatum L.	Punica granatum L.	FLOW, FRU, SEED, SUBT	
Pyrus spp.	Pyrus communis L.	FRU	
Quercus ilex L.	Quercus ilex L.	BARK, FRU, LEAF, SEED	POS-397
Quercus robur L.	Quercus robur L.	BARK, FRU, LEAF, SEED	
Raphanus raphanistrum; Raphanus sativus	Raphanus raphanistrum L.	LEAF, SEED, SUBT	
Reseda spp.	Reseda alba L.	SEED	POS-23
Rhamnus spp.	Rhamnus lycioides L.	HERB	POS-895
Rheum spp.	Rheum rhaponticum L.	SUBT	
Rhus coriaria L.	Rhus coriaria L.	FRU, LEAF	POS-298
Ricinus communis L.	Ricinus communis L.	LEAF, OIL, SEED	POS-131
Rosa spp.	Rosa canina L.	FRU	
Rosa spp.	Rosa gallica L.	FLOW, LEAF	POS-944
Rosmarinus officinalis L.	Rosmarinus officinalis L.	HERB	POS-165
Rubia spp.	Rubia peregrina L.	FRU, HERB, SUBT	POS-46, POS-498
Rubus idaeus L.	Rubus idaeus L.	FLOW, FRU, HERB, LEAF	
Rubus sectio rubus	Rubus vulgaris Weihe & Nees	FLOW, FRU, HERB, LEAF	

Taxon in Matthioli (1568)[1]	Collected species	Collected part(s)[2]	Specimen number(s)
Rumex spp.	Rumex crispus L.	LEAF, SEED, SUBT	POS-965
Ruscus aculeatus L.	Ruscus aculeatus L.	FRU, HERB, SUBT	POS-64
Ruscus hypoglossum L.	Ruscus hypoglossum L.	HERB, SUBT	POS-502
Ruscus hypophyllum L.	Ruscus hypophyllum L.	LEAF	POS-403
Ruta spp.	Ruta chalepensis L.	HERB, SEED, SUBT	POS-3
Salix spp.	Salix alba L.	BARK, LEAF, SEED	POS-304
Salvia spp.	Salvia officinalis L.	LEAF	POS-164
Salvia viridis L.	Salvia viridis L.	HERB, SEED	
Sambucus spp.	Sambucus nigra L.	FRU, LEAF, SUBT	
Sanguisorba spp.	Sanguisorba minor Scop.	LEAF	
Saponaria officinalis L.	Saponaria officinalis L.	SUBT	POS-312
Sarcopoterium spinosum (L.) Spach	Sarcopoterium spinosum (L.) Spach	LEAF, SEED	POS-7
Satureja thymbra L.	Satureja thymbra L.	HERB	
Scandix pecten-veneris L.	Scandix pecten-veneris L.	HERB	POS-179
Scirpoides holoschoenus (L.) Soják	Scirpoides holoschoenus (L.) Soják	HERB, SEED	POS-961
Scrophularia peregrina L.	Scrophularia peregrina L.	HERB, SEED	POS-134, POS-879, POS-966
Securigera securidaca (L.) Degen & Dorfl.	Securigera securidaca (L.) Degen & Dorfl.	SEED	
Sedum cepaea L.	Sedum cepaea L.	LEAF	POS-921
Sedum roseum (L.) Scop.	Sedum roseum (L.) Scop.	SUBT	POS-725
Senecio vulgaris L.	Senecio vulgaris L.	HERB	
Serapias spp.	Serapias parviflora L.	SUBT	POS-109, POS-882
Sesamum indicum L.	Sesamum indicum L.	HERB, OIL, SEED	
Seseli tortuosum L.	Seseli tortuosum L.	SEED, SUBT	POS-377, POS-503

Taxon in Matthioli (1568)[1]	**Collected species**	**Collected part(s)**[2]	**Specimen number(s)**
Setaria italica; Sorghum spp.	Setaria italica (L.) P.Beauv.	SEED	
Silene vulgaris (Moench) Garcke	Silene vulgaris (Moench) Garcke	SEED	
Silybum marianum (L.) Gaertn.	Silybum marianum (L.) Gaertn.	HERB, SUBT	POS-883
Sinapis alba; Brassica nigra	Sinapis alba L.	SEED	
Sison amomum L.	Sison amomum L.	SEED	
Sisymbrium irio L.	Sisymbrium irio L.	SEED	POS-595
Sium sisarum L.	Sium sisarum L.	SUBT	
Smilax aspera L.	Smilax aspera L.	FRU, LEAF	POS-110
Smyrnium olusatrum L.	Smyrnium olusatrum L.	LEAF, SEED, SUBT	POS-1
Smyrnium perfoliatum L.	Smyrnium perfoliatum L.	LEAF, SEED, SUBT	POS-194
Solanum americanum Mill.	Solanum americanum Mill.	LEAF	
Sonchus spp.	Sonchus sp.	LEAF, SUBT	
Sorbus domestica L.	Sorbus domestica L.	FRU	POS-819
Sparganium spp.	Sparganium erectum L.	SEED, SUBT	POS-361
Spartium junceum L.	Spartium junceum L.	FLOW, HERB, SEED	POS-118
Stachys spp.	Stachys cretica L.	LEAF	POS-892
Streptopus amplexifolius (L.) DC.	Streptopus amplexifolius (L.) DC.	SUBT	POS-993
Symphytum officinale L	Symphytum officinale L	SUBT	
Tamarix spp.	Tamarix sp.	BARK, FRU, HERB, WOOD	POS-171, POS-866
Tanacetum parthenium (L.) Sch.Bip.	Tanacetum parthenium (L.) Sch.Bip.	FLOW, HERB	
Taxus baccata L.	Taxus baccata L.	HERB	
Teucrium chamaedrys L.	Teucrium chamaedrys L.	HERB	
Teucrium flavum L.	Teucrium flavum L.	HERB	POS-203, POS-942
Teucrium polium L.	Teucrium polium L.	HERB	POS-209
Teucrium scordium L.	Teucrium scordium L.	HERB	POS-343
Thalictrum spp.	Thalictrum minus L.	LEAF	POS-905

Taxon in Matthioli (1568)[1]	**Collected species**	**Collected part(s)**[2]	**Specimen number(s)**
Thapsia garganica L.	Thapsia garganica L.	HERB, SUBT	
Thymbra capitata (L.) Cav.	Thymbra capitata (L.) Cav.	HERB	POS-197
Thymus spp.	Thymus serpyllum L.	HERB	
Tordylium apulum L.	Tordylium apulum L.	HERB, SEED, SUBT	POS-640
Trapa natans L.	Trapa natans L.	FRU, HERB	
Tribulus terrestris L.	Tribulus terrestris L.	FRU, HERB	POS-242
Trifolium spp.	Trifolium pratense L.	HERB	
Trigonella foenum-graecum L.	Trigonella foenum-graecum L.	SEED	
Triticum spp.	Triticum aestivum L.	SEED	
Triticum spp.	Triticum dicoccon (Schrank.) Schübl.	SEED	
Tussilago farfara L.	Tussilago farfara L.	LEAF, SUBT	
Typha spp.	Typha sp.	SEED	
Ulmus spp.	Ulmus minor Mill.	BARK, LEAF, SUBT	POS-827
Umbilicus spp.	Umbilicus rupestris (Salisb.) Dandy	LEAF	POS-66
Urtica spp.	Urtica dioica L.	HERB, SEED	
Valeriana celtica L.	Valeriana celtica L.	HERB, SUBT	
Valeriana spp.	Valeriana officinalis L.	SUBT	POS-306
Valeriana tuberosa L.	Valeriana tuberosa L.	HERB, SUBT	POS-645
Veratrum album L.	Veratrum album L.	SUBT	
Verbascum spp.	Verbascum thapsus L.	LEAF, SUBT	
Verbena spp.	Verbena officinalis L.	HERB, LEAF, SUBT	
Vicia cracca L.	Vicia cracca L.	SEED	POS-213
Vicia ervilia (L.) Willd.	Vicia ervilia (L.) Willd.	SEED	
Vicia faba L.	Vicia faba L.	SEED	
Vinca spp.	Vinca minor L.	HERB	
Vincetoxicum hirundinaria Medik.	Vincetoxicum hirundinaria Medik.	LEAF, SUBT	POS-325
Viola spp.	Viola odorata L.	LEAF	

Taxon in Matthioli (1568)[1]	Collected species	Collected part(s)[2]	Specimen number(s)
Vitex agnus-castus L.	Vitex agnus-castus L.	LEAF, SEED	POS-158
Vitis spp.	Vitis vinifera L.	FRU, HERB, LEAF, SEED	
Withania somnifera (L.) Dunal	Withania somnifera (L.) Dunal	FRU, SEED, SUBT	POS-800
Xanthium strumarium L.	Xanthium strumarium L.	FRU	POS-505
Zingiber officinale Roscoe.	Zingiber officinale Roscoe.	LEAF, SUBT	POS-975
Ziziphus jujuba Mill.	Ziziphus jujuba Mill.	FRU, LEAF, SUBT	

Figure 7-4 Permit for Plant collection in Greece

ΑΔΑ: 6Ω8Κ4653Π8-ΑΚ7

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ΥΠΟΥΡΓΕΙΟ ΠΕΡΙΒΑΛΛΟΝΤΟΣ
ΚΑΙ ΕΝΕΡΓΕΙΑΣ
ΓΕΝΙΚΗ Δ/ΝΣΗ ΑΝΑΠΤΥΞΗΣ & ΠΡΟΣΤΑΣΙΑΣ
ΔΑΣΩΝ & ΑΓΡΟΠΕΡΙΒΑΛΛΟΝΤΟΣ
Δ/ΝΣΗ ΔΙΑΧΕΙΡΙΣΗΣ ΔΑΣΩΝ& Δ.Π.
ΤΜΗΜΑ ΔΑΣΙΚΩΝ ΠΡΟΣΤΑΤΕΥΟΜΕΝΩΝ
ΠΕΡΙΟΧΩΝ & ΔΑΣΙΚΗΣ ΑΝΑΨΥΧΗΣ

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Αθήνα 14-04-2016

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ΚΟΙΝ.: Πίνακας κοινοποιήσεων

ΘΕΜΑ: Άδεια έρευνας

Έχοντας υπόψη:

1. Τις διατάξεις του αρθρ. 19 του Ν. 998/79, τις διατάξεις του Π.Δ. 67/81 «περί προστασίας της Ελληνικής Άγριας Πανίδας και Αυτοφυούς Χλωρίδας» (ΦΕΚ 23/Α/ 30-1-81 και 43/Α/18-2-81), του Ν.2637/98 (ΦΕΚ 200/Α/27-8-98) και του Ν. 3937/2011 (ΦΕΚ 60/Β/31-3-2011).
2. Την Κ.Υ.Α. αριθ.33318/3028/11-12-1998(Β΄1289) «Καθορισμός μέτρων και διαδικασιών για την διατήρηση των φυσικών οικοτόπων (ενδιαιτημάτων) καθώς και της άγριας πανίδας και χλωρίδας», όπως τροποποιήθηκε με την ΚΥΑ αριθ. Η.Π. 14849/853/Ε103/04-04-2008(Β΄645) «Τροποποίηση των υπ, αριθ. 33318/1510/2005 κοινών υπουργικών αποφάσεων(Β΄992), σε συμμόρφωση με τις διατάξεις της οδηγίας 2006/104 του Συμβουλίου της 20ης Νοεμβρίου 2006 της Ευρωπαϊκής Ένωσης».
3. Την Σύμβαση για την διατήρηση της άγριας ζωής και του φυσικού περιβάλλοντος στη Ευρώπη(Σύμβαση Βέρνης), που κυρώθηκε με τον Ν.1335/83(Α΄32).
4. Τις αριθ. 105067/2901/14-06-2004 και 127557/2178/07-07-2015 εγκυκλίους μας.
5. Της απόφασης του Πρωθυπουργού 2876/7.10.2009 "Αλλαγή τίτλου Υπουργείων" (ΦΕΚ Β' 2234).
6. Τον Ν. 3852/2010 (ΦΕΚ 87/Α/2010) «Νέα Αρχιτεκτονική της Αυτοδιοίκησης και της Αποκεντρωμένης Διοίκησης – Πρόγραμμα Καλλικράτης (ΦΕΚ Α΄ 87).
7. Τις διατάξεις του ν.1650/86 (ΦΕΚ Α 160), όπως ισχύει «Για την προστασία του περιβάλλοντος» και συγκεκριμένα του άρθρου 28 του Κεφαλαίου Ζ περί κυρώσεων και αστικής ευθύνης.
8. Το Π.Δ υπ' αριθμό 100/2014, (ΦΕΚ 167/Α/28-08-2014) «Οργανισμός Υπουργείου Περιβάλλοντος, Ενέργειας και Κλιματικής Αλλαγής».
9. Το Π.Δ. υπ' αριθμό 25/2015, «Διορισμός Αντιπροέδρου της Κυβέρνησης, Υπουργών, Αναπληρωτών Υπουργών και Υφυπουργών (ΦΕΚ 21/Α΄/21-01-2015)».
10. Το Προεδρικό Διάταγμα υπ' αριθμό 70/2015 (ΦΕΚ 114/Α΄/22-09-2015) «Ανασύσταση Υπουργείων».
11. Το Π.Δ. υπ' αριθμό 73/2015, (ΦΕΚ 116/Α΄/23-09-2015), «Διορισμός Αντιπροέδρου της Κυβέρνησης, Υπουργών, Αναπληρωτών Υπουργών και Υφυπουργών».
12. Την από 04-05-2015 ηλεκτρονική αίτησή σας.
13. Το γεγονός ότι η έρευνα σας οφείλει να διεξαχθεί με τρόπο που δεν θα προκαλέσει προβλήματα στην επιβίωση των ειδών και ότι τα αποτελέσματα της έρευνας σας ενδιαφέρουν άμεσα την υπηρεσία.

Ε γ κ ρ ί ν ο υ μ ε

1) Την χορήγηση άδειας έρευνας στον κ. **Peter Staub** του Πανεπιστημίου του Κάγκλιαρι (University of Cagliari), ο οποίος είναι επιστημονικά υπεύθυνος και συνεργάζεται με τον καθηγητή **Θεοφάνη Κωνσταντινίδη** από το Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών (ΚΠΑ).

ΑΔΑ: 6Ω8Κ4653Π8-ΑΚ7

2) Η έρευνα αφορά τα φαρμακευτικά φυτά που αναφέρονται στο βιβλίο De Materia Medica (Περί Ύλης Ιατρική) του Διοσκουρίδη του Πεδάνιου (1[ος] αι. μ.χ) και συγκεκριμένα να δοκιμαστεί πως η θεραπευτική χρήση του φυτού, (όπως ορίζεται από τον Διοσκουρίδη τον Πεδάνιο), συνδέεται με τη γεύση και την οσμή του.

3) Ο στόχος της έρευνας είναι να μελετήσει το ρόλο της γεύσης και της όσφρησης στη διαμόρφωση της εξέλιξης για ιατρική χρήση των φυτών στην Ευρώπη και τη Μεσόγειο.

4) Τα είδη που θα μελετηθούν είναι: **Convolvulus scammonia L**, (2 τεμάχια από υπόγειο τμήμα του φυτού), **Polygala venulosa Sm**, (2 τεμάχια από υπέργειο τμήμα του φυτού), **Origanum dictamnus L**, (2 τεμάχια ολόκληρο το φυτό), **Euphorbia acanthothamnus Heldr. & Sart. ex Boiss**, (2 τεμάχια από υπόγειο τμήμα του φυτού), **Lagoecia cuminoides L**, (σπόροι), **Ferula tingitana L**, (τμήματα φυτού), **Gagea graeca (L.)** (σπόροι), **Irmsch**, **Origanum sipyleum L**. (2 τεμάχια από υπέργειο τμήμα του φυτού). ***Το φυτικό υλικό που θα συλλεχθεί προορίζεται για την εν λόγω έρευνα και απαγορεύεται η πώληση και η αναπαραγωγή του.***

5) Το χρονικό διάστημα διεξαγωγής της έρευνας είναι από 15 Απριλίου 2016 έως και 15 Μαΐου 2016. Οι περιοχές που θα πραγματοποιηθεί η έρευνα είναι στη **Κρήτη**, στη **Ρόδο** και στη **Σάμο**. ***Πριν από την μετάβαση στις τοποθεσίες που θα πραγματοποιηθεί η έρευνα, θα πρέπει ο ενδιαφερόμενος να έρθει σε επικοινωνία με τις τοπικές δασικές υπηρεσίες, (βλέπε πίνακα ανακοινώσεων), προκειμένου να οριστούν οι τοποθεσίες στις οποίες θα μεταβεί.***

6) Όλες οι εργασίες πεδίου θα πρέπει να γίνουν με τρόπο που δεν θα προκαλούν προβλήματα στα είδη ή σε άλλα βιοτικά στοιχεία της περιοχής.

7) Η παρούσα άδεια που ισχύει **μέχρι 30 Μαΐου 2016**, είναι ανεξάρτητη από άδειες, πιστοποιητικά κ.α. που τυχόν απαιτούνται από άλλες υπηρεσίες (στρατιωτικές αρχές κ.α.).

8) Για την εξαγωγή των δειγμάτων θα πρέπει να αποκτήσετε άδεια CITES από τα κατά τόπους γραφεία CITES.

9) Παρακαλούμε να μας ενημερώσετε (με email), σε τυχόν ακύρωση του ταξιδιού σας για την διεξαγωγή της έρευνας.

10) Οι Δασικές υπηρεσίες στις οποίες κοινοποιείται η παρούσα άδεια παρακαλούνται για την εποπτεία της έρευνας, τη συνοδεία του ερευνητή από δασικό υπάλληλο, καθώς και τη θέσπιση επί πλέον όρων, εφ' όσον κρίνουν ότι απαιτούνται. Σε περίπτωση μη επικοινωνίας του ενδιαφερόμενου με τις υπηρεσίες, παρακαλούμε για την σχετική ενημέρωσή μας.

11) Μετά το πέρας των εργασιών, ο ενδιαφερόμενος οφείλει να στείλει τα αποτελέσματα των εργασιών επί της έρευνας πεδίου, του εργαστηρίου και ένα αντίγραφο της εργασίας του στην Υπηρεσία μας, καθώς και από ένα αντίγραφο στον επιστημονικό συνεργάτη του ΚΠΑ.

Ο Προϊστάμενος
της Δ/νσης α/α

Δημήτριος Γερμανός
Δασολόγος

Πίνακας κοινοποιήσεων

ΑΠΟΚΕΝΤΡΩΜΕΝΗ ΔΙΟΙΚΗΣΗ ΑΙΓΑΙΟΥ
ΓΕΝΙΚΗ ΔΙΕΥΘΥΝΣΗ ΔΑΣΩΝ &
ΑΓΡΟΤΙΚΩΝ ΥΠΟΘΕΣΕΩΝ

1. **ΔΙΕΥΘΥΝΣΗ ΣΥΝΤΟΝΙΣΜΟΥ & ΕΠΙΘΕΩΡΗΣΗΣ ΔΑΣΩΝ**
   Ακτή Μιαούλη 83 & Μπότσαρη 2 – 8, 185 38, **ΠΕΙΡΑΙΑΣ**

- ΤΜΗΜΑ ΠΡΟΣΤΑΣΙΑΣ ΔΑΣΩΝ ΚΑΙ ΔΑΣΙΚΩΝ ΕΚΤΑΣΕΩΝ
  (ΠΕΡΙΦΕΡΕΙΑΚΗ ΔΙΑΧΕΙΡΙΣΤΙΚΗ ΑΡΧΗ CITES **ΒΟΡΕΙΟΥ ΑΙΓΑΙΟΥ**)
  Ακτή Μιαούλη & Μπότσαρη 2-8, 18538 Πειραιάς
  s.karapournalidis@apdaigaiou.gov.gr , gdd@apdaigaiou.gov.gr Fax: +30 (2104) 29 12 63

ΑΔΑ: 6Ω8Κ4653Π8-ΑΚ7

- ΤΜΗΜΑ ΠΡΟΣΤΑΣΙΑΣ ΔΑΣΩΝ ΚΑΙ ΔΑΣΙΚΩΝ ΕΚΤΑΣΕΩΝ
  (ΠΕΡΙΦΕΡΕΙΑΚΗ ΔΙΑΧΕΙΡΙΣΤΙΚΗ ΑΡΧΗ CITES **ΝΟΤΙΟΥ ΑΙΓΑΙΟΥ**)
  Γ. Μαύρου 2, 85100 **ΡΟΔΟΣ**
  d.dason@gmail.com Fax: +30 (22410) 2 06 74 , +30 (22410) 4 36 9

2. **Διεύθυνση Δασών Σάμου**
   Δερβενακίων 8
   83 100 **ΣΑΜΟΣ** - Email : pvaddass@otenet.gr

3. **Διεύθυνση Δασών Δωδεκανήσου**
   Γ. Μαύρου 2, 851 00, **ΡΟΔΟΣ email: d.dason@gmail.gr**

ΑΠΟΚΕΝΤΡΩΜΕΝΗ ΔΙΟΙΚΗΣΗ ΚΡΗΤΗΣ
ΓΕΝΙΚΗ ΔΙΕΥΘΥΝΣΗ ΔΑΣΩΝ &
ΑΓΡΟΤΙΚΩΝ ΥΠΟΘΕΣΕΩΝ

4. ΔΙΕΥΘΥΝΣΗ ΣΥΝΤΟΝΙΣΜΟΥ & ΕΠΙΘΕΩΡΗΣΗΣ ΔΑΣΩΝ
   ΑΠΟΚΕΝΤΡΩΜΕΝΗΣ ΔΙΟΙΚΗΣΗΣ ΚΡΗΤΗΣ
   Περιοχή Τ.Ε.Ι. (Δασικό Φυτώριο Φοινικιάς)
   71 410 **ΗΡΑΚΛΕΙΟ**
   - ΤΜΗΜΑ ΠΡΟΣΤΑΣΙΑΣ ΔΑΣΩΝ ΚΑΙ ΔΑΣΙΚΩΝ ΕΚΤΑΣΕΩΝ
     ΓΡΑΦΕΙΟ ΔΙΕΘΝΩΝ ΣΥΜΒΑΣΕΩΝ
     (ΠΕΡΙΦΕΡΕΙΑΚΗ ΔΙΑΧΕΙΡΙΣΤΙΚΗ ΑΡΧΗ CITES **ΚΡΗΤΗΣ**)
     Περιοχή ΤΕΙ (Δασικό Φυτώριο Φοινικιάς),71410
     Ηράκλειο dsed@apdkritis.gov.gr ,
     d.stamataki@apdkritis.gov.gr Fax: +30 (2810) 26 49 56

5. ΔΙΕΥΘΥΝΣΗ ΔΑΣΩΝ ΗΡΑΚΛΕΙΟΥ
   Περιοχή Τ.Ε.Ι. (Δασικό Φυτώριο Φοινικιάς)
   71 410 **ΗΡΑΚΛΕΙΟ** - Email : ddh@apdkritis.gov.gr

6. **ΔΙΕΥΘΥΝΣΗ ΔΑΣΩΝ ΛΑΣΙΘΙΟΥ**
   Ρ. Καπετανάκη 8
   72 100 **ΛΑΣΙΘΙ** - Email : forestlas@yahoo.gr

7. ΔΙΕΥΘΥΝΣΗ ΔΑΣΩΝ ΡΕΘΥΜΝΟΥ
   Κόμβος Αμαρίου –
   74 100 **ΡΕΘΥΜΝΟ** - Email : das_reth@otenet.gr

8. **ΔΙΕΥΘΥΝΣΗ ΔΑΣΩΝ ΧΑΝΙΩΝ – ΧΡΥΣΟΠΗΓΗ**
   73 100 **ΧΑΝΙΑ** - Email : ddchania@otenet.gr

Figure 7-5 Permit for photography in Greece

ΑΔΑ: 7ΨΞ24653Π8-ΝΜΑ

INFORMATICS DEVELOPMENT AGENCY
Digitally signed by INFORMATICS DEVELOPMENT AGENCY
Date: 2016.04.13 11:52:40 EEST
Reason:
Location: Athens

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
ΥΠΟΥΡΓΕΙΟ ΠΕΡΙΒΑΛΛΟΝΤΟΣ ΚΑΙ ΕΝΕΡΓΕΙΑΣ
ΓΕΝΙΚΗ Δ/ΝΣΗ ΑΝΑΠΤΥΞΗΣ & ΠΡΟΣΤΑΣΙΑΣ ΔΑΣΩΝ & ΑΓΡΟΠΕΡΙΒΑΛΛΟΝΤΟΣ
Δ/ΝΣΗ ΔΙΑΧΕΙΡΙΣΗΣ ΔΑΣΩΝ& Δ.Π.
ΤΜΗΜΑ ΔΑΣΙΚΩΝ ΠΡΟΣΤΑΤΕΥΟΜΕΝΩΝ ΠΕΡΙΟΧΩΝ & ΔΑΣΙΚΗΣ ΑΝΑΨΥΧΗΣ

Ταχ. Δ/νση : Χαλκοκονδύλη 31
Ταχ. Κωδ. :104 32 ΑΘΗΝΑ
Πληροφ. : Θωμάς Αγγέλου
Τηλέφωνο : 210 214699
eimail : diaxeirisi.dason@gmail.com

Αθήνα 12-04-2016

Αριθμ. Πρωτ.: 139635/1186

ΠΡΟΣ: Peter Staub c/o Dr.ssa. Laura Casu
Department of Biomedical Sciences
University of Cagliari
Via Ospedale 72
09124 Cagliari staub@unica.it
ITALY

ΚΟΙΝ.: Πίνακας κοινοποιήσεων

ΘΕΜΑ: Άδεια φωτογράφησης.

Έχοντας υπόψη:

1. Τις διατάξεις του αρθρ. 19 του Ν. 998/79, τις διατάξεις του Π.Δ. 67/81 «περί προστασίας της Ελληνικής Άγριας Πανίδας και Αυτοφυούς Χλωρίδας» (ΦΕΚ 23/Α/ 30-1-81 και 43/Α/18-2-81), του Ν.2637/98 (ΦΕΚ 200/Α/27-8-98) και του Ν. 3937/2011 (ΦΕΚ 60/Β/31-3-2011).
2. Την Κ.Υ.Α. αριθ.33318/3028/11-12-1998(Β΄1289) «Καθορισμός μέτρων και διαδικασιών για την διατήρηση των φυσικών οικοτόπων (ενδιαιτημάτων) καθώς και της άγριας πανίδας και χλωρίδας», όπως τροποποιήθηκε με την ΚΥΑ αριθ. Η.Π. 14849/853/Ε103/04-04-2008(Β΄645) «Τροποποίηση των υπ, αριθ. 33318/1510/2005 κοινών υπουργικών αποφάσεων(Β΄992), σε συμμόρφωση με τις διατάξεις της οδηγίας 2006/104 του Συμβουλίου της 20ης Νοεμβρίου 2006 της Ευρωπαϊκής Ένωσης».
3. Την Σύμβαση για την διατήρηση της άγριας ζωής και του φυσικού περιβάλλοντος στη Ευρώπη(Σύμβαση Βέρνης), που κυρώθηκε με τον Ν.1335/83(Α΄32).
4. Τις αριθ. 105067/2901/14-06-2004 και 127557/2178/07-07-2015 εγκύκλίους μας.
5. Της απόφασης του Πρωθυπουργού 2876/7.10.2009 "Αλλαγή τίτλου Υπουργείων" (ΦΕΚ Β' 2234).
6. Τον Ν. 3852/2010 (ΦΕΚ 87/Α/2010) «Νέα Αρχιτεκτονική της Αυτοδιοίκησης και της Αποκεντρωμένης Διοίκησης – Πρόγραμμα Καλλικράτης (ΦΕΚ Α΄ 87).
7. Τις διατάξεις του ν.1650/86 (ΦΕΚ 160/Α΄), «Για την προστασία του Περιβάλλοντος», όπως ισχύει και συγκεκριμένα του άρθρου 28 του Κεφαλαίου Ζ, περί κυρώσεων και αστικής ευθύνης
8. Το Π.Δ υπ' αριθμό 100/2014, (ΦΕΚ 167/Α/28-08-2014) «Οργανισμός Υπουργείου Περιβάλλοντος, Ενέργειας και Κλιματικής Αλλαγής».
9. Το Π.Δ. υπ' αριθμό 25/2015, «Διορισμός Αντιπροέδρου της Κυβέρνησης, Υπουργών, Αναπληρωτών Υπουργών και Υφυπουργών (ΦΕΚ 21/Α΄/21-01-2015)».
10. Το Προεδρικό Διάταγμα υπ' αριθμό 70/2015 (ΦΕΚ 114/Α΄/22-09-2015) «Ανασύσταση Υπουργείων».
11. Το Π.Δ. υπ' αριθμό 73/2015, (ΦΕΚ 116/Α΄/23-09-2015), «Διορισμός Αντιπροέδρου της Κυβέρνησης, Υπουργών, Αναπληρωτών Υπουργών και Υφυπουργών».
12. Την από 04-05-2015 ηλεκτρονική αίτησή σας.

ΑΔΑ: 7ΨΞ24653Π8-ΝΜΑ

13. Το γεγονός ότι η έρευνα σας οφείλει να διεξαχθεί με τρόπο που δεν θα προκαλέσει προβλήματα στην επιβίωση των ειδών και ότι τα αποτελέσματα της έρευνας σας ενδιαφέρουν άμεσα την υπηρεσία.

Ε γ κ ρ ί ν ο υ μ ε

Την άδεια φωτογράφισης – καταγραφής της χλωρίδας, στον κ. **Peter Staub** του Πανεπιστημίου του Κάγκλιαρι **(**University of Cagliari), ο οποίος είναι επιστημονικά υπεύθυνος για την φωτογράφηση και συνεργάζεται με τον καθηγητή **Θεοφάνη Κωνσταντινίδη** από το Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών.

Η φωτογράφηση θα γίνει στα πλαίσια ερευνητικής εργασίας σχετικά με την τεκμηρίωση της βοτανικής από φωτογραφίες των φυτών, κατά το χρονικό διάστημα από **15 Απριλίου 2016** έως και **15 Μαΐου 2016**.

Οι Περιοχές που θα πραγματοποιηθεί η λήψη φωτογραφιών θα είναι στη **Κρήτη**, στη **Ρόδο** και στη **Σάμο**. *Πριν από την μετάβαση στις τοποθεσίες που θα πραγματοποιηθούν οι λήψεις, θα πρέπει ο ενδιαφερόμενος να έρθει σε επικοινωνία με τις τοπικές δασικές υπηρεσίες*, (βλέπε πίνακα ανακοινώσεων), *προκειμένου να οριστούν οι τοποθεσίες στις οποίες θα μεταβεί*.

Οι Δασικές υπηρεσίες στις οποίες κοινοποιείται η παρούσα άδεια παρακαλούνται για την εποπτεία της φωτογράφησης, καθώς και την θέσπιση επί πλέον όρων, εφ' όσον κρίνουν ότι απαιτούνται. Σε περίπτωση μη επικοινωνίας από τον ενδιαφερόμενο με τις υπηρεσίες, παρακαλούμε για την σχετική ενημέρωσή μας.

Όλες οι εργασίες φωτογράφησης θα πρέπει να γίνουν με τρόπο που δεν θα προκαλούν προβλήματα στα είδη ή σε άλλα βιοτικά στοιχεία της περιοχής.

Η παρούσα άδεια που ισχύει μέχρι **15 Μαΐου 2016**, είναι ανεξάρτητη από άδειες, πιστοποιητικά κ.α. που τυχόν απαιτούνται από άλλες υπηρεσίες (στρατιωτικές αρχές κ.α.).

Παρακαλούμε να μας ενημερώσετε σχετικά με email σε τυχόν ακύρωση του ταξιδιού σας στις περιοχές φωτογράφησης.

Μετά το πέρας των εργασιών σας, οφείλετε να στείλετε ένα αντίγραφο της εργασίας σας στην υπηρεσία μας, καθώς και στον υπεύθυνο καθηγητή του Καποδιστριακού Πανεπιστημίου Αθηνών.

Ο Προϊστάμενος
της Δ/νσης α/α

Δημήτριος Γερμανός
Δασολόγος

Πίνακας κοινοποιήσεων

ΑΠΟΚΕΝΤΡΩΜΕΝΗ ΔΙΟΙΚΗΣΗ ΑΙΓΑΙΟΥ
ΓΕΝΙΚΗ ΔΙΕΥΘΥΝΣΗ ΔΑΣΩΝ &
ΑΓΡΟΤΙΚΩΝ ΥΠΟΘΕΣΕΩΝ

1. **ΔΙΕΥΘΥΝΣΗ ΣΥΝΤΟΝΙΣΜΟΥ & ΕΠΙΘΕΩΡΗΣΗΣ ΔΑΣΩΝ**
   Ακτή Μιαούλη 83 & Μπότσαρη 2 – 8, 185 38, **ΠΕΙΡΑΙΑΣ**

ΑΔΑ: 7ΨΞ24653Π8-ΝΜΑ

2. **Διεύθυνση Δασών Σάμου**
   Δερβενακίων 8
   83 100 **ΣΑΜΟΣ** - Email : pvaddass@otenet.gr

3. **Διεύθυνση Δασών Δωδεκανήσου**
   Γ. Μαύρου 2, 851 00, **ΡΟΔΟΣ email: d.dason@gmail.gr**

ΑΠΟΚΕΝΤΡΩΜΕΝΗ ΔΙΟΙΚΗΣΗ ΚΡΗΤΗΣ
ΓΕΝΙΚΗ ΔΙΕΥΘΥΝΣΗ ΔΑΣΩΝ &
ΑΓΡΟΤΙΚΩΝ ΥΠΟΘΕΣΕΩΝ

4. ΔΙΕΥΘΥΝΣΗ ΣΥΝΤΟΝΙΣΜΟΥ & ΕΠΙΘΕΩΡΗΣΗΣ ΔΑΣΩΝ
   ΑΠΟΚΕΝΤΡΩΜΕΝΗΣ ΔΙΟΙΚΗΣΗΣ ΚΡΗΤΗΣ
   Περιοχή Τ.Ε.Ι. (Δασικό Φυτώριο Φοινικιάς)
   71 410 **ΗΡΑΚΛΕΙΟ**

5. ΔΙΕΥΘΥΝΣΗ ΔΑΣΩΝ ΗΡΑΚΛΕΙΟΥ
   Περιοχή Τ.Ε.Ι. (Δασικό Φυτώριο Φοινικιάς)
   71 410 **ΗΡΑΚΛΕΙΟ** - Email : ddh@apdkritis.gov.gr

6. **ΔΙΕΥΘΥΝΣΗ ΔΑΣΩΝ ΛΑΣΙΘΙΟΥ**
   Ρ. Καπετανάκη 8
   72 100 **ΛΑΣΙΘΙ** - Email : forestlas@yahoo.gr

7. ΔΙΕΥΘΥΝΣΗ ΔΑΣΩΝ ΡΕΘΥΜΝΟΥ
   Κόμβος Αμαρίου –
   74 100 **ΡΕΘΥΜΝΟ -** Email : das_reth@otenet.gr

8. **ΔΙΕΥΘΥΝΣΗ ΔΑΣΩΝ ΧΑΝΙΩΝ – ΧΡΥΣΟΠΗΓΗ**
   73 100 **ΧΑΝΙΑ** - Email : ddchania@otenet.gr

Supplementary material of Chapter 6

Figure 7-6 Ballot sheet used for sensory analysis

Valutazione Sensoriale

Nome/Esperimento/Campione:

	Odore			Gusto		
	leggero 1	medio 2	forte 3	leggero 1	medio 2	forte 3
01) Astringente / Tannico						
02) Amaro / Amarognolo						
03) Aspro / Acido / Agro						
04) Salato / Umami / Brodo						
05) Dolce / Dolciastro						
06) Fruttato / Agrodolce						
07) Muschiato / Ambrato / Incenso						
08) Balsamico / Eterico / Canforato						
09) Aromatico / Speziato						
10) Affumicato						
11) Rinfrescante						
12) Caldo						
13) Acuto / Pungente / Pizzicore / Frizzante						
14) Bruciante / Piccante						
15) Legnoso						
16) Amido						
17) Erbaceo / Clorofilla						
18) Paglia / Fieno						
19) Letame / Stalla						
20) Terroso / Bosco						
21) Muffa / Fungo / Umidità						
22) Puzzolente / Sgradevole						
23) Sapone / Profumo / Deodorante						
24) Floreale / Fiorito						
25) Di Noci						
26) Viscido						

Note e osservazione:	Inodore	
	Insapore	

Figure 7-7 Ethical approval for Sensory Analysis

AZIENDA OSPEDALIERO UNIVERSITARIA DI CAGLIARI

COMITATO ETICO INDIPENDENTE
Azienda Ospedaliero Universitaria di Cagliari
P.O. San Giovanni di Dio: via Ospedale 54 – 09124 Cagliari
Segreteria Tecnico Scientifica
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FOGLIO FIRME PRESENZE RIUNIONE COMITATO ETICO
20 luglio 2016

2.16) alle ore
Esame del progetto di ricerca dal titolo: **Analisi descrittiva per i prodotti a base di erbe (Sensory Panel; Medplant.eu)**
Responsabile della U.O.: **Prof. Gabriele Finco**
Responsabile Clinico dello studio: **Dott. Paolo Mura**
Responsabile Scientifico dello studio: **Dott. Marco Leonti – Dip.to Scienze Biomediche Università di Cagliari**
Centro di Sperimentazione: **U.O. Anestesia e Rianimazione**
Presidio Ospedaliero: **Duilio Casula Monserrato**
Struttura di appartenenza: **AOU**

PARERE: si approva		
	COMPONENTI EFFETTIVI DEL COMITATO ETICO	
Nominativo	*Qualifica*	*Firma*
Prof. Ernesto d'Aloja	**Presidente:** Esperto in materia giuridica e assicurativa o un medico legale	[signature]
Dott. Pietro Greco	**Vicepresidente:** Clinico	[signature]
Dott.ssa Luisa Cossu Giua	Rappresentante del volontariato o dell'associazionismo di tutela dei pazienti	[signature]
Dott.ssa Caterina Chillotti	Farmacologo	[signature]
Dott.ssa Maria Teresa Galdieri	Farmacista del SSN	[signature]
Dott.ssa Francesca Ibba	Rappresentante dell'area delle professioni sanitarie interessata alle sperimentazioni	[signature]
Dott. Sandro Loche	Clinico	assente giustificato
Dott. Luigi Minerba	Biostatistico	[signature]
Dott. Salvatore Pisu	Esperto in bioetica	[signature]
Dott. Pier Paolo Pusceddu	Pediatra	[signature]
Dott. Luigi Salvatore Giuseppe Serreli	Sostituto permanente Direttore Sanitario AOU Cagliari (*in relazione* agli studi svolti nella AOU Cagliari)	assente
Dott. Francesco Ronchi	Esperto di dispositivi medici	assente giustificato
Dott. Francesco Scarpa	Medico di medicina generale	[signature]
Dott. Tonio Sollai	Clinico	[signature]
	DIRETTORI SANITARI	
Dott.ssa Marinella Spissu	Sostituto permanente Direttore Sanitario AOB di Cagliari (*in relazione* agli studi svolti nella AOB)	assente
Dott. Sergio Laconi	Sostituto permanente Direttore Sanitario ASL8 di Cagliari (*in relazione* agli studi svolti nella ASL8)	[signature]
Segreteria Scientifica C.E.I.	Dott.ssa Caterina Chillotti – Farmacologa – responsabile Segreteria	[signature]
Segretario verbalizzante	Dott.ssa Sabrina Chabert	[signature]

Prof. Carlo Carcassi Esperto in genetica [signature]

AZIENDA
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CAGLIARI, 25/07/2016 PROT. NP/2016/4522

ALLEGATO N° 2.16
al VERBALE N.13 della Riunione del 20 luglio 2016

COMITATO ETICO AZIENDA OSPEDALIERO UNIVERSITARIA DI CAGLIARI

Comitato Etico Indipendente istituito con delibera N° 753 del 24/09/2013 della Direzione Generale della Azienda Ospedaliero Universitaria di Cagliari

Il giorno **20 luglio 2016** alle ore **15,00** presso l'**Aula della Direzione Medica del P.O. San Giovanni di Dio** di Cagliari si è riunito il Comitato Etico Indipendente dell'Azienda Ospedaliero di Cagliari per esprimere il proprio parere etico motivato sulla richiesta di cui al punto **2.16** dell'ordine del giorno dal titolo:

Analisi descrittiva per i prodotti a base di erbe (Sensory Panel; Medplant.eu)
Responsabile della U.O.: **Prof. Gabriele Finco**
Responsabile Clinico dello studio: **Dott. Paolo Mura**
Responsabile Scientifico dello studio: **Dott. Marco Leonti – Dip.to Scienze Biomediche Università di Cagliari**
Centro di Sperimentazione: **U.O. Anestesia e Rianimazione**
Presidio Ospedaliero: **Duilio Casula Monserrato**
Struttura di appartenenza: **AOU**

Verificata

la presenza del numero legale come da foglio firma allegato

Valutati i seguenti documenti:

- protocollo di studio
- sinossi
- foglio informativo e modulo di consenso informato
- assicurazione LLOYD'S polizza numero A1201640522 scadenza 31/03/2017 massimale 5.000.000,00 per protocollo, 1.000.000,00 per paziente , copertura postuma 36 mesi

VERIFICATA

a) l'adeguatezza delle motivazioni e le ipotesi della ricerca
b) l'adeguatezza delle attese dello studio
c) la correttezza dei criteri di analisi e di interpretazione dei risultati
d) la proposta di analisi statistiche appropriate
e) la trasparenza delle sponsorizzazioni ed i relativi aspetti economici
f) la proprietà dei dati e la trasparenza dei risultati
g) il rispetto dei diritti dei partecipanti alla ricerca per quanto concerne le informazioni sullo studio
h) l'adeguatezza della tutela della privacy
i) la possibilità di individuare un comitato scientifico che abbia la responsabilità della gestione/conduzione dello studio

CONSTATATO CHE

AZIENDA
OSPEDALIERO
UNIVERSITARIA
DI CAGLIARI

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fa riferimento ai codici deontologici (in particolare alla revisione corrente della Dichiarazione di Helsinki e/o alle norme di Buona Pratica Clinica CEE secondo l'allegato 1 del DM 27/4/1992 e/o al DM 18/3/1998 e seguenti)

SI APPROVA

la richiesta in oggetto

Si precisa che per la valutazione dello studio il Comitato Etico ha ritenuto non necessario convocare lo Sperimentatore.

La valutazione scientifica della richiesta è stata espletata dalla Dott.ssa Caterina Chillotti.

Si ricorda che lo sperimentatore è obbligato ad informare il CE sull'andamento della sperimentazione ogni sei mesi, con relazione scritta riportante il numero dei casi arruolati tramite compilazione dell'Allegato L della modulistica di questo CE (rapporto sullo stato di avanzamento D.M. 15 Luglio 1997). Lo Sperimentatore è inoltre tenuto ad informare lo scrivente CE dell'inizio e della conclusione della sperimentazione.

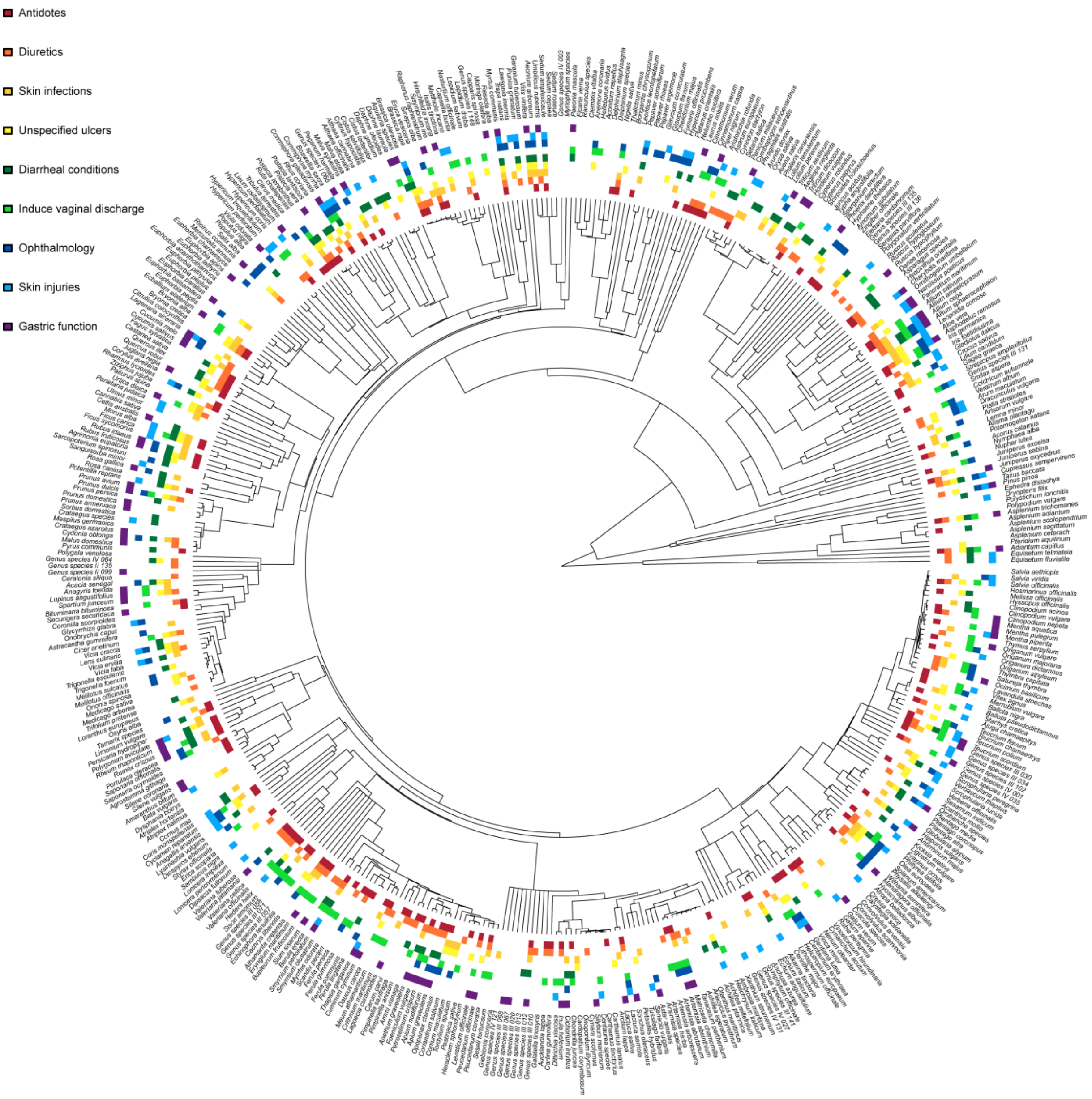
Il parere sopra espresso s'intende limitato esclusivamente alle versioni citate in oggetto ed alla documentazione presentata ed espressamente citata. Ogni variazione allo stesso deve obbligatoriamente essere sottoposta al parere di questo CE, così come previsto dalle vigenti norme nazionali ed europee. Tutte le segnalazioni relative ad eventi avversi seri e inattesi, la conclusione dello studio ed ogni eventuale sua integrazione dovranno essere comunicati allo scrivente CE. ***Lo studio potrà essere intrapreso solo a seguito della autorizzazione del Direttore Generale formalizzato da apposito atto deliberativo**. I farmaci per la sperimentazione dovranno essere consegnati esclusivamente per il tramite del Servizio di Farmacia dell'Azienda ospedaliera. Lo sperimentatore è tenuto ad interpellare in qualsiasi momento il CE ogni qual volta si renda necessaria una nuova valutazione etica.

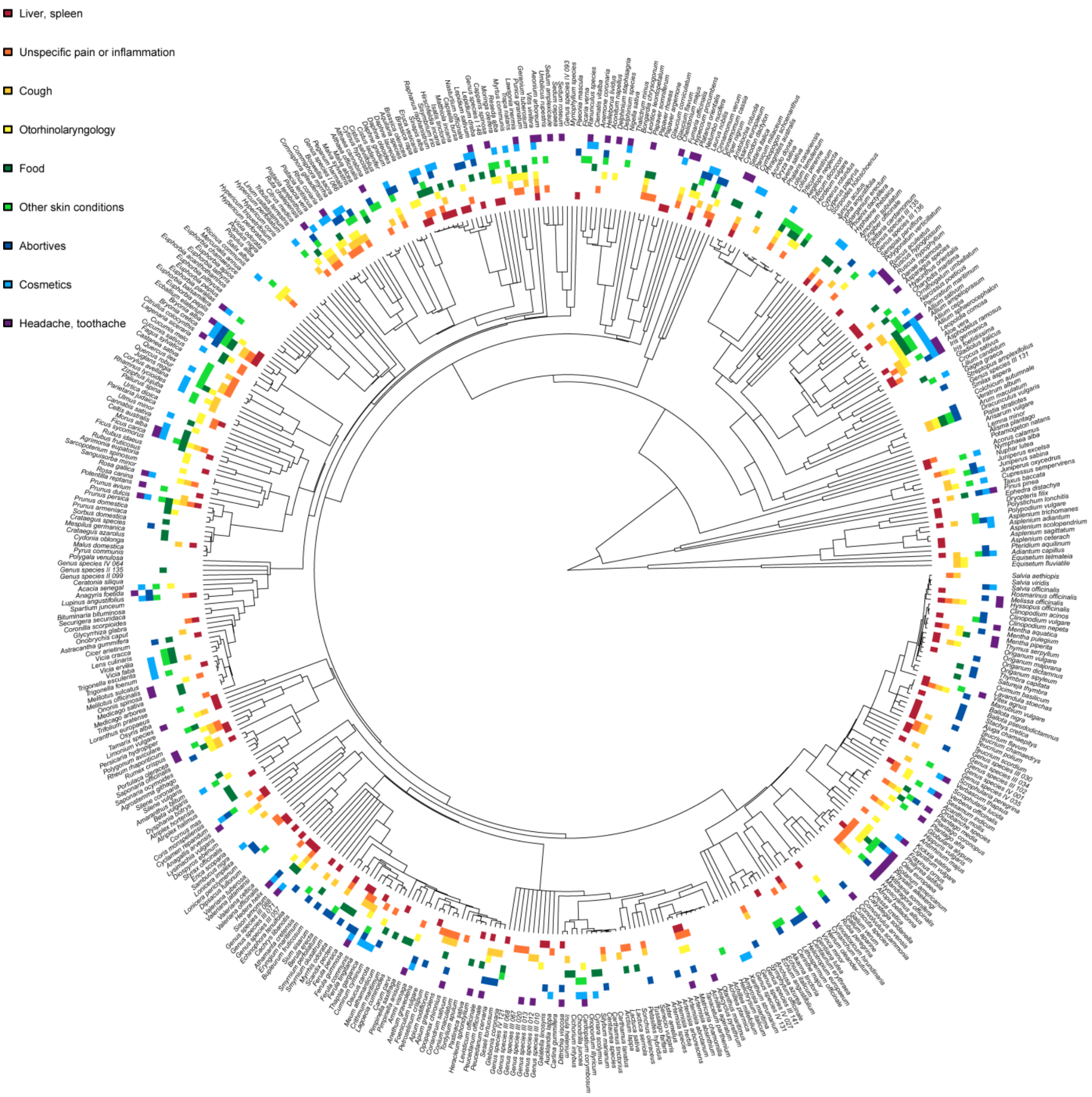
***"Si attesta che questo Comitato Etico è organizzato ed opera in conformità alla normativa vigente in Italia in materia di GCP-ICH, in osservanza a quanto previsto dall'allegato del D.M. 15/07/1997, dal D.M. 18/03/1998 e dal D.L. n. 211/2003" (Recepimento delle linee guida dell'Unione Europea di buona pratica clinica per l'esecuzione delle sperimentazioni cliniche dei medicinali), nonché della Legge n. 189 del 08/11/2012 e del D.M. della Salute 08/02/2013.**
Si allega lista dei presenti e assenti e delle relative funzioni.

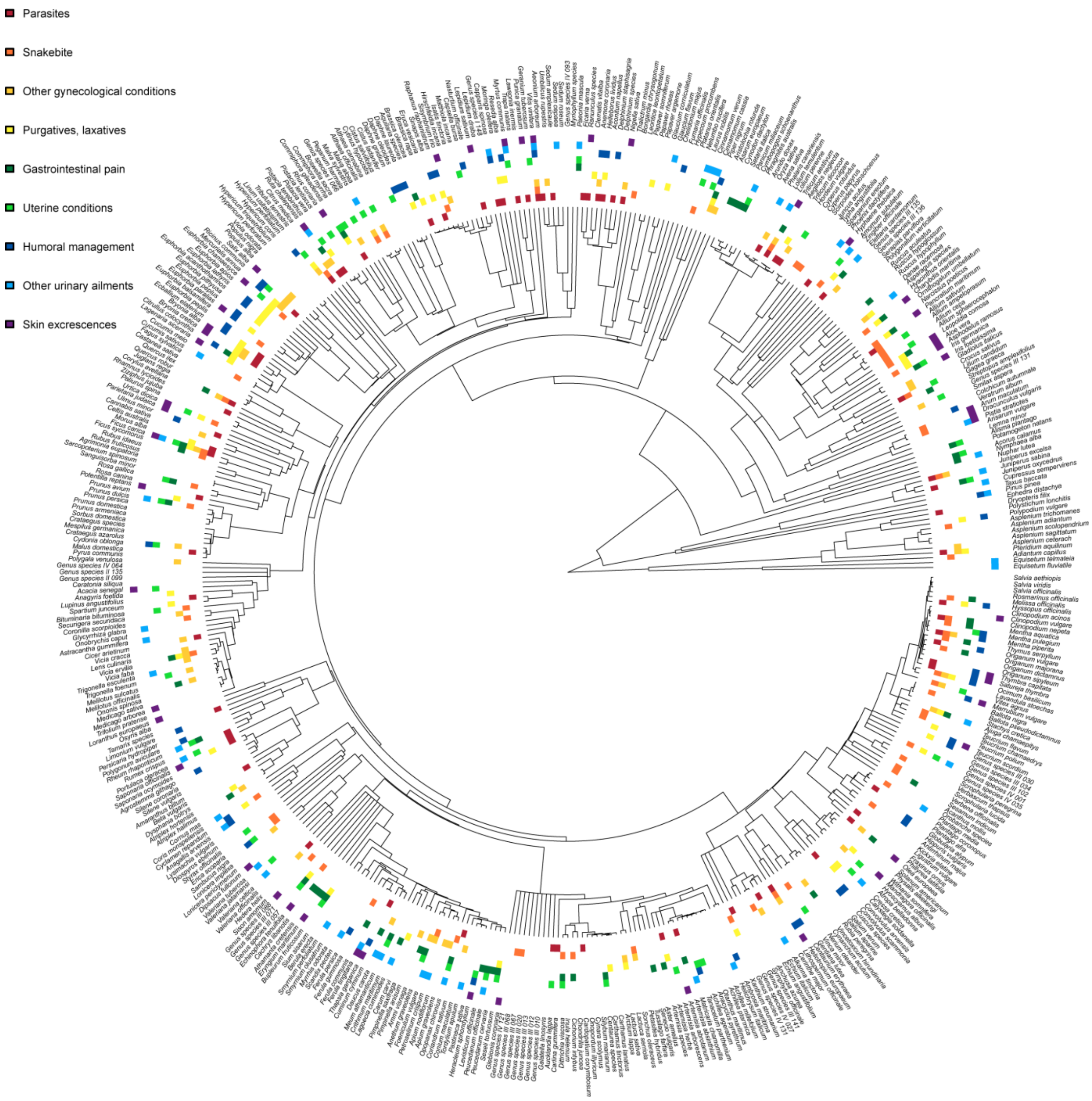
Il Presidente
Prof. Ernesto d'Aloja

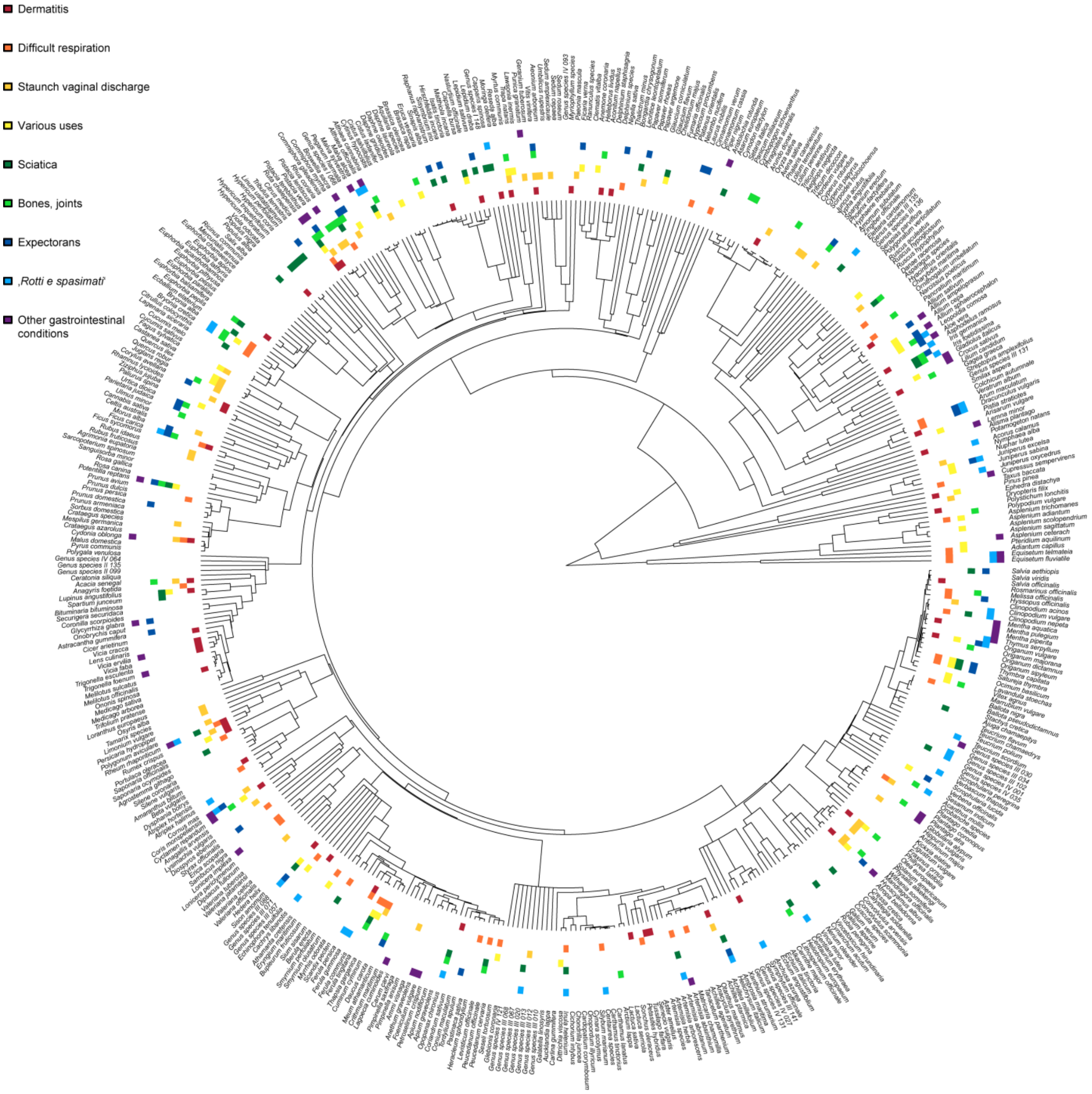
Phylogenetic visualization of plant uses

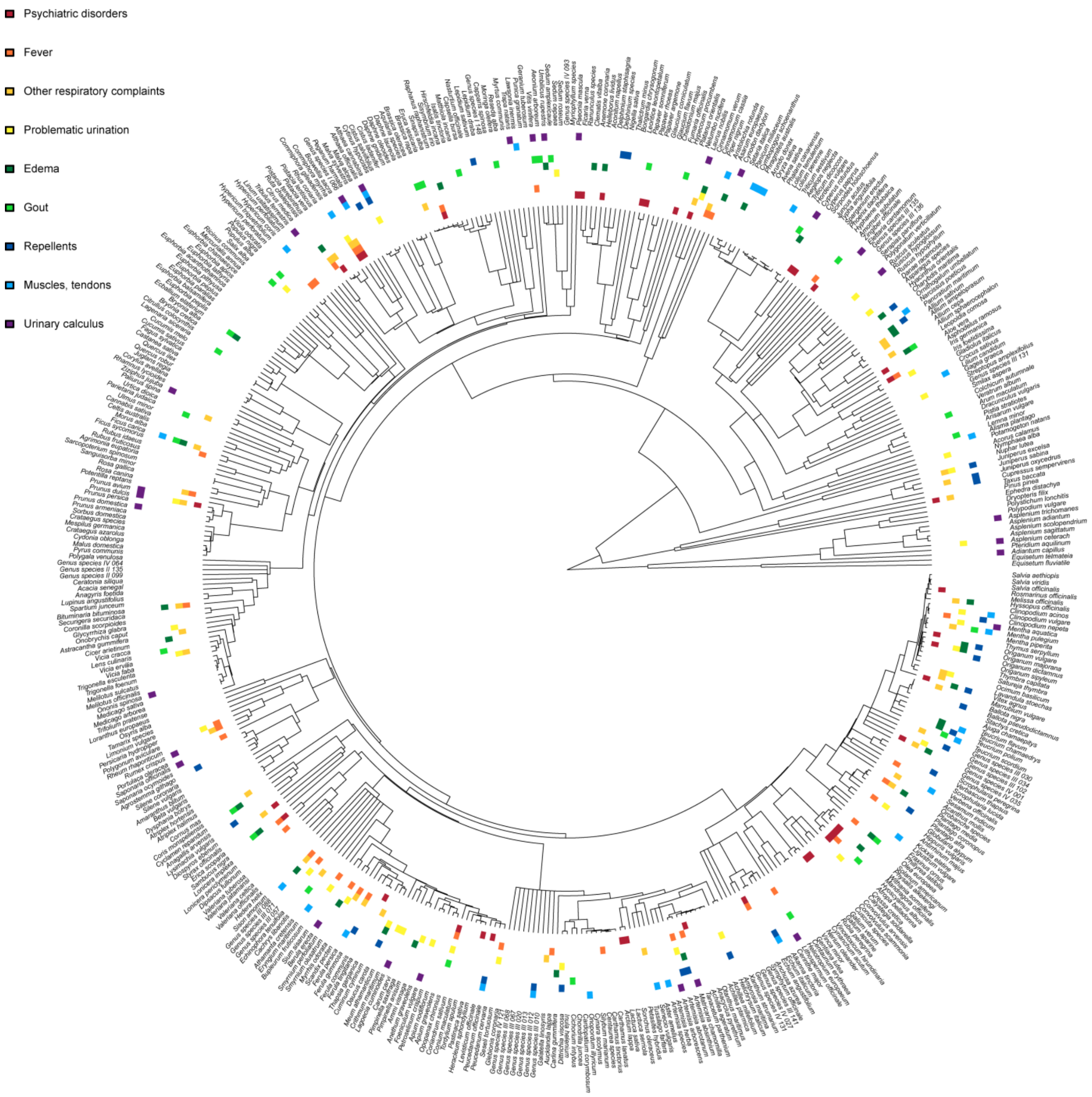
Figure 7-8 Therapeutic uses mapped across a phylogeny of all plant species described in *De Materia Medica* (*ex* Matthioli, 1568)

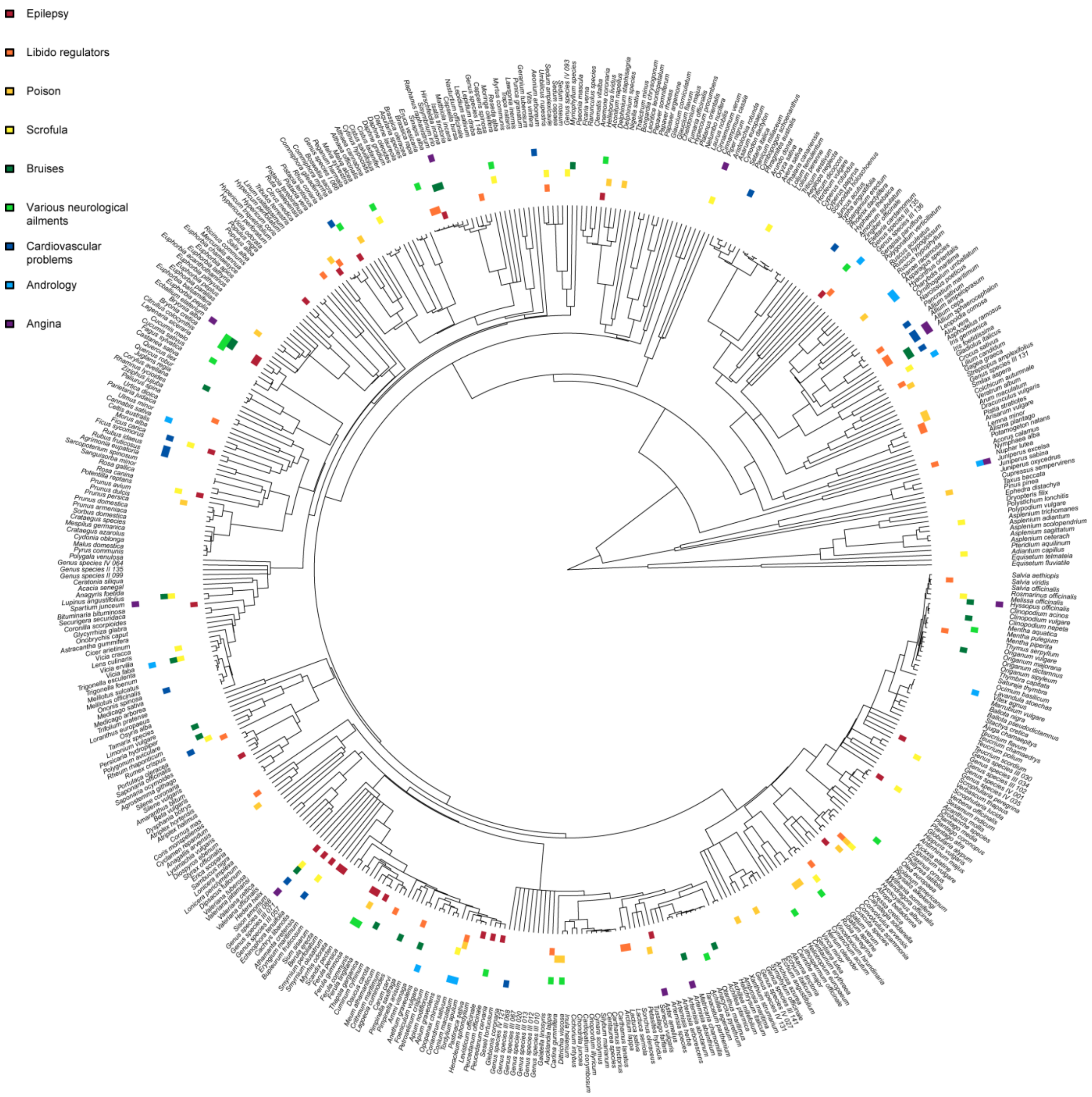



Liver, spleen
Unspecific pain or inflammation
Cough
Otorhinolaryngology
Food
Other skin conditions
Abortives
Cosmetics
Headache, toothache


Parasites
Snakebite
Other gynecological conditions
Purgatives, laxatives
Gastrointestinal pain
Uterine conditions
Humoral management
Other urinary ailments
Skin excrescences


Dermatitis
Difficult respiration
Staunch vaginal discharge
Various uses
Sciatica
Bones, joints
Expectorans
‚Rotti e spasimati'
Other gastrointestinal conditions


Psychiatric disorders
Fever
Other respiratory complaints
Problematic urination
Edema
Gout
Repellents
Muscles, tendons
Urinary calculus


Epilepsy
Libido regulators
Poison
Scrofula
Bruises
Various neurological ailments
Cardiovascular problems
Andrology
Angina