Ethnopharmacological communication

Traditional Mediterranean and European Herbal Medicines

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http://dx.doi.org/10.1016/j.jep.2017.01.052

Received 2 October 2016; Received in revised form 29 November 2016; Accepted 25 January 2017

Journal of Ethnopharmacology 199 (2017) 161–167

Available online 05 February 2017

Abstract

Ethnopharmacological relevance: Written history allows tracing back Mediterranean and European medical traditions to Greek antiquity. The epidemiological shift triggered by the rise of modern medicine and industrialization is reflected in contemporary reliance and preferences for certain herbal medicines.

Materials and methods: We sketch the development and transmission of written

herbal medicine through Mediterranean and European history and point out the opportunity to connect with modern traditions.

Results: An ethnopharmacological database linking past and modern medical traditions could serve as a tool for crosschecking contemporary ethnopharmacological field-data as well as a repository for data mining. Considering that the diachronic picture emerging from such a database has an epidemiological base this could lead to new hypotheses related to evolutionary medicine.

Conclusion: The advent of systems pharmacology and network pharmacology opens new perspectives for studying past and current herbal medicine. Since a large part of modern drugs has its roots in ancient traditions one may expect new leads for drug development from novel systemic studies, as well as evidence for the activity of certain herbal preparations.

Keywords: Traditional medicine, evolutionary medicine, Mediterranean, Europe, herbals in history

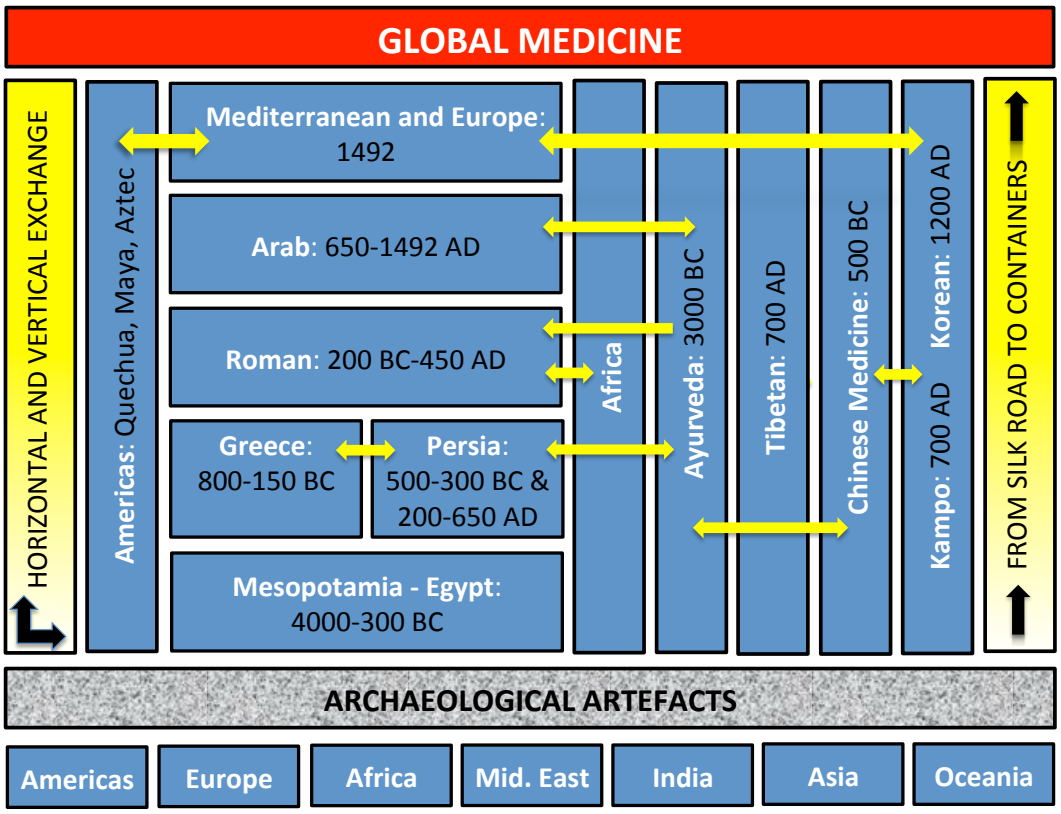
1. Introduction

Throughout written history, medicine, horticulture and agriculture have guided the study of plants, animals, organic and inorganic products. Valuable insights into the history of medicine can be gained through cross-cultural studies of medical texts, archaeological remains, contemporary folk medicines and ethnomedical practices (Tschirch, 1910; Arber, 1953). This commentary is an integration to the supplementary series recently published by Science magazine dedicated to the Arts and Science of Traditional Medicine highlighting modern scientific approaches and

perspectives to global traditional medicine with a special focus on TCM (The art and science of traditional medicine Part 1-3, 2014-2015).

Hygiene and preventive medicines, such as vaccines and the introduction of antibiotics brought about an epidemiological shift away from the burden of infectious diseases in the western world (Mann, 1984). Propelled by industrialization and warfare between the late 18th and mid 20th century, this development led to a steady decline in the reliance on herbal products for primary care and endowed us with a rising life expectancy. In parallel, changes in working habits led to a decline in everyday physical activity, while dietary patterns shifted towards the overconsumption of meat, dairy and refined products, and a lower intake of fruits, vegetables, fibres and phytochemicals in general. As a consequence multifactorial age related and life style diseases such as cancers, type II diabetes, cardiovascular diseases and neurodegenerative disorders, as well as chronic inflammatory autoimmune diseases are now at the forefront among health problems in affluent societies (Bray, 1996).

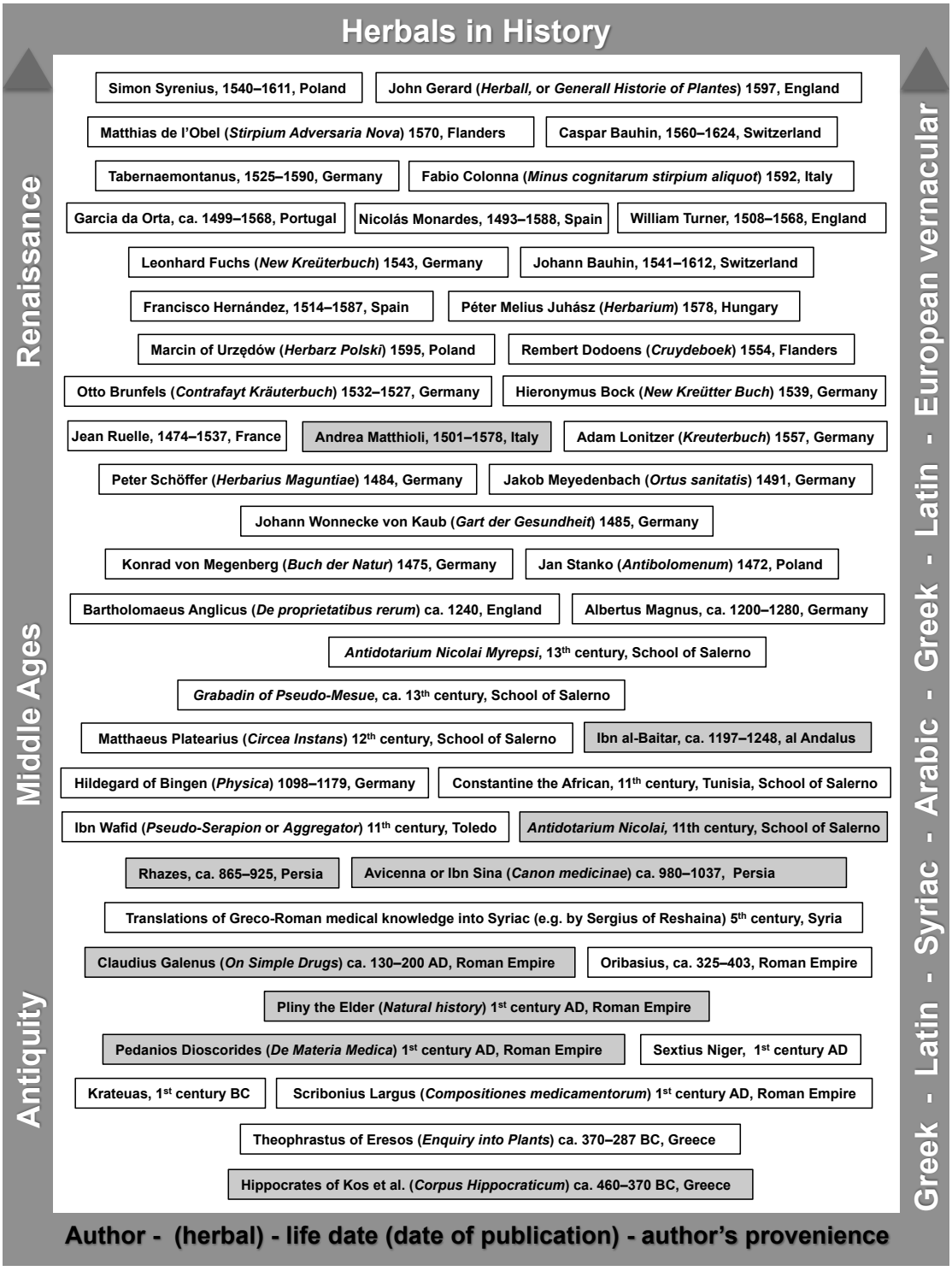
Fig 1. Mutual influence and development of major traditional medicinal systems with focus on the Mediterranean and Europe. A range of other, more local but still important traditional medicinal systems exist in parallel. The width of the arrows does not exactly correspond with scale of imports from the specific regions.



Today consumers perceive herbal medicine and plant based food products as an adjuvant or more gentle and holistic way of coping with chronic health problems and self-limiting infectious diseases. This perception is paralleled by the progress in omics approaches and network pharmacology, which have allowed the synergistic properties of herbal products to shed the "quackery" label, as they acquire a firm evidence base.

In Europe and the Mediterranean medicinal plants are being collected for use as home remedies from wild habitats and private yards, or bought in shops and markets. The renewed interest in alternative, traditional and herbal medicines in the economically more developed societies needs to be considered against the backdrop of the historical process and epidemiological changes outlined above (c.f. Etkin, 2006).

Fig. 2. Chronology of influential herbals and authors of traditional Mediterranean and European medicine (Those highlighted in grey are considered of major importance).



The written tradition

Though traditional medicine and the use of medicinal plants can be traced back to Mesopotamia and Egypt (**Fig. 1**), the basis of Mediterranean and European medicine was laid down during Greek antiquity and the period of the Roman Empire by physicians and philosophers, who started building a written consensus about what was considered efficacious medical knowledge (**Fig. 2**). The 9th book of Theophrastus of Eresos' (ca. 370–287 BC) *Enquiry into Plants*, about the juices and the medicinal properties of plants, has preserved the earliest known fraction of a Greek herbal (Hort, 1977). The most eminent and influential classic authors were Hippocrates of Kos (ca. 460–370 BC), Galen (129– ca. 199/200 or 216/217 AD) and Pedanios Dioscorides (1st century AD), who with great success combined both botanical and medical skills. Dioscorides' *De Materia Medica* together with Galen's first alphabetical collection of simple drugs (*De simplicium medicamentorum facultatibus libri XI*), are regarded as the most influential herbals ever written. Through the repeated copying and dissemination of their content, both texts shaped Mediterranean and European medicinal plant use until the 18th century (Singer, 1927; Urdang 1951; Arber, 1953). Dioscorides described the medicinal use of some 600 medicinal plant species and around 900 herbal, 35 animal and 90 mineral drugs (Riddle, 1985). Around a century later Galen reported about 850 simple drugs largely overlapping with those mentioned in Dioscorides but indicating considerably fewer medicinal uses (c.f. Galenus, 1561; Leonti et al., 2015). Often, each specific plant taxon was referred to by a "code" comprising the list of its known vernacular names in different languages, the strict cross-referencing of names and uses serving as a protocol for academic rigour to ensure correct plant identification between regions, and hence the applicability of herbal texts in a wider geographical and cultural context, allowing scientific

knowledge to grow and become consolidated.

The development, mutual influence and phylogeny of Greek herbals are relatively well documented, including the detection of lost copies through missing links (Tschirch, 1910; Singer, 1927). Dioscorides for instance, quotes and makes reference to a range of different authors and texts that have been preserved (e.g. works ascribed to Theophrastus and Hippocrates) and others, that are now lost or survive only in fragments (e.g. works by Sextius Niger (late 1st century BC to first half of 1st century AD) and Krateuas (ca. 100 BC)). An important intermediate step, which facilitated the transmission of Greek and Byzantine medical knowledge into Arabic and to the medieval Islamic world were translations into Syriac (Russell, 2010). The Arab culture not only preserved classic medical knowledge, but also developed it further and enabled the transmission back to the Occident through the School of Salerno (ca. 1000–1300 AD) as well as al-Andalus (711–1492; Urdang 1951). New and valuable insights regarding the transmission of Greco-Roman medical knowledge to the Arabic world are expected from the study of the so-called "Syriac Galen Palimpsest". This manuscript is currently the oldest known copy of Galen's work on herbal preparations and is crucial because it provides variant readings that differ from the younger Greek copies and therefore can be used to identify interpolations as well as different textual interpretations (Bhayro et al., 2013).

The classic Mediterranean *materia medica* also influenced the structure, the literary form and the content of the middle and northern European herbals. During the Middle-ages Benedictine monks were directed by monastic rule to duplicate herbals and to tend medicinal herb gardens such as those of the Abbeys of Montecassino (Italy) and St. Gall (Switzerland) (Tschirch, 1910). During the Renaissance, the classic Greco-Roman herbals and medical texts were critically analysed, commented

upon and translated into modern languages receiving important print runs. However, Renaissance herbals also contained the consensus on central and northern European medical folk knowledge and were accompanied by woodcut illustrations imposing the plant identifications of the commentators. The *Gart der Gesundheit* written by Johann Wonnecke von Kaub (ca. 1430–1504), physician to the city of Frankfurt a. M. and illustrated by Erhard Reuwich (1450–1505), a Dutch graphic artist, is regarded as the first comprehensive German herbal (Müller, 2011). The *Gart der Gesundheit* contains 435 monographs and draws on Mediterranean sources, such as Pliny's Natural history (1st century AD), the *Canon medicinae* by Avicenna (Ibn Sina, ca. 980–1037), the *Pseudo-Serapion* (*Aggregator*) by Ibn Wafid (11th century, Toledo) and the *Circea Instans* by Matthaeus Platearius (12th century, School of Salerno), as well as on texts written in German and containing Middle-European knowledge such as the *Buch der Natur* (Book of Nature) by Konrad von Megenberg (1309–1374) and the *Physica* by Hildegard of Bingen (1098–1179; Mayer, 2011). The invention of the printing press triggered a boom in producing European herbals and a race among authors, who were not always exempt of nationalist sentiments. Ancient Greco-Roman knowledge was translated, commented and integrated with the documentation of traditional folk knowledge on central and northern European *materia medica* by Peter Schöffer (ca. 1425-1503), Jan Stanko (1430-1493), Jean Ruelle (1474-1537), Otto Brunfels (1488–1534), Adam Lonitzer (1528–1586), Leonhard Fuchs (1501–1566), Hieronymus Bock (1498–1554), William Turner (1508–1568), Marcin of Urzędów (1500-1573), Andrea Matthioli (1501–1578), Rembert Dodoens (ca. 1516-1585), Tabernaemontanus (1525–1590), Péter Melius Juhász (1532-1572), Simon Syrenius (1540-1611), Caspar Bauhin (1560–1624), John Gerard (1545–1612), Fabio Colonna (1567-1640) and other authors (**Fig. 2**). A systematic analysis regarding the

questions as to what plant taxa and uses were described for the first time in which herbal, and how much information was directly adopted from the classic literature, is still lacking, however.

Also the first official pharmacopoeias drew heavily on the Greco-Roman and Arabic medical treatises. Besides Hippocrates, Pliny, Dioscorides and Galen, of particular importance were Matthaeus Platearius (12th century), Rhazes (865–925) and Avicenna (ca. 980–1037; Urdang, 1951). Due to the format and presentation adopted, the *Compositiones medicamentorum*, a formulary by the Roman Scribonius Largus (1st century AD) and three texts written after 1000 AD at the School of Salerno, i.e. the *Antidotarium Nicolai* (ca. 1100), the *Antidotarium Nicolai Myrepsi* (13th century) and the *Antidotarium* or *Grabadin of Pseudo-Mesue* (ca. 13th century), are regarded as precursors of the official city-pharmacopoeias (Urdang, 1951). Another important part of the body of work crafted at the School of Salerno stems from Constantinus Africanus (11th century), a Carthaginian herbal merchant who gathered Arabic medical texts in North Africa and translated them into Latin (Müller, 2011).

Evidence of early imports of herbal drugs and spices from the orient exist for the Roman period and is well documented for the New World and South-east Asia highlighting the importance of exotic commodities for Europe and Mediterranean pharmacopoeias (Mann, 1984; Van der Veen and Morales, 2015). However, factors which have counteracted attempts to synchronize pharmacopoeias, official or otherwise, prior to the birth of the European Pharmacopoeia, include the belief that the beneficial effects of locally sourced drugs would be particularly high, and the economic rationale of promoting locally grown products (Urdang, 1951). At the same time the search for potent remedies, also called trial and error approach, during the emergence of new epidemics (e.g. syphilis) and the experimentations with introduced

"exotic" plant species, provided the playground for experimentations. The syphilis epidemic was brought to Europe from the Americas after the Conquest, on the return of Christopher Columbus and his fleet from the Caribbean. Since it was thought that the origin of particular diseases would be connected with the source of effective medicines, the core wood of *Guaiacum officinale* L. a remedy of the indigenous people of the West Indies was imported to Europe and advertised against syphilis, but later found to be ineffective (Mann, 1984). While Arabian pharmacists introduced mercury as a treatment for skin disorders to Europe it was Matthioli who recognized its specific effectiveness against syphilis (Mann, 1984).

The Swiss physician Paracelsus (1493–1541), known for introducing the basic principle of toxicology ("the dose makes the poison"), tried to break with the medicinal thinking of the old authorities, particularly with Galen and Avicenna, and advocated high hygienic standards for surgery (Mann, 1984). However, as an alchemist Paracelsus was not immune to symbolic and esoteric thinking. In *De natura rerum*, of 1537, Paracelsus proposed the "doctrine of signatures" as a holistic and harmonic concept able to predict the therapeutic virtues of plants based on attributes such as shape, colour, smell and taste (Müller, 2011). While the principle idea of the doctrine of signatures is rooted in folk medicines around the world, Paracelsus systematized it in conceptual opposition to the humoral pathology of Galen (Müller, 2011). Today the doctrine of signatures lingers on in alternative medicines and homeopathy, which was created by the German physician Samuel Hahnemann (1755-1843) while their importance in traditional herbal medicine in Europe and the Mediterranean is very probably declining.

Generally, the earlier herbals were more influential, because there were fewer of them and because they had more time to exercise causal effects on popular herbal

knowledge and the development of medicine. Others such as Matthioli's Renaissance commentary on Dioscorides' *Materia Medica* (*I Discorsi*), first published in 1544, also had a strong influential effect due to their high print-run, which is said to have been over 30.000 for the earlier editions of *I Discorsi* alone (Matthioli 1568; Leonti et al., 2010). Matthioli's herbal integrated Dioscorides' work and described an additional 600 medicinal species. Apart from receiving Latin editions it was also published in Italian, and was translated into other vernacular languages such as French, German, Czech and Arabic, with around 60 different editions altogether (Barberi, 1967-1970). Matthioli was a medical doctor and botanist familiar with the Mediterranean flora and therefore *I Discorsi* based on practical medical and botanical knowledge, which renders Matthioli's translation readily accessible (for an overview see Staub et al., 2016). However, some interpretations seem to be premature, which becomes for instance apparent in the case of garlic (Book II, Chap. 141, p. 587) where garlic's appropriateness for treating dropsy is mentioned twice. Max Wellmann's (1863-1933) well-respected Greek edition (Wellmann, 1907), however reads in one occasion "…eaten it [garlic] is useful against the disturbances, which derive from the change of water…" (pp. 217-219, but see also Berendes, 1902, p. 234), which could be interpreted as "used to treat the effects of (contaminated) water the body is not used to". At this point Beck's translation (Beck, 2005, p. 156-157) of Wellmann's Greek edition reads: "…is suitable to use against the injurious effects of change" without mentioning "water" at all. Becks English translation, although easily accessible suffers from arbitrary plant identifications and is at times incomprehensible, which becomes apparent in another excerpt from the chapter on garlic: "there is nothing better than it [garlic]…for those who haemorrhage if they should drink wine continuously or if it is triturated with the wine then drunk" (p. 156).

A new English translation of Max Wellmann's Greek edition would be greatly appreciated.

Linking past and contemporary traditions with databases

A requirement for the registration of herbal medicine in the EU is a proof of tradition, citing a documented medicinal use over a period of at least 30 years, including 15 years in the EU. A standard definition and interpretation of the concept of "tradition" among the different regulatory authorities is still lacking. The term "traditional" can have different meanings and has been criticized as being unspecific, evoking a conservative character and implying that knowledge is passed on orally, from one generation to the next (McClatchey, 2005; Helmstädter, 2012). Importantly, it was argued that technical improvements and standardizations of herbal products should be understood as a continuation of traditions and not as a break with them (Helmstädter, 2012).

While the continuity of medicinal plant uses indicated in herbal texts and revealed by field-studies (e.g. Pieroni, 2000) can help to provide a basis for the tradition of use, diachronic studies can also help to detect the discontinuity of herbal applications (Leonti et al., 2015). Comparisons of contemporary medicinal plant uses in Southern Italy with those of Dioscorides and Galen showed that uses related to women's medicine and the treatment of eye and ear conditions are less common today, while treating fever and feverish diseases with medicinal plants seems to have become more frequent (Leonti et al., 2015). Drugs that were important therapeutics in classical times but no longer relied upon today such as different Fabaceae seeds for dermatological afflictions and Apiaceae exudates for neurological problems offer opportunities for drug discovery and the evaluation of classic medicines (Staub et al.,

2016). Texts documenting the use of *materia medica* in preindustrial Europe include remedies for diseases and health disorders now controlled by industrially produced drugs mostly based on single chemical entities and are therefore regarded as promising starting points for bioprospecting endeavours (Holland, 1996; Lardos, 2015; Totelin, 2016; Helmstädter, 2016).

Plant based remedies for the treatment of potentially life threatening infections and conditions such as tuberculosis, whooping cough, pneumonia, malaria, epilepsy and cutaneous ulcers are generally not used anymore by Europeans. Remedies for other infectious diseases and ailments such as abscesses, dysentery, ear infections, infestations by scabies, tapeworms, erysipelas and gangrene are very frequently described in *De Materia Medica* indicating different hygienic standards when compared to modern times (Staub et al., 2016). As a hypothesis, such remedies and recipes may bear effective clues for the development of new treatments for the growing burden of infections by bacterial strains including those resistant to conventional antibiotics. Before the development of antibiotics Garlic (*Allium sativum* L.) was one of the main remedies against wound infections and infective diseases in use until the Second World War and known as Russian penicillin (Petrovska and Cekovska, 2010). Today garlic is known in popular herbal medicine as a hypotensive and for treating high cholesterol levels. These cardiovascular uses are not recorded in ancient literature and evidently reached the popular domain via biomedical literature during modern times (Leonti et al., 2010; **Table 1**).

Popular herbal medicine, documented through field-studies in Europe and the Mediterranean, shows a strong link, including causal relationships, with written herbal knowledge (Leonti et al., 2015; Dal Cero et al., 2015). Also, science generated herbal knowledge filters down to the popular level where it is assimilated and enters folk

knowledge. This is particularly true for economies dependent on international commerce with modern communication and information technologies. Field-surveys on the use of herbal medicines in Europe and the Mediterranean thus increasingly risk the uncritical documentation of medicinal plant uses deriving from this feedback process, or the re-recording of uses long since consolidated in herbal medicine (Leonti, 2011). Ethnopharmacology would benefit if results of field-surveys dedicated to the popular use of medicinal plants would encompass a comparison with historical as well as modern mainstream herbal practices. Particular medicinal uses sustained by intra-cultural or even inter-cultural consensus, definitely warrant the ethnopharmacological approach. Uses not (or only rarely) described in the scientific, historical and popular literature and related to treatments of modern epidemics including diabetes, irritable bowel syndrome, anxiety disorders, arthritis or cardiovascular problems, merit special attention. Nevertheless, the well-preserved but scattered documentation of herbal medicine in Europe and the Mediterranean, from antiquity to modern times, renders comparisons with bibliographical sources a tedious undertaking (e.g. Dal Cero et al., 2014). A possible solution for facilitating the simultaneous crosschecking of field-data and data mining would be a repository in the form of an ethnopharmacological database, which could result in a comprehensive global herbal (Verpoorte, 2008).

In other parts of the world undocumented oral traditions are still alive, but threatened by extinction. The global and local use of specific herbal medicines, shaped by epidemiology, cultural interaction and medical beliefs could be connected over timescales to furnish a diachronic picture facilitating the formulation of new hypotheses and strengthen the link with Darwinian or evolutionary medicine (c.f. Nesse, 2001).

An existing database not specially designed for, but also covering (albeit not comprehensively), ethnomedical literature worldwide from 1975 until 2003, is the NAPRALERT® database (https://www.napralert.org). A database tailored more towards the needs of ethnopharmacological data mining that might be used as a model for a worldwide repository is the "Native American Ethnobotany Database" (http://naeb.brit.org/). Knowledge discovery should be possible through hierarchically structured keyword queries (e.g. gastrointestinal > diarrhoea > bloody diarrhoea) for symptoms, diseases, modes of application, plant taxa, excipients, ingredients geography and time period, so that it could also serve as a starting point for drug development (**Table 1**). The use of such a database would benefit from the continuous updating of accepted Latin binomials or a cross-link with an up-to-date plant names index. The inclusion of quantitative data providing information on the depth of a survey study would obviate the need to crosscheck the original survey article. Publicly accessible historical databases are not available yet but their construction and compilation have been conceptualized (c.f. Touwaide and Appetiti, 2015). Combining historical and modern data in an appropriately designed ethnopharmacological database, or merging already existing databases, could lead to a simplification of the data mining process.

Since primary field-data often form the basis for applied studies, such as the validation and integration of medicinal plants into healthcare programs or drug discovery projects, there is a need for a proper and reproducible way of data collection and recording (Verpoorte, 2012). Quantitative data gathering approaches are essential for studies focusing on the description of uniqueness, variation and consensus of local medical plant use. As consensus occurs at the point where answers converge, the consensus on a specific plant use can be estimated through the absolute

number of individual informants reporting a specific use as well as the overall number of interviewees approached in the study. Another essential methodological requirement for ethnomedical surveys is that herbarium vouchers of the medicinally used plant species are prepared and deposited at an indexed herbarium. This serves as a solid point of reference allowing future identity checks as well as the sampling of material for DNA and metabolomic profiling (Verpoorte, 2012).

Assessing traditional medicines with modern technologies

The tradition of Western medicine, as it developed over the past 400 years, is the belief in technology for developing essential compounds from traditionally used plant extracts. The successes started some 200 years ago when some major alkaloids were purified and proved to be very useful medicines. Aspirin, too, was based on the purification and identification of salicylic acid. This led to a firm believe in pure compounds and the synthesis of these compounds, and analogues, to further improve the therapeutic properties of the natural products. At the end of the last century the paradigm in Western medicine was “single target - single compound” so that any mixture of plant extracts had to be considered unscientific. However, the stalling drug development process and the success in treating HIV with a combination of several medicines, questions this paradigm. Also the treatment of elderly people with often 5-10 different single compounds, each with different targets, is now common practice, although often with limited scientific evidence for efficacy and safety. For example in The Netherlands in the age group 65-70 already 22% is using more than 5 different medicines, in the group above 75 years 23% is using more than 7 different medicines (SFK, 2015). Pharmacogenomic insights from the activities of the pharmaceutical industry, include this statement from Allen Roses (vice-president of genetics at

GlaxoSmithKline), in 2003: “The vast majority of drugs - more than 90 per cent - only work in 30 to 50 per cent of the people” (Roses, 2003), also fits this rethinking, and the realization that traditions are useful, but need to be continuously adapted as knowledge develops. Other examples include the new insights into the role of the GI-tract microbiome (Foster and Neufeld, 2013) and the liver catabolism in the metabolism of medicines and their bioavailability, that are fully in line with the discovery in the 19th century of salicylic acid. Salicylic acid is named after the willow tree (*Salix*), whose bark was used as an analgesic drug (Mahdi et al., 2006). The bark does not contain any salicylic acid, but the prodrug salicin (Julkunen-Tiitto and Meier, 1992 and references cited therein), which is converted in the GI-tract and liver into salicylate. Through the conversion into the pharmacologically active metabolite after passage through the stomach, the formation of stomach ulcers, one of the side effects of salicylic acid, is avoided.

Since synthesis always needs a model to copy or improve upon, “learning from nature, learning from our ancestors” is the lesson derived from some 50 years of believing that biotechnology, combinatorial chemistry and synthesis would provide self-sufficient approaches to drug development. The strength of Western medicine is that it is continuously trying to develop better treatments and therapies based on extensive research, adopting new perspectives and including new technologies. The advent of the “omics”, enabled systems biology approaches integrating results with biochemical and physiological data. This opens totally new perspectives for studying our ancestors’ medical knowledge (Briggs, 2014; Leung et al., 2014; Wang and Xu, 2014; Williamson et al., 2015; Witt et al., 2015). It has been shown that combinations of compounds, including prodrugs, exerting synergistic and polyvalent effects, are involved in the activity of plants used as medicine such as for example for *Hypericum*

perforatum L., *Valeriana officinalis* L. or *Ginkgo biloba* L. (Yoshitake et al., 2004; Sarris et al., 2011). Purposefully prepared mixtures of medicinal plants are commonly applied as personalized medicines (Wang, 2005). Also, designing extracts by combining pure compounds with determined synergic and poly-pharmacological profiles could be an innovative way towards a pathology-tailored therapy and personalized medicine (Gertsch, 2011). Holistic, systemic approaches are thus very promising for studying medicinal plants and may eventually lead to evidence-based uses, or even novel leads for drug development. The huge efforts presently made for the validation of Chinese herbal medicine such as for *Polygala tenuifolia* Willd. (e.g. Ikeya et al., 2004; Guo et al., 2016) and *Angelica sinensis* (Oliv.) Diels (Hook, 2014; Wei et al., 2016) or Ayurvedic herbal medicine such as *Bacopa monnieri* (L.) Wettst. (e.g. Kongkeaw et al., 2014) allows for comparative pharmacological studies with neglected European taxa (e.g. *Polygala* spp. and *Angelica archangelica* L.). Together with the development of novel approaches to obtain evidence for safe traditional uses this could rekindle the interest in Mediterranean and European traditional medicines. While a large part of Western medicine already has its roots in this tradition the importance of traditional medicine was recognized in the awarding of the 2016 Nobel Prize for Medicine to Youyou Tu, for the development of the anti-malaria compound artemisinin from a Chinese traditional medicine (Tu, 2011; Efferth et al., 2015), and for the development of ivermectin from microbes to fight roundworms by biodiversity screening (Van Voorhis et al., 2015). Youyou Tu reproduced a recipe against malaria appearing in an ancient Chinese prescription handbook following the cold maceration extraction of *Artemisia annua* L. (qinghao) when discovering the antimalarial effect of this herb. Malaria was also widespread in Europe and Renaissance herbals make reference to *malaria tertiana* and *quartana* (Adams et al., 2011a) while in

contemporary herbal medicine in Europe remedies for malaria have disappeared together with the disease. Frog's spoon (*Alisma plantago-aquatica* L., Alismataceae), however, described in different 16th and 17th century herbals as a remedy for malaria was included in an antimalarial screening and afforded protostane triterpenoids with moderate *in vitro* anti-plasmodial activity (Adams et al., 2011b).

Traditional European and Mediterranean *materia medica* and medical thinking set the foundation of modern pharmacology bringing about higher life expectancy and an epidemiological shift to affluent societies. The neglected drugs and medical recipes recorded over the course of the past two millennia are worth to be analysed adopting a diachronic perspective of continuity and discontinuity considering the epidemiological constraints of their times. An ethnopharmacological database linking past and present uses would facilitate such an analysis and may lead to new hypotheses, that could be tested with modern technologies and approaches such as systems biology and network pharmacology.

Acknowledgements

The authors thank Antony Challenger for a critical reading of the article.

References

Adams, M., Alther, W., Kessler, M., Kluge, M., Hamburger, M., 2011a. Malaria in the Renaissance: remedies from European herbals from the 16th and 17th century. J Ethnopharmacol. 133, 278−288.

Adams, M., Gschwind, S., Zimmermann, S., Kaiser, M., Hamburger, M., 2011b.

Renaissance remedies: Antiplasmodial protostane triterpenoids from *Alisma plantago-aquatica* L. (Alismataceae). J Ethnopharmacol. 135, 43−47.

Arber, A., 1953. Herbals, their origin and evolution. A chapter in the history of botany 1470–1670. Cambridge University Press, Cambridge MA.

Barberi, F., 1967-1970. I discorsi di Pietro Andrea Mattioli su Dioscoride. in: I Discorsi di M. Pietro Andrea Matthioli. Sanese, Medico Cesareo, et del Serenissimo Principe Ferdinando Archiduca d'Austria & c.Nelli Sei Libri Di Pedacio Dioscoride Anazarbeo della Materia Medicale, Matthioli, A. (Anastatic reproduction in 6 Volumes, Rome, 1967-1970) Books 5 & 6.

Beck, L.Y., 2005. Pedanius Dioscorides of Anazarbus De materia medica. Translated by L.Y. Beck. Olms-Weidmann, Hildesheim.

Berendes, J., 1902. Des Pedanios Dioskurides aus Anazarbos Arzneimittellehre in fünf Büchern. F. Enke, Stuttgart.

Bhayro, S., Hawley, R., Kessel, G., Pormann, P.E., 2013. The syriac galen palimpsest: Progress, prospects and problems. J. Semitic Studies 58, 131−148.

Bray, R.S., 1996. Armies of Pestilence. The Impact of Disease on History. Barnes & Noble, New York.

Briggs, J.P., 2014. A global scientific challenge: Learning the right lessons from

ancient healing practices. The art and science of traditional medicine Part 1: TCM today-a case for integration. Science 346, (6216 Suppl) S7–S9.

Dal Cero, M., Saller, R., Weckerle, C.S., 2014. The use of the local flora in Switzerland: a comparison of past and recent medicinal plant knowledge. J Ethnopharmacol. 151, 253–264.

Dal Cero, M., Saller, R., Weckerle, C.S., 2015. Herbalists of Today's Switzerland and Their Plant Knowledge. A Preliminary Analysis from an Ethnobotanical Perspective. Forsch. Komplementmed. 22, 238–245.

Efferth, T., Zacchino, S., Georgiev, M.I., Liu, L., Wagner, H., Panossian, A., 2015. Nobel Prize for artemisinin brings phytotherapy into the spotlight. Phytomedicine 22, A1–3.

Etkin, N., 2006. Edible Medicines. An Ethnopharmacology of Food. The University of Arizona Press, Tucson.

Foster, J.A., Neufeld, K.A.M., 2013. Gut-brain: how the microbiome influences anxiety and depression. Trends Neurosci. 36, 305–312.

Galenus, C., 1561. *Claudii Galeni - De simplicium medicamentorum facultatibus libri XI. Theodorico Gerardo Gaudano interprete. Apud Gulielmum Rouillium*, Venice. (http://www.google.com/books?id=Z4aGl1yavZMC&hl=it) (accessed: 01.11.2015).

Gertsch, J., 2011. Botanical drugs, synergy, and network pharmacology: forth and back to intelligent mixtures. Planta Med. 77, 1086–1098.

Guo, C., Shen, J., Meng, Z., Yang, X., Li, F., 2016.Neuroprotective effects of polygalacic acid on scopolamine-induced memory deficits in mice. Phytomedicine 23, 149–155.

Helmstädter, A., Staiger, C., 2012. Traditionelle Anwendung: Eine Betrachtung zu pflanzlichen Arzneimitteln aus pharmaziehistorischer Sicht. Forsch. Komplementmed. 19, 93–98.

Helmstädter, A., 2016. The botanical explorer's legacy: a promising bioprospecting tool. Drug Discov Today. pii: S1359-6446(16)30429-9. doi: 10.1016/j.drudis.2016.11.011 *In press*

Hook, I.L., 2014. Danggui to *Angelica sinensis* root: are potential benefits to European women lost in translation? A review. J Ethnopharmacol. 152, 1–13.

Holland, B.K., 1996. Prospecting for drugs in ancient and medieval European texts: a scientific approach. Holland, B.K. (Ed.). Harwood Academic Publishers, Australia.

Kongkeaw, C., Dilokthornsakul, P., Thanarangsarit, P., Limpeanchob, N., Norman Scholfield, C., 2014. Meta-analysis of randomized controlled trials on cognitive effects of Bacopa monnieri extract. J Ethnopharmacol. 151, 528–535.

Hort, A., 1977. Theophrastus Enquiry into Plants - and Minor Works on Odours and Weather Signs. Volume II. Harvard University Press, Cambridge MA.

Ikeya, Y., Takeda, S., Tunakawa, M., Karakida, H., Toda, K., Yamaguchi, T., Aburada, M., 2004. Cognitive improving and cerebral protective effects of acylated oligosaccharides in *Polygala tenuifolia*. Biol Pharm Bull. 27, 1081–1085.

Julkunen-Tiitto, R., and Meier, B., 1992. The Enzymatic Decomposition of Salicin and Its Derivatives Obtained from Salicaceae Species. J. Nat. Prod. 55, 1204–1212.

Lardos, A., 2015. Historical approaches in ethnopharmacology. In Heinrich, M., Jäger, A.K. (Eds.), Ethnopharmacology. Wiley, Singapore, pp. 333–341.

Leonti, M., Cabras, S., Weckerle, C.S., Solinas, M.N., Casu, L., 2010. The causal dependence of present plant knowledge on herbals - Contemporary medicinal plant use in Campania (Italy) compared to Matthioli (1568). J Ethnopharmacol. 130, 379–391.

Leonti M., 2011. The future is written: impact of scripts on the cognition, selection, knowledge and transmission of medicinal plant use and its implications for ethnobotany and ethnopharmacology. J Ethnopharmacol. 134, 542–555.

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. Front Pharmacol. 6:207.

Leung, E.L.-H., Wong, K.-W.V., Jang, Z-H., Li, T., Liu, L., 2014. Integrated network-based medicine: The role of traditional Chinese medicine in developing a new generation of medicine. The art and science of traditional medicine Part 1: TCM today-a case for integration. Science 346, (6216 Suppl) S16–S18.

Mahdi, J.G., Mahdi, Mahdi, A.J., and Bowen, I.D., 2006. The historical analysis of aspirin discovery, its relation to the willow tree and antiproliferative and anticancer potential. Cell Prolif. 39, 147–155.

Mann, R.D., 1984. Modern drug use: An Enquiry on Historical Principles. Lancaster, UK: MTP Press Limited.

Mayer, J.G., 2011. Die Wahrheit über den Gart der Gesundheit (1485) und sein Weiterleben in den Kräuterbüchern der frühen Neuzeit. In: A passion for plants: *materia medica* and botany in scientific networks from the 16th to 18th centuries. S. Anagnostou, S., Egmond, F., Friedrich C., Eds. (Quellen und Studien zur Geschichte der Pharmazie, Band 95, Stuttgart) pp. 119–128.

McClatchey, W.C., 2005. Exorcizing misleading terms from ethnobotany. Ethnobot. Res. Appl. 3, 1–4.

Müller, I., 2011. Gart der Gesundheit. Botanik im Buchdruck von den Anfängen bis 1800. Verlag der Franckeschen Stiftungen zu Halle, Schweinfurt.

NAPRALERT database (https://www.napralert.org) (accessed: 29.09.2016).

Native American Ethnobotany Database (http://naeb.brit.org) (accessed: 29.09.2016).

Nesse, R.M., 2001. How is Darwinian medicine useful? West J Med. 174, 358–360.

Petrovska, B.B., Cekovska., S., 2010. Extracts from the history and medical properties of garlic. Pharmacogn Rev. 4, 106–110.

Pieroni, A., 2000. Medicinal plants and food medicines in the folk traditions of the upper Lucca Province, Italy. J Ethnopharmacol. 70, 235–273.

Riddle, J.M., 1985. Dioscorides on Pharmacy and Medicine. University of Texas Press, Austin.

Roses, A., 2003. (https://badscienceblindtruth.wordpress.com/2013/05/28/glaxo-chief-our-drugs-do-not-work-on-most-patients) (accessed: 01.11.2015).

Russell, G.A., 2010. Chapter 6: after Galen Late Antiquity and the Islamic world. Handb Clin Neurol. 61−77.

Sarris, J., Panossian, A., Schweitzer, I., Stough, C., Scholey, A., 2011. Herbal medicine for depression, anxiety and insomnia: a review of psychopharmacology and clinical evidence. Eur Neuropsychopharmacol. 21, 841–860.

Singer, C., 1927. The Herbals in Antiquity and its Transmission to Later Ages. J. Hell. Stud. 47, 1–52.

SFK, 2015. Stichting Farmaceutische Kengetallen. Kwart 75-plussers gebruikt zeven of meer geneesmiddelen. Pharm. Weekbl. 26 juni 2015;150–26.

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.

The art and science of traditional medicine Part 1: TCM today-a case for integration, 2014. Science 346, (6216 Suppl) S1–S25.

The art and science of traditional medicine Part 2: Multidisciplinary Approaches for Studying Traditional Medicine, 2015. Science 347 (6219 Suppl) S26–S52.

The art and science of traditional medicine Part 3: The Global Impact of Traditional Medicine, 2015. Science, 350 (6259 Suppl) S53–S85.

Totelin, L., 2016. Technologies of knowledge: pharmacology, botany, and medical recipes. Oxford Handbooks Online.

Touwaide, A., Appetiti, E., 2015. Food and medicines in the Mediterranean tradition. A systematic analysis of the earliest extant body of textual evidence. J Ethnopharmacol. 167, 11–29.

Tschirch, A., 1910. Handbuch der Pharmakognosie. Allgemeine Pharmakognosie, Erster Band II. Abteilung. Chr. Herm. Tauchnitz, Leipzig.

Tu, Y., 2011. The Discovery of Artemisinin (qinghaosu) and Gifts from Chinese Medicine. Nature Medicine 17, 1217–1220.

Urdang, G., 1951. The development of pharmacopoeias; a review with special reference to the pharmacopoea Internationalis. Bull. World Health Organ. 4, 577−603.

Van der Veen, M., Morales, J., 2015. The Roman and Islamic spice trade: New archaeological evidence. J Ethnopharmacol. 167, 54–63.

Van Voorhis, W.C., Hooft van Huijsduijnen, R., Wells, T.N., 2015. Profile of William C. Campbell, Satoshi Ōmura, and Youyou Tu, 2015 Nobel Laureates in Physiology or Medicine. Proc Natl Acad Sci USA 112, 15773–15776.

Verpoorte, R., 2008. Repository for ethnopharmacological survey data? J Ethnopharmacol. 120, 127–128.

Verpoorte, R., 2012. Primary data are the basis of all science! J Ethnopharmacol. 139, 683–684.

Yoshitake, T., Iizuka, R., Yoshitake, S., Weikop, P., Müller, W.E., Ogren, S.O., Kehr, J., 2004. *Hypericum perforatum* L (St John's wort) preferentially increases extracellular dopamine levels in the rat prefrontal cortex. Br J Pharmacol. 142, 414–418.

Wang, M., Lamers, R.J., Korthout, H.A., van Nesselrooij, J.H., Witkamp, R.F., van der Heijden, R., Voshol, P.J., Havekes, L.M., Verpoorte, R., van der Greef, J., 2005. Metabolomics in the context of systems biology: bridging traditional Chinese medicine and molecular pharmacology. Phytother Res. 19, 173–182.

Wang, Y., Xu, A., 2014. Zheng: A systems biology approach to diagnosis and treatments. The art and science of traditional medicine Part 1: TCM today-a case for integration. Science 346, (6216 Suppl) S13–S15.

Wellmann, M., 1907. *Pedanii Dioscuridis De materia medica libri quinque Vol. I. Apud Weidmannus, Berolini* (Berlin).

Williamson, M., Chan, K., Xu, O., Nachtergael, A., Brunel, V., Zhang, L., Ouedraogo, M., Nortier, J., Qu, F., Shaw, D., Liu, X., Stévigny, C., Kahumba, J., Pelkonen, O., Duez, P., 2015. Evaluating the safety of herbal medicines: Integrated toxicological approaches. The art and science of traditional medicine Part 2: Multidisciplinary Approaches for Studying Traditional Medicine. Science 347 (6219 Suppl) S47–S49.

Witt, C.M, Liu, J., Robinson, N., 2015. Combining 'omics and comparative

effectiveness research: Evidence-based clinical research decision-making for Chinese medicine. The art and science of traditional medicine Part 2: Multidisciplinary Approaches for Studying Traditional Medicine. Science 347 (6219 Suppl) S50–S51.

Tabl 1. Subt: subterranean parts; EXT: external; INT: internal; FUMI: fumigation; ANTI: antidotes; CARD: cardiovascular problems; DERM: dermatology; FOOD: food; GYN: gynaecology; MUSK: musculoskeletal ailments; NERV: neurology; PARA: parasites; RESP = respiratory system; SKMU = URO = urology.

ID: *Allium sativum* L. (Amaryllidaceae) & *Allium* sp. **Name**: Aglio Domestico Ophioscor & Elaphoscordon	**Source**: Dioscorides *ex* Matthioli 1568, Book II, Chap. 141, p. 587 **Time period**: 1st century AD **Region**: Mediterranean **Language**: Italian/Tuscan

Virtue: Sharp, hot, biting, produces wind, moves and disturbs the body, dries the stomach, makes thirsty, drives out the wind, ulcerates the skin and is detrimental to the sight.

Therapeutic use original text	**Therapeutic use (English)**	**Drug**	**Application**	**Excipient or ingredient**	**Appl.**
Secondine (provocare)	Placenta (to promote expulsion)	Leaf	Hipbath		EXT
Mestrui (provocare)	Menstruation (to induce)	Leaf	Hipbath		EXT
Ulcere del capo, che menano	Spreading ulcers of the head	Subt	Smeared on	Honey	EXT
Lentigini	Freckles	Subt	Smeared on	Honey	EXT
Farfarella; il capo dalla (sanare)	Dandruff (to cure)	Subt	Smeared on	Honey	EXT
Bolle, che escono per la persona (sanare)	Blisters (to cure)	Subt	Smeared on	Oil and salt	EXT
Capelli cascati per pelagonie (fare rinascere)	Lost hair (to let regrow)	Subt	Smeared on	Unguent of spikenard	EXT
Volatiche	Facial eruptions	Subt	Smeared on	Honey	EXT
Vitiligini	Vitiligo	Subt	Smeared on	Honey	EXT
Morsi de gli animali rabbiosi	Bites of rabid animals	Subt	Eaten and applied		EXT/INT
Morso del topo ragno	Shrew bite	Subt	Applied	Fig leaves and cumin	EXT
Dolore dei denti	Toothache	Subt	Mouthwash	Boiled with pinewood and frankincense	EXT
Scabbia	Scabies		Smeared on	Honey	EXT
Mestrui (provocare)	Menstruation (to induce)	Subt	Steambath		FUMI
Morsi delle vipere	Viper bites	Subt	Eaten		INT
Hemorrhoidi	Haemorrhoids	Subt	Drunk	Macerated in wine	INT
Cibo	Food	Subt	Eaten		INT
Lendini (ammazzare)	Nits (to kill)	Subt	Decoction	with *Origanum* sp.	INT
Pidocchi (ammazzare)	Lice (to kill)	Subt	Decoction	with *Origanum* sp.	INT
Vermini larghi (cacciare fuori)	Large intestinal worms (to drive out)	Subt	Eaten		INT
Voce (chiarificare)	Voice (to clear up)	Subt	Eaten raw or cooked		INT
Tosse vecchia (alleggerire)	Chronic cough (to alleviate)	Subt	Eaten raw or cooked		INT
Orina (provocare)	Diuretic	Subt	Eaten		INT
Hidropici	Dropsy	Subt	Eaten		INT
Lividi	Haematoma	Subt	Burned to ashes	Mixed with honey	EXT