Revista Brasileira de Farmacognosia (2020) 30:451–466
https://doi.org/10.1007/s43450-020-00074-w

REVIEW

Ecological Theories and Major Hypotheses in Ethnobotany: Their Relevance for Ethnopharmacology and Pharmacognosy in the Context of Historical Data

Marco Leonti[1] · **Laura Casu**[2] · **Domingos Tabajara de Oliveira Martins**[3] · **Eliana Rodrigues**[4] · **Guillermo Benítez**[5]

Received: 30 April 2020 / Accepted: 20 May 2020 / Published online: 17 July 2020

Abstract

The cross-cultural exchange of plant resources between societies across the globe added to the diversification of medicinal floras and pharmacopeias. Understanding how and why people select plants for medicine is still a common focus and topic addressed by the interdisciplinary research fields of ethnobotany, anthropology, ethnopharmacology, ethnomedicine, pharmacy, phytochemistry, and pharmacognosy. Here, we scrutinize recently reviewed ethnobotanical theories and hypotheses, which focus on the selection of plants as medicine by putting them into historical, ecological, and pharmacological perspective. We contextualize the availability, versatility, and diversification hypotheses, often presented in association with the inclusion of non-native species or imported herbal drugs into medicinal floras or ethnopharmacopeias. We also discuss the relevance of the concept of utilitarian redundancy and the apparency hypothesis, as well as the appropriateness of various statistical models applied for assessing non-random plant selection. It appears that the concept of utilitarian redundancy has been applied in a too reductionist and uncritical way, while the apparency theory is conceptually inconsistent and contradictive allowing for multiple interpretations. While the availability, versatility, and diversification hypotheses are not contextualized historically, they are used to explain retrospectively deliberate and well-documented human activities and cultural developments. Therefore, considering the cultural history and the pharmacology of plants is essential for the formulation of hypotheses related to the selection of plants as medicine and food. Ecological research questions applied to human-plant relationships should consider the historical impact of human culture as a framework and confounder to be integrated into the analysis.

Keywords Apparency theory · Diversification hypothesis · Non-random plant selection · Availability theory · Utilitarian redundancy · Versatility hypothesis

Introduction

Communication between cultures has ever since highlighted the importance of exchanging medical knowledge and efficacious *materia medica*. The basis of our current pharmacopeias and local herbal medicines (also popular or folk medicines, medicinal floras, and sometimes referred to as "ethnopharmacopeias" or "traditional pharmacopeias") evolved along the same lines and principles until the official application of a "regulatory character" to pharmacopeias came into place (Urdang 1951; Martins et al. 2019). Considering the rich body of literature about the historical development of *materia medica* (*e.g.*, Tschirch 1910; Heffter 1914; Mann 1984; Balick and Cox 1996; Dal Cero et al. 2014, Rivera et al. 2017; Leonti and Verpoorte 2017; and references therein), it becomes clear that ethnobotanical studies did not start with the publication

---

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s43450-020-00074-w) contains supplementary material, which is available to authorized users.

✉ Marco Leonti
marcoleonti@netscape.net; mleonti@unica.it

[1] Dipartimento di Scienze Biomediche, Università degli Studi di Cagliari, Via Ospedale 72, 09124 Cagliari, Italy

[2] Dipartimento di Scienze della Vita e dell'Ambiente, Università degli Studi di Cagliari, Via Ospedale 72, 09124 Cagliari, Italy

[3] Departamento de Ciências Básicas em Saúde, Faculdade de Medicina, Universidade Federal de Mato Grosso, Cuiabá 78060-900, Brazil

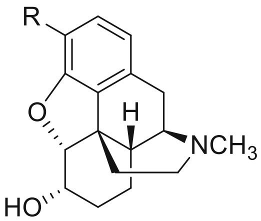
[4] Centro de Estudos Etnobotânicos e Etnofarmacológicos, Universidade Federal de São Paulo, Diadema, SP, Brazil

[5] Departmento de Botánica, Universidad de Granada, Campus Universitario de Cartuja s/n, 18071 Granada, Spain

by Harshberger (1896: “The purpose of ethnobotany”) and that ethnopharmacological investigations did not begin with Efron et al. (1970: “Ethnopharmacologic search for psychoactive drugs”; see also Heinrich 2014). The merits of these two publications were merely the introduction and diffusion of new terms, which were, however, describing already established scientific concepts and fields of research pursued in pharmacognosy, pharmacology, pharmacy, medicine, natural history, and cultural anthropology.

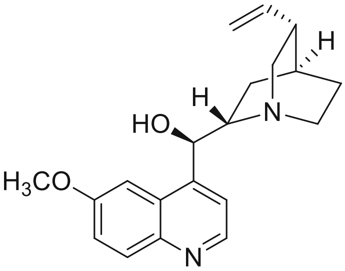
This review aims to bring the importance of the historical background of medicinal plant use and research to the forefront and argues that only in the light of cultural history of plants (see, *e.g.*, Bye 1993; Balick and Cox 1996; Prance and Nesbitt 2005) does the interpretation of current plant use make sense (Leonti 2011; Martins et al. 2019). Valuable plants and their products have been deliberately exchanged across continents at least since the beginning of the Neolithic age (Zohary and Hopf 2000; Diamond 2002; Prance and Nesbitt 2005) while non-intentional exchange of plant germplasm seems to have accompanied human activity ever since (Willerding 1986). The detection of azulene and coumarin derivatives in the dental calculus of Neanderthal remains from Spain suggests that plants belonging to the Asteraceae were used for medical purposes already in the Middle Paleolithic (Hardy et al. 2012).

“Plants have determined the very course of civilization. In the thirteenth century, Marco Polo described an island producing pepper [*Piper nigrum* L., Piperaceae; Fig. 1], nutmegs [*Myristica fragrans* Houtt., Myristicaceae], spikenard [*Nardostachys jatamansi* (D.Don) DC., Caprifoliaceae], galingale [*Alpinia* spp., Zingiberaceae], cubebs [*Piper cubeba* L.f., Piperaceae], and all the precious spices that can be found in the world. This report spurred a search for the Spice Islands, which inadvertently resulted in Europeans’ discovery of America and culminated in Magellan’s circumnavigation of the globe. Since the Renaissance, patterns of international trade in rubber [*Hevea brasiliensis* (Willd. ex A.Juss.) Müll.Arg. (Euphorbiaceae)], opium [which contains the analgesic alkaloid morphine (**1**) and the antitussive codeine (**2**) from *Papaver somniferum* L., Papaveraveae; Fig. 2], and quinine [(**3**) from *Cinchona* spp. (Rubiaceae; Fig. 3) to treat malaria] have altered the fates of entire nations” (Balick and Cox 1996).



1 R=OH
2 R=OCH$_3$

Fig. 1 Pepe (*Piper nigrum* L.) taken from Matthioli 1568



3

Global geographical and biological predispositions, such as the extension of landmasses and the availability of species amenable to domestication, causally conditioned the interchange and acceptance of knowledge, technology, and germplasm (Diamond 2005). Garlic (*Allium sativum* L., Amaryllidaceae), for instance, is thought to have its origin in a wild progenitor native to eastern Turkey, Iran, and central Asia (Zohary and Hopf 2000). Following cultural exchange, garlic was gradually incorporated into diets and medicines and now is consumed as food and (preventive) medicine across the globe (Rivlin 2001). Another example consists of a medicinal plant complex that has lost therapeutic importance in recent times including different *Ipomoea* species (Convolvulaceae) with cathartic, acrid-tasting, and resin-producing roots used by the Aztec and indigenous populations of Mexico for their purgative properties (Linajes et al. 1994; Pereda-Miranda et al. 2006). The roots known as “jalaps” were imported to Europe and used as substitutes for the Mediterranean scammony (*Convolvulus scammonia* L., Convolvulaceae; Fig. 4) (Linajes et al. 1994; Pereda-Miranda et al. 2006). *Ipomoea*

Fig. 2 Opium poppy (*Papaver somniferum* L.) in the wild, from ancient cultures. Granada Province, Spain, May 11, 2009. Photo: G. Benítez

Fig. 3 Cinchona tree (*Cinchona officinalis* L.) cultivated at José Celestino Mutis botanical garden in Bogota, Colombia, August 19, 2016, Photo: G. Benítez

Fig. 4 Scammonea (*Convolvulus scammonia* L.) from Matthioli 1568

purga L. was first introduced to botanical gardens in England, France, and Germany and later cultivated in Jamaica and India to satisfy the demand of Europe and North America (Linajes et al. 1994; Pereda-Miranda et al. 2006).

From the perspective of causal historical developments, this article critically discusses some of the ecological theories and hypotheses currently pursued in ethnobotany (Gaoue et al. 2017). We focus on those hypotheses and theories related to plants used as medicines, discussing their relevance for ethnopharmacology and their coherence with cultural-historical and ecological facts and argue that (a) it is of basic importance to understand the historical background and development of plant use in order to contextualize specific theories and concepts about plant use in a meaningful way and (b) that for a meaningful formulation of ecological hypotheses applied to the selection of medicinal plants, hypotheses need to be contextualized by a multidisciplinary framework, respecting the standards and knowledge of each of the disciplines involved.

According to Gaoue et al. (2017) “The most promising hypothesis-driven approaches to date have come from testing whether patterns of human use of medicinal plants align with the predictions of the theoretical frameworks from ecology…[Moreover,] …it is important for ethnobotanists to recognize the breadth of current ethnobotanical theories and understand how these theories can be used to develop testable hypotheses”. We agree that theoretical ecological frameworks may contribute to our understanding of plant selection and use but consider them shortsighted regarding underlying historical and socio-cultural developments and, therefore, not sufficient for addressing human plant use, especially when applied exclusively. We also agree that "it is critical for emerging ethnobotanists to be exposed to these theories in a systematic way" (Gaoue et al. 2017) specifically, because one needs to have basic historical background knowledge for understanding theories and hypotheses and to judge whether they are meaningful and scientifically sound, outdated, or anachronistic (Anderson 2017).

Theories, Hypotheses, and Main Criticisms

The hypotheses and theories focused on in this discussion and our main points of critique are:

(a) The utilitarian redundancy model, which "proposes that species that share the same therapeutic function (*i.e.*, functional redundancy) are redundant and are predicted to experience reduced use-impact as the use pressure is diffused across a greater number of species" (Albuquerque and de Oliveira 2007; Gaoue et al. 2017). Main criticism: we discuss the relevance of the utilitarian redundancy theory of herbal medicines in the light of the genetic variability of humans compared to the species and drug-specific chemistry of plant-based pharmacology and criticize the undifferentiated and reductionist concept of "therapeutic function," which appears to be conceived as being diagnosis independent classifications into more or less finely tuned etic categories of medical use without contemplating the pharmacology or chemistry of the specific herbal drugs.

(b) The availability hypothesis, which according to Gaoue et al. (2017) "states that plants are used for medicine because they are more accessible or locally abundant" (see also Albuquerque 2006). Main criticism: it is rather intuitive that resources need to be available in order to be used. We argue that instead of talking about an availability hypothesis for describing this circumstance, it would be more appropriate to build on the well-established law of demand and supply.

(c) The versatility hypothesis (Gaoue et al. 2017), which suggests "that introduced plants are incorporated as medicine by way of experimentation with introduced food and ornamental plants" (Bennett and Prance 2000; Alencar et al. 2010). Main criticism: the way by which this hypothesis is applied ignores the fact that culturally important and already versatile plants were introduced to other places and cultures with the intent to diversify food and medicine and useful resources at large.

(d) The diversification hypothesis (Gaoue et al. 2017), which "suggests that exotic plant species are selected to fill therapeutic vacancies in an ethnopharmacopoeia, perhaps due to novel bioactivity, thereby diversifying the set of treatment options" (Albuquerque 2006; Alencar et al. 2010, 2014). Main criticism: introduced dietary plant species often had already established uses as medicines in their place of origin. That profiles of secondary metabolites are the outcome of phylogenetic history reflecting ecological constraints is accepted knowledge. Therefore, introduced species have a high probability of containing bioactive secondary metabolites not found in local sources.

(e) The insect-plant coevolution related apparency theory defines "something bound to be found" as being "apparent" ("visible, plainly seen, conspicuous, palpable, obvious" (Feeny 1976)) and explains why short-lived, "non-apparent" species contain qualitative defense compounds "whereas species with long lifespans (apparent) face higher herbivore pressure and invest in more expensive quantitative defenses" (Feeny 1976; Gaoue et al. 2017). "Thus, non-apparent plants (short lived, herbaceous, early successional) are more likely to be used for medicine than "apparent" plants (perennial, woody, dominant plants)" (Gaoue et al. 2017). Main criticism: we explain that Feeny's concept of "apparency" is convoluted and the definition of apparency open to arbitrary interpretation as Feeny also considered "apparency to mean 'susceptibility to discovery' by whatever means…since animals, fungi and pathogens may use means other than vision to locate their host-plants" (Feeny 1976). We believe that Feeny's consideration of other senses besides vision being used by organisms to detect food (Feeny 1976) is compatible with reality but not reconcilable with the division into annuals and perennials or plants with qualitative and quantitative defense compounds. As an alternative and inclusive theory, explaining and synergizing with the observation that weeds and non-apparent species are frequently included in medicinal floras, we highlight the circumstance that the degree of geographical range size of a taxon correlates with the probability to be included in the medicinal flora at the local as well as the global level (Leonti et al. 2013).

(f) Finally, we discuss the epistemological appropriateness of various statistical models applied for assessing non-random plant selection and to test for overused and underused plant taxa with respect to the overall available flora.

Discussion

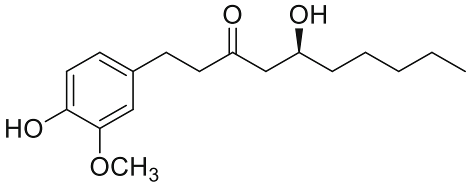
Utilitarian Redundancy

Disease Classification

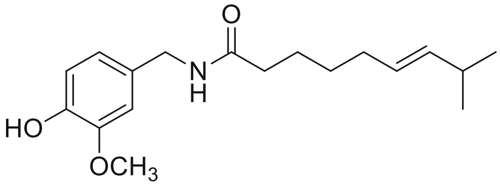
The concept of utilitarian redundancy proposes that different species, which "share the same therapeutic function (*i.e.*, functional redundancy) are redundant" (Gaoue et al. 2017, p. 278). Redundant species have initially been defined by

Albuquerque and Oliveira (2007, p. 158) "as those that share the same function in a given local medical system. Function is used to define the local therapeutic action category (*e.g.*, stomachaches, coughs, fever etc." Studies using the concept of utilitarian redundancy, such as Alencar et al. (2014) or Santoro et al. (2015), do not specify which species are redundant and instead point out disease categories and body system disorders, which are considered more or less redundant based on the number of medicinal species with uses arranged into these categories.

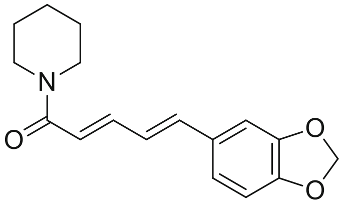
Redundancy would thus depend on species richness per category of use. Depending on such reductionist approaches, ginger (*Zingiber officinale* Roscoe, Zingiberaceae), pepper (*Piper* spp., Piperaceae), and chili pepper (*Capsicum* spp., Solanaceae) would, for instance, turn out to be redundant for several uses considering the existing overlap (*vide infra*). Chemically, gingerol (**4**) is related to capsaicin (**5**) and piperine (**6**), the compounds which give ginger, chili peppers, and black pepper, respectively, their particular spiciness and make them "hot". These compounds determine the therapeutic uses, which are often related to digestive problems due to their capacity to increase digestive fluids that can help speeding up the digestion process and relieve diarrhea.



4



5



6

Moreover, for identifying the redundancy of therapeutic functions, the multiple pharmacological mechanisms of action of herbal drugs as well as precise diagnoses, including the identification of pathogenic agents, physiological and histological markers would be necessary. This would require specific information about the network pharmacology of complex mixtures as well as diagnostic tools and techniques generally not available in ethnomedical contexts, which is the reason why the International Classification of Diseases (ICD) cannot be used for classifying ethnomedical data.

Besides all this, the idea of redundancy also ignores the concept and existence of medicinal plant complexes including taxonomically unrelated assemblages of herbal drug species. Influenced by common key morphological and organoleptic features, such medicinal plant complexes share common names and therapeutic uses (Linares and Bye 1987) while their chemical content is dissimilar.

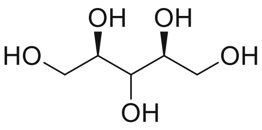
Polymorphism and Personalized Medicine

Due to inherent polymorphisms, not all individuals respond in the same way to xenobiotics. Genetic factors influence epidemiology (Khoury et al. 1993), and the response of individuals towards herbal and pharmaceutical drugs is affected by polymorphisms at different levels. This includes polymorphisms of pharmacological targets, *e.g.*, receptors; enzymes; the system responsible for detoxifying and metabolizing xenobiotics, *e.g.*, efflux pumps; and the microbiome at large (Rizkallah et al. 2010). Major components underlying differential drug metabolism and drug response are about 12 enzymes belonging to the cytochrome 450 (CYP) superfamily. Physiological, ontological, and genetic factors are responsible for the expression of each CYP, and therefore, differences between populations and individuals exist (Cambria-Kiely and Gandhi 2002; Zanger and Schwab 2013; Lazalde-Ramos et al. 2014). Biomedicine, in fact, addresses polymorphisms in pursuing a pharmacogenomics approach considering individual differences in pharmacokinetics (absorption, distribution, biotransformation, and excretion) and pharmacodynamics (dose-response relationships) with the aim of offering personalized drug treatment (Clayton et al. 2006; Relling and Evans 2015). The individual reaction to pharmaceutical drugs and the specific and still often unknown chemical composition of herbal drugs (Evans 1998; Bent and Ko 2004; Heinrich 2010; Pferschy-Wenzig and Bauer 2015) is the reason why the utilitarian redundancy hypothesis applied in such an undifferentiated way does not do justice to herbal medicine.

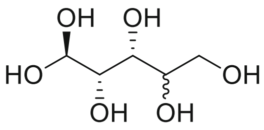
Knowing a range of different treatment options for apparently similar health problems moreover represents a rational strategy in herbal and traditional medicine and medicine at large (Porter and Kaplan 2011): In case a specific remedy does not show the desired efficacy, along the trial-and-error approach, alternative remedies can be sought. In popular medicine, such therapeutic alternatives are often subsumed under the same vernacular name and considered herbal drug complexes (Linares and Bye 1987; Estrada-Reyes et al. 2004; Pardo-de-Santayana et al. 2005; Obón et al. 2012). Apart from the relevance of individual drug metabolism and response, it is important for people living in biologically and ecologically diverse areas to recognize medicinal plants for the same health problem in each of the ecosystems used for their livelihood.

Pharmaceutical Redundancy: Where This Concept Makes Sense

Generally, woody species (see also the apparency theory by Feeny 1976) have the tendency to defend themselves from herbivory with polyphenolic anti-digestive metabolites. The widely spread tanninic and galloylated polyphenols interact with proteins through covalent bonding or hydrogen bridges and form protein-polyphenol complexes on the oral and vaginal mucosa, gastrointestinal lining, and cutaneous lesions (Wagner, et al. 2007). The protein-polyphenol interaction is exploited by the tanning industry for the production of leather and in medicine for curing diarrhea, dysentery, and cutaneous and mucosal irritations and lesions. In herbal and traditional medicine, often tree barks (*Quercus* spp., Fagaceae, *Hamamelis virginiana* L., Hamamelidaceae, *Psidium guajava* L., Myrtaceae), the (un)-ripe fruits of chestnut (*Castanea sativa* Mill., Fagaceae), pomegranate peel (*Punica granatum* L., Lythraceae), bilberry (*Vaccinium myrtillus* L., Ericaceae), and tea leaves (*Camellia sinensis* (L.) Kuntze, Theaceae) are used interchangeably for these purposes. Kinos are tannin-rich wood exudates that can be obtained from a variety of species and genera (Locher and Currie 2010). They are used for their styptic properties and were formerly also included in European pharmacopeias and used for treating diarrhea, dysentery, hemorrhages, and cutaneous lesions (Locher and Currie 2010). Although the specific compositions of phenolic constituents between different types of kinos differ, redundancy most probably exists. Other examples of herbal drugs with a certain degree of redundancy are those containing mucilage, alditols (*e.g.*, xylitol (**7**), sorbitol (**8**), and D-mannitol (**9**)) and triacylglycerides applied as mild laxatives and sweeteners (Wagner et al. 20,807). Xylitol (E967) is present in, *e.g.*, *Brassica oleracea* var. *botrytis* L., Brassicaceae, and fruits of *Fragaria vesca* L., *Rubus idaeus* L., and *Prunus domestica* L., all Rosaceae; sorbitol (E420) is present in fruits of *Sorbus aucuparia* L., Rosaceae, and D-mannitol (E421) is contained in manna obtained from *Fraxinus ornus* L., Oleaceae.

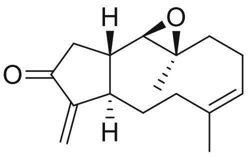


7

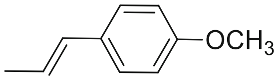


8 5*S*
9 5*R*

Triacylglycerides are present in a variety of seed and fruit oils such as olive oil (*Olea europaea* L., Oleaceae), peanut oil (*Arachis hypogaea* L., Fabaceae), and linseed oil (*Linum usitatissimum* L., Linaceae) while mucilages are present in seeds of *Plantago afra* L., *Plantago ovata* Forssk., Plantaginaceae, and *L. usitatissimum*, for example. Also, laxative anthranoid-containing drugs such as leaves and fruits of *Senna alexandrina* Mill., Fabaceae, roots of *Rheum palmatum* L. and *Rheum officinale* Baill., Polygonaceae, cortex of *Frangula alnus* Mill. and *Frangula purshiana* (DC.) A. Gray ex J.G. Cooper, Rhamnaceae as well as the sap of *Aloe* spp., Asphodelaceae show some redundancy. Herbal drugs containing mucilage and used for oral and respiratory problems (*e.g.*, derived from Malvaceae and *Cetraria islandica* (L.) Ach., Parmeliaceae) show redundancy for their soothing quality (Bruneton 1999; Hänsel and Sticher 2007; Wagner et al. 2007). Sesquiterpene lactones are known at the same time for their anti-inflammatory, cytotoxic, and allergenic properties, owing their activity to the α-methylene-γ-lactone moiety, which is able to alkylate nucleophiles of biomolecules by a Michael-type addition, especially cysteine sulfhydryl residues of proteins in general and specifically pro-inflammatory nuclear factor-kappa B, leading to undesirable cytotoxicity (Siedle et al. 2004). This is probably the reason why sesquiterpene lactone-rich herbal drugs from Asteraceae are frequently used as topical anti-inflammatory drugs (Moujir et al. 2020) and show a certain degree of redundancy. In the late 1970s, sesquiterpene lactones were excluded by the US National Cancer Institute for therapeutical use because their highly reactive groups were thought to interact with any thiol group. However, structure–activity relationship studies of parthenolide (**10**) from the shoots of feverfew (*Tanacetum parthenium* (L.) Sch.Bip., Asteraceae), demonstrated that the chemical diversity imposed by its stereochemistry and conformational changes, probably restrain from nonspecific attacks onto thiol groups. Derivatives, with better hydrophilicity and retaining their potency, have been developed by conjugate addition of aromatics, particularly a tyramine moiety, or aliphatic amines to the a-methylene group. Among those products is the aliphatic acyclic amine, dimethylaminoparthenolide with specificity towards crucial cancer signaling pathways (Ghantous et al. 2013).



10



11

Although flavor properties are not identical, herbal drugs used as natural low caloric sweeteners may also show some degree of redundancy (Soejarto et al. 2019) as well as the essential oil obtained from anise (*Pimpinella anisum* L., Apiaceae), fennel (*Foeniculum vulgare* Mill., Apiaceae) and star anise, (*Illicium verum* Hook.f., Schisandraceae) fruits, all three with a high content of *E*-anethole (**11**), also known as anise camphor, 80–95%, 80%, and 80–90%, respectively (Bruneton 1999; Rocha et al. 2016). Above all, does utilitarian redundancy exist in the case of generic drugs (Kesselheim et al. 2008).

The Availability, Versatility, and Diversification Hypotheses

The expected profit, benefit, and availability of any resource determines its demand and value. Culturally important and versatile plants as well as their products were deliberately exchanged for economic reasons with the intention of diversifying food, medicine, and agricultural crops but also for sheer curiosity and experimentation (Tschirch 1910; Balick and Cox 1996; Bennett and Prance 2000; Diamond 2005; Prance and Nesbitt 2005; El-Gharbaoui et al. 2017; Martins et al. 2019). To describe this circumstance and the result of this well-known historical interchange, sometimes, the availability, diversification, and versatility hypotheses are applied (Alencar et al. 2010; Gaoue et al. 2017; Hart et al. 2017). According to Gaoue et al. (2017), "The versatility, availability, and diversification hypotheses attempt to explain the increasing or disproportionately large number of exotic plants utilized in traditional medicine".

The Idea of Availability

With regard to the availability theory (Goaue et al. 2017), it is quite obvious that a plant or herbal drug (or anything else) needs to be available in one way or another; otherwise, its application is not possible. The costs invested to obtain a certain herbal drug or remedy depends on the balance between supply and demand while the demand may be influenced by a range of parameters (Benítez et al. 2016). Textual and archaeological evidence demonstrate that spices and herbal drugs were imported from Africa, Arabia, Central Asia, Himalaya, or the Indo-Malayan region integrating the European and Mediterranean *materia medica* with exotic drugs since 2000 years (Heffter 1914; Miller 1969; Mann 1984; Touwaide and Appetiti 2013; Van der Veen and Morales 2015; Staub et al. 2016; El-Gharbaoui et al. 2017; Rivera et al. 2017). When the availability of a product is strictly limited such as for example with exotic and rare species or when the collection of a crude drug is laborious, the expected benefits driving the demand have a more dramatic impact on the value chain (Lopes 2019).

Looking back at the herbal drug trade in the Middle Ages, Tschirch (1910) distinguished three large economic regions: the Indian and Arabic Ocean, the Mediterranean Sea, and the North and Baltic Sea. The first was controlled by Alexandria (Egypt), the second by the Italian city states (Venice, Genoa, and Pisa), and the third by Bruges (northwest Belgium) and Lübeck (northern Germany). In the thirteenth century, for example, 100 kg pepper (*P. nigrum*) did cost the equivalence of 481 M [Marks] in Marseille, 512 M in Lombardy, 620 M in the Champagne, and between 683 and 796 M in England. At the beginning of the sixteenth century, ginger (*Z. officinale*) was three times as expensive in Alexandria compared to Calicut (Kozhikode, India), and incense (*Boswellia* sp., Burseraceae) did cost five times more in Alexandria compared to Mecca (Tschirch 1910). Instead of pursuing the vague idea of availability, it would be more rewarding to apply the concept of balance of supply and demand in accordance with economic sciences (Nicholson and Snyder 2007; Varian 2010). As a proxy for calculating the balance between supply and demand when sales figures are not available, one could correlate the number of communities making use of a specific botanical drug and its general ecological abundance assessed by the number of Universal Transverse Mercator grids, or through citations in phytosociological inventories (Pardo-de-Santayana et al. 2017). The availability and cultural valuation of a product influence its use, expenditure, and price following economic concepts and the availability theory is already reflected in the well-established economic law of balance and supply.

The Idea and Concept of Versatility and Diversification

The versatility hypothesis proposes that by way of experimentation, introduced plant species as food and ornamentals (Bennett and Prance 2000) account with a higher diversity of medical uses than native species (Gaoue et al. 2017). The diversification hypothesis proposes that introduced species with their novel chemistry and pharmacology may diversify the options of medical treatments (Alencar et al. 2010; Gaoue et al. 2017). "The diversification hypothesis suggests that exotic plant species are selected to fill therapeutic vacancies in an ethnopharmacopoeia, perhaps due to novel bioactivity, thereby diversifying the set of treatment options" (Albuquerque 2006; Alencar et al. 2010, 2014; Gaoue et al. 2017).

The idea of versatility was presented by Bennett and Prance (2000, p. 91) who argued that from their compilation of 216 introduced species medicinally used in South America, 88 "were originally introduced as foods" and that "only 14 species likely were introduced for their therapeutic value." Bennett and Prance (2000) made this assessment without showing any historical data that would sustain their claim and did not specify which species they were alluding to. As it turns out, however, most of the 216 species listed are used as medicines in their place of cultural origin (Europe and Africa) since thousands of years, which is in agreement with the notion that food is used as medicine and vice versa in the Old

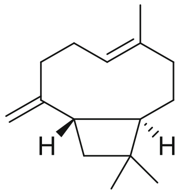
World. Compare the 216 species with, for instance, the chapters in Matthioli (1568) or Avicenna (1998, 2014) and see Supplementary Material B for 106 chapters about species and genera in Matthioli's (1568) translation of Dioscorides' *De Materia Medica* (*DMM*) overlapping with the plant list in Bennett and Prance (2000). Cultural plants are often used for multiple purposes. Therefore, the most versatile species are the most likely to be interchanged exactly as a function of these multiple reasons.

The cultural perspective on versatility and diversification can be examined by means of the spice trade, which offers a historical and practical perspective for understanding the mechanism of inclusion of exotic drugs into local cuisine, pharmacopeias, and medical floras. The high content in fragrant essential oil and the presence of secondary metabolites with antimicrobial properties render spices versatile and multipurpose herbal drugs. They are used in medicine, in perfumery, as incense, and to conserve food, and they have been used in embalming practices and for making decaying food more palatable (Sherman and Billing 1999; Prance 2005; Papageorgopoulou et al. 2009). Each odor, taste, and flavor is associated with a specific chemical profile able to transmit nutritional and pharmacological cues to varying degrees (Goff and Klee 2006; Chaudhari and Roper 2010; Breslin 2013). The fact that fragrant plant parts such as spices were exchanged between cultures implies that the associated chemosensory qualities were not found among the local floral resources. This circumstance can be appreciated by contemplating the collection of spices in our kitchens.

Under alien ecological conditions, exotic food species and spices are mostly dependent on horticulture and agriculture and are thus readily available for further experimentations (Johns 1990; Harlan 1992; Etkin 2006). For culturally accepted plants and herbal drugs with already established uses, accidental, experimental, or post-prandial observations can occur more easily, especially as food items are often ingested in considerable amounts. This intimate relationship has thus the potential to lead to new therapeutic uses.

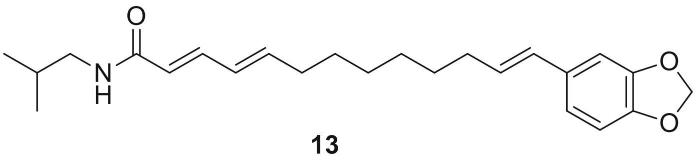
Chemical and Pharmacological Perspectives on Versatility and Diversification

Fruits of black and the infructescences of long pepper (*P. nigrum* and *P. longum* L.), for instance, are important Ayurvedic herbal drugs used since ancient times for digestive problems, to stimulate appetite, and to increase peristalsis and the flow of saliva, as well as for pain relief, rheumatism, increased blood circulation, and treatment of fever and cold (Meghwal and Goswami 2013). Black pepper is also used in perfumery and to preserve food (Srinivasan 2007). Dioscorides' *DMM* testified the importance of pepper fruits as medicine in the Roman Empire during the first century of the current era (CE). Matthioli's (1568) translation of *DMM* mentions the promotion of appetite and digestion, induction of labor, the use as an analgesic, for treating disorders of the respiratory tract (angina [tonsillitis], cough, purge phlegm from the head), in ophthalmology, for contraception, treatment of swelling of glands, vitiligo, snake bites, and the importance and pepper fruits as an antidote in general. Similarly, Ibn al-Baytar (thirteenth century CE) described the importance of black pepper in Arabic medicine for problems of the gallbladder, stomach, liver, teeth, circulatory system, and skin as well as nervous disorders (Leclerc 1877–1883). The flavor of pepper is determined mainly by the hot piperine (**6**) and volatile terpenes such as germacrene D, limonene, α and β-pinene, β-caryophyllene (**12**), and α-phellandrene (Jirovetz et al. 2002). The global use and commercial value of pepper species have motivated scores of pharmacological studies, which became the basis for new therapeutic applications augmenting the versatility of pepper. The hot taste of pepper fruits results from an interaction of the main alkaloid piperine with heat- and acid-sensitive transient receptor potential cation channels (TRPVs), which induce sweating and enhance the release of saliva and gastric juices. Piperine has shown a range of other biological properties including antimicrobial effects and the capacity to enhance metabolism in general (Srinivasan 2007; Meghwal and Goswami 2013; Butt et al. 2013). Piperine is currently exploited for improving the poor bioavailability of other drugs such as curcumine as well as a fat burner due to its metabolism-enhancing property (Shoba et al. 1998; Srinivasan 2007; Meghwal and Goswami 2013).

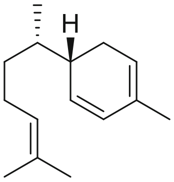


12

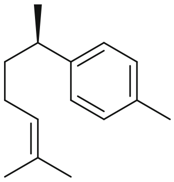
Moreover, fruits of *P. nigrum* and *P. longum*, as well as those of other *Piper* species, contain *N*-isobutylamide guineensine (up to 0.5%), which inhibits the cellular uptake of endocannabinoids ($EC_{50} = 290$ nM; Nicolussi et al. 2014). Guineensine (**13**) showed dose-dependent and significant anti-inflammatory and anti-nociceptive effects in a mouse model when given *i.p.* (Reynoso-Moreno et al. 2017). Also, β-caryophyllene (BCP; **12**), a ubiquitous sesquiterpene, for which pepper fruits are one of the major dietary sources, interacts with the endocannabinoid system. By acting selectively and as a functional agonist to the CB_2 receptor (Ki of 155 nM), BCP contributes to the anti-inflammatory effects of pepper (Gertsch et al. 2008). Also, gingerols and shogaols, the arylalkanones present in ginger, mediate their pungency via TRPV receptors. In addition, the flavor of ginger is determined by its essential oil content, which is dominated by the presence of sesquiterpenes such as (−)-zingiberene (**14**) and (+)-*ar*-curcumene (**15**) and characterized by the presence by zingiberol (mixture of *cis*- and *trans*-β-eudesmol) and citral (mixture of the isomers geranial and neral; Wichtl 2002). Besides being used as a spice and food ingredient, ginger has become a globally used botanical drug available in a range of galenic forms and used to treat rheumatoid arthritis, headache and migraine, digestive disorders, nausea related to pregnancy, and motion sickness as well as upper respiratory tract infections (Barnes et al. 2002; Williamson 2002; Wichtl 2002). Similar to pepper also ginger was imported to the Roman Empire as a condiment and used for medicinal purposes such as for improving digestion and eyesight as well as an antidote (Matthioli 1568).



13



14



15

Extracts and pure compounds derived from ginger have shown a range of anti-inflammatory mechanisms and effects *in vitro* and *in vivo* as well as in clinical studies (Barnes et al. 2002; Nievergelt et al. 2011). Gingerols, shogaols, and gingerdiones have also been found to interact with the human serotonin 5-HT$_{1A}$ receptor *in vitro* with a K_i between 3 and 20 μM providing an explanation for the anti-emetic and possibly mood-modulating effects of ginger products (Nievergelt et al. 2010).

The most potent activator of TRPV1 is capsaicin (**5**), the pungent and hot principle of chili peppers being about 100 times more potent than piperine (Lawless and Heymann 2010). Similar to pepper and ginger, also hot chili peppers (*Capsicum* spp.; Fig. 5) are used to flavor dishes and applied in traditional medicine and phytotherapy around the world. *Capsicum* species are used for their stimulant, antispasmodic, carminative, diaphoretic, counterirritant, and antiseptic properties while capsaicin preparations are topically applied as rubifacients and to treat rheumatism, arthritis, and neuralgia (Barnes et al. 2002; Wichtl 2002).

The examples of pepper, ginger, and chili pepper showcase how a wider cultural diffusion of herbal drugs (availability) will lead to the establishment of new local uses (augmented versatility) and, as a feedback thereof, attract more toxicological and pharmacological studies. These three spices share several uses and properties and, not by chance, they are presented in sequencing chapters in Matthioli (1568: Chapters 148 and 149, pp. 605–614). According to the utilitarian redundancy model by Albuquerque and Oliveira (2007), the uses of the three drugs would be redundant for rheumatism and analgesics but the phytochemical and pharmacological data reviewed here disprove this at the molecular level. Notwithstanding all three spices are used for similar therapeutic categories and all interact with TRPVs, piperine, guineensine, capsaicine, gingerols, and shogaols all have a unique profile of molecular interactions and pharmacological properties.

608 Diſcorſi del Matthioli

PEPE D'INDIA.

Fig. 5 Pepe d'India (*Capsicum* spp.) from Matthioli 1568

Ecological Perspective on Versatility and Diversification

The evolutionary and ecological history of plants determines allelochemistry and secondary metabolites, which can be used for assessing taxonomic relationships (“chemotaxonomy”; Wink 2003). Although chemical and consequently pharmacological convergence exist, *e.g.*, nicotine, polyacetylenes, purine alkaloids (Dewick 2002; Wink 2003), it is well accepted in plant sciences that phylogenetically distant taxa and those which evolved under different ecological constraints reflect evolutionary history through disparate chemical profiles and, consequently, through different pharmacological properties (Wink and Waterman 1998; Wink 2003). In fact, the concept of chemotaxonomy (chemosystematics) has a long history (De Candolle 1804; Hegnauer 1962–1996) and can inversely be used as a tool in the search for alternative drug sources in closely related taxa (Ge et al. 2008; Pellicer et al. 2018).

Main Criticism of the Versatility and Diversification Hypothesis

The several studies highlighted here and in Gaoue et al. (2017) present the versatility and diversification hypothesis uncoupled from causal historical, bio-cultural, pharmacological, and ecological backgrounds. Ecological connections between plant phylogeny and allelopathy are not considered either. Those studies dealing with the versatility hypothesis do not contextualize the versatility of introduced species with the versatile uses these species experience in the geographical regions of origin (Martins et al. 2019). It is also worth considering that the idea or concept of availability, versatility, and diversification are all interconnected. Conclusively, the power of each of these conceptual factors for assessing plant selection would be difficult to estimate as they are intrinsically and historically tied.

Apparency Theory

Feeny’s apparency theory is a thumb rule based on observations of insect-plant interactions and the more frequent presence of qualitative defense compounds (*e.g.*, alkaloids, sesquiterpene lactones, *inter alia*) in short-lived, herbaceous species, considered “non-apparent” and the accentuated presence of quantitative defense compounds (tannins, lignins) in woody perennials, which are classified as “apparent” (Feeny 1976). Feeny (1976) defined apparent as “something bound to be found” as being “visible, plainly seen, conspicuous, palpable, obvious” (Feeny 1976) and unapparent as the contrary of this. Moreover, Feeny (1976) considered also abundance as a factor for apparency as well as the factors involved with the need of flowering plants to attract pollinators—and in case producing endochorous fruits—also frugivors. Finally, Feeny (1976) meant apparency to include also “susceptibility to discovery” by whatever means… “since animals, fungi and pathogens may use means other than vision to locate their host-plants.” With such a definition, everything is potentially apparent independent of its lifecycle and life form and renders the concept of the apparency theory arbitrary, confusing, and open to interpretations. As a consequence, the division into species with qualitative (non-apparent) and quantitative (apparent) defense compounds would have no more relevance. Not surprisingly, testing the apparency hypothesis across medicinal floras derived from more primary and more disturbed ecological systems, or biomes with a marked seasonality, resulted in mixed results (Albuquerque 2006; Ribeiro et al. 2014; Gaoue et al. 2017). Knowledge not considered by the apparency hypothesis is that herbaceous plant taxa have wider-ranging geographical distributions compared to that of woody taxa, which are more restricted to the species-rich tropical latitudes and that northern-hemispheric plant taxa have wider ecological amplitudes tending more towards woodyness compared to neotropical taxa (Hawkins et al. 2011).

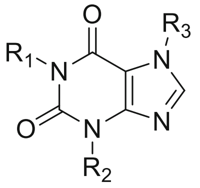
Several studies highlighted the overrepresentation of weedy species in medicinal floras of peoples living in environments disturbed by human activity (Stepp and Moerman 2001; Voeks 2004; Leonti et al. 2013). The selection of invasive species for medicinal purposes is a function of human activity and globalization. Weeds grow successfully in disturbed habitats, frequently contain qualitative defense compounds, are often herbaceous, and would thus, according to the apparency hypothesis, be “non-apparent.” Stepp (2004) pointed out that weeds are a rich source of pharmaceuticals and, therefore, suggested to screen this group of taxa for new medicinal compounds. However, how can it be that plants that are said to be non-apparent and hard to detect are overrepresented in medicinal floras? Whether something is apparent depends on the context, such as the type of ecosystem and specific herbivore-plant interaction. Apparency evidently lies in the senses of the beholder: whether it is subterranean truffle (fruiting body, *Tuber* sp.), cabbage (leaves, *Brassica* spp.), kawa-kawa (root; *Piper methysticum* G. Forst.), or tea (leaves; *C. sinensis*), the factors which attract or repel humans and other herbivores are the particular organoleptic, chemosensory, nutritional, and pharmacological properties and not their life form or life cycle. For instance, Brassicaceae metabolites, *e.g.*, glucosinolates, serve as feeding cues for Pieridae caterpillars, and make Brassicaceae species apparent, *i.e.* detectable to these herbivore insects but are considered non-apparent (“hard to find”) by Feeny (1976). Therefore, it is not true that herbivores attack the most apparent or abundant species (Gaoue et al. 2017) as many herbivores, especially insects, are adapted to specific chemical marker compounds for identifying their diet (Kessler and Baldwin 2002) whether the associated taxa is abundant, apparent or not.

What remains is the fact that many woody taxa use quantitative defense compounds while annual and weedy taxa usually rely on qualitative defense compounds. This does, however, not exclude the presence of tannins in herbaceous and short-lived plants (*e.g.*, *Potentilla* spp., Rosaceae) or qualitative defense compounds in woody perennials (*e.g.*, quinine (**3**) in *Cinchona* spp., caffeine (**16**) in *C. sinensis* or *Cola* spp., (Malvaceae)). Moreover, Fabaceae (4th largest plant family), whether perennials or woody, have their own endogenous nitrogen source due to the activity of symbiotic nitrobacteria and are capable of producing qualitative nitrogen-containing defense compounds. The analysis of the life forms of the 225 taxa used for FDA approved or clinical trial drugs (Zhu et al. 2011) showed that around half (98) derive from shrubby or woody taxa exploited above all for the presence of qualitative defense compounds; for example, see Table A, Supplementary Material and the supplementary file associated with Zhu et al. (2011). A comparison of the 63 drug and clinical trial-drug productive angiosperm and gymnosperm families censed by Zhu et al. (2011) with the overall 457 angiosperm and gymnosperm families revealed that the 63 drug-producing families comprise around half of all species worldwide overlapping with major weed taxa and those used in rural medicinal floras (Leonti et al. 2013). It has been suggested that this is related to "a broader range of ecologically-relevant information encoded in their genes with respect to locally occurring taxa" (Leonti et al. 2013). This theory entails that the synthesis of allelochemicals in species-rich and widespread taxa is driven by a broader range of ecologically relevant information leading to metabolites with wider biological interactions than in more locally evolved taxa. The theory of geographical range size as a dependent factor is compatible with both observations: that of the inclusion of weeds and that of non-apparent species in medicinal floras. Moreover, this theory does not depend on more or less arbitrary definitions of apparency and the question what constitutes a weed but is based on molecular data representing phylogenetic relatedness together as well as biogeography.

For testing the apparency hypothesis in a rigorous way, the composition and accessibility of the overall flora would need to be compared with that of the medicinal flora. The result would always either highlight the overproportional use of weedy and annual species (non-apparent) and underrepresentation of woody and apparent species or vice versa. But what would this tell us? What would be the relevance for ethnopharmacology or pharmacognosy? The outcome ultimately depends on the degree of ecological integrity, globalization, and acculturation and whether the focus is on the northern or southern hemispheric realm. Instead of simply focusing on weedy species for drug discovery (Stepp 2004), it might be more rewarding to focus the attention on widespread and species-rich plant taxa (Leonti et al. 2013).

Theory of Non-random Plant Selection

The large cultural diversity expressed by human societies comes along with a relatively homogenous human genome (Pagel and Mace 2004) and human societies show common needs and cravings for macro- and micronutrients and stimulants as well as therapeutics. For example, stimulating herbal drugs containing the purine alkaloids, caffeine (**16**), theophylline (**17**), and theobromine (**18**) functioning as antagonists of the adenosine receptor, such as coffee (*Coffea* spp., Rubiaceae), cacao (*Theobroma cacao* L., Malvaceae; Fig. 6), tea (*Camellia sinensis* (L.) Kuntze, Theaceae), guarana (*Paulinia cupana* Kunth., Sapinadaceae), mate (*Ilex paraguariensis* A.St.-Hil., Aquifoliaceae), and cola (*Cola* spp.) have been selected independently by human cultures residing on different continents (Heffter 1914; Weckerle et al. 2010).



16 $R_1=R_2=R_3=CH_3$
17 $R_1=R_2=CH_3$; $R_3=H$
18 $R_1=H$; $R_2=R_3=CH_3$

The use of purgative Convolvulaceae roots is known from pre-Hispanic Mexico (Linajes et al. 1994), Brazil (Lira-Ricárdez et al. 2019), and Europe (Castañeda-Gómez and Pereda-Miranda 2011), and similarly, the use of laxative anthranoids containing drugs such as the dried sap of *Aloe* spp., the roots of *Rheum* spp., fruit and bark of *Rhamnus* spp., and fruits and

Fig. 6 Cacao pods and beans (*Theobroma cacao* L.) from cultivated trees near Basupú, Bioko Island, Equatorial Guinea, May 20, 2015. Photo: G. Benítez

leaves of *Senna* spp. are reported from different time periods and continents (van Gorkom et al. 1999; Heinrich et al. 2004). In the same way, closely related phloroglucinol derivatives are the pharmacologically active principles of different anthelmintic drugs: *Dryopteris filix-mas* (L.) Schott, Dryopteridaceae, used to treat tapeworm infection in the Old World and *Dryopteris athamantica* (Kunze) Kuntze, Dryopteridaceae, "uncomocomo" in South Africa used for the same purpose; the kosso-flowers of *Hagenia abyssinica* (Bruce ex Steud.) J.F.Gmel., Rosaceae, used in Abyssinia for getting rid of intestinal parasites in general as well as "kamala" obtained from *Mallotus philippensis* (Lam.) Muell.Arg., Euphorbiaceae. This cross-cultural selection of botanical drugs containing anthelmintic phloroglucinols bears evidence for the observatory skills of human societies when it comes to the selection of efficacious remedies (Heffter 1914).

In order to counter the argument put forward by some medical scholars that plant selection for therapeutic use would be guided by placebo effects alone, Moerman (1979) postulated that in such a case plant selection would be taxonomically random (Moerman 1979). However, this would not necessarily be so because morphological and other organoleptic properties are culturally molded into symbolic interpretations along the doctrine of signatures and act as a mnemonic aid, which can also help to transmit placebo effects (Etkin 1988; Casagrande 2000; Leonti et al. 2002) or a "meaning response" (Moerman and Jonas 2002). Since morphological and organoleptic properties show a non-random phylogenetic distribution, non-random distribution is not necessarily an indicator for inherent pharmacotherapeutic properties of botanical drugs and can lead to multiple and disparate therapeutic applications between individuals and cultures (Shepard 2004; Leonti 2011).

What Moerman's approach did show is that certain families are overrepresented (and others underrepresented) in terms of number of species in indigenous medicinal floras when compared to the overall available flora of a specific region (Moerman et al. 1999). The question of over and underrepresented plant families in medicinal *florae* was approached with different statistical methodologies sparking a scientific debate (Leonti et al. 2012; Moerman 2012). Bennett and Husby (2008) suggested to use a binomial model instead of the linear regression model initially introduced by Moerman (1979). However, both the binomial and the linear regression model use percentage values for estimating the true proportion of averagely used species per family as if both, the plants used as medicine and the overall flora were assessed by a census. Since medicinal plant use is never assessed by a census but by means of samples, Weckerle et al. (2011) introduced a Bayesian approach, which takes the uncertainty around the true proportion of plants used as medicine into account. Since, however, also floral checklists are never complete and generally not congruent with the living space of human populations Weckerle et al. (2012) proposed an imprecise probability approach, which additionally considers the uncertainty around the overall flora and, therefore, reflects the ecological realty more accurately.

Conclusions

Literature about the medicinal use of herbal drugs has been continuously published over the past 2000 years. Studies about the selection and inclusion of herbal drugs into medicinal floras and pharmacopeias have been conducted from various perspectives. The recent call for more hypothesis-driven research in ethnobotany resulted in an uncritical and sometimes erratic application of hypotheses also used for describing well-accepted knowledge and cultural realities. Since the hypotheses and theories discussed herein ignore the cultural history that guided and shaped human-plant interactions, we highlight its importance. Cultural history of plants contains causal cues and rationales for plant selection and the transmission of associated knowledge. Plants were selected for food and medicine due to their particular organoleptic, chemosensory, nutritional, and pharmacological properties. Plants and their uses have often been intentionally introduced to other regions of the world in relation to their dietary and medicinal qualities adding to the diversification of local medicinal floras and pharmacopeias. This resulted in an increased versatility of specific drugs. The often-perceived higher versatility of exotic species is a consequence of the simple fact that the most valuable, effective, and versatile species are the most likely to be cross-culturally exchanged. This constitutes a positive effect of globalization.

Many more hypotheses related to the selection of plants used as medicine than the ones focused on here do exist. Interdisciplinary approaches including medicine, epidemiology, pharmacy, pharmacognosy, pharmacology, anthropology, botany, ecology and history have the highest potential to result in equilibrated appraisals and power to tackle relevant and new research questions. Therefore, identifying gaps in knowledge, which can be addressed with intelligent hypotheses, whether including concepts from ecology or not is not trivial. It requires comprehensive knowledge of the specific research situation and its historical context in order not to oversimplify the inherent complexity of human-plant relationships. Ecological research questions applied to human-plant relationships should thus always consider the historical impact of human culture as a backdrop and confounder and integrate this parameter into the model and analysis.

Acknowledgments We would like to thank Caroline Weckerle and Franz Huber for critical commentaries on a draft version of this paper.

Availability of Data and Material All data submitted incl. supplementary material.

Code Availability Not applicable

Authors' Contributions ML designed the review. LC, DTOM, ER, GB, and ML wrote the paper.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

References

Albuquerque UP (2006) Re-examining hypotheses concerning the use and knowledge of medicinal plants: a study in the Caatinga vegetation of NE Brazil. J Ethnobiol Ethnomed 2. https://doi.org/10.1186/1746-4269-2-30

Albuquerque UP, Oliveira RF (2007) Is the use impact on native Caatinga species in Brazil reduced by the high species richness of medicinal plants? J Ethnopharmacol 113:156–170. https://doi.org/10.1016/j.jep.2007.05.025

Alencar NL, de Sousa Araújo TA, de Amorim ELC, Albuquerque UPd (2010) The inclusion and selection of medicinal plants in traditional pharmacopoeias-evidence in support of the diversification hypothesis. Econ Bot 64:68–79. https://doi.org/10.1007/s12231-009-9104-5

Alencar NL, Santoro RS, Albuquerque UP (2014) What is the role of exotic medicinal plants in local medical systems? A study from the perspective of utilitarian redundancy. Rev Bras Farmacogn 24:506–515. https://doi.org/10.1016/j.bjp.2014.09.003

Anderson JGT (2017) Why ecology needs natural history. AmSci 105:290

Avicenna (1998) Canon of medicine. Book II Materia Medica, by Hakim Ibn-Sina. English translation of the critical Arabic text. Department of Islamic Studies. Hamdard University, New Dehli

Avicenna (2014) The canon of medicine (al-Qānūn fī'l-tibb). The law of Natural healing. Great Books of the Islamic World Inc, Chicago

Balick MJ, Cox PA (1996) Plants, people, and culture: the science of ethnobotany. Scientific American Library, New York, p 5

Barnes J, Anderson LA, Phillipson JD (2002) Herbal medicines. A guide for healthcare professionals. Pharmaceutical Press, Chicago

Benítez G, Molero-Mesa J, González-Tejero MR (2016) A model to analyse the ecology and diversity of ethnobotanical resources: case study for Granada Province, Spain. Biodivers Conserv 25:771–789. https://doi.org/10.1007/s10531-016-1092-z

Bennett BC, Husby CE (2008) Patterns of medicinal plant use: an examination of the Ecuadorian Shuar medicinal flora using contingency table and binomial analysis. J Ethnopharmacol 116:422–430. https://doi.org/10.1016/j.jep.2007.12.006

Bennett BC, Prance GT (2000) Introduced plants in the indigenous pharmacopoeia of northern South America. Econ Bot 54:90–102. https://doi.org/10.1007/BF02866603

Bent S, Ko R (2004) Commonly used herbal medicines in the United States: a review. Am J Med 116:478–485. https://doi.org/10.1016/j.amjmed.2003.10.036

Breslin PA (2013) An evolutionary perspective on food and human taste. Curr Biol 23:R409–R418. https://doi.org/10.1016/j.cub.2013.04.010

Bruneton J (1999) Pharmacognosy, phytochemistry, medicinal plants, 2nd edn. Lavoisier publishing, Hampshire

Butt MS, Pasha I, Sultan MT, Randhawa MA, Saeed F, Ahmed W (2013) Black pepper and health claims: a comprehensive treatise. Crit Rev Food Sci Nutr 53:875–886. https://doi.org/10.1080/10408398.2011.571799

Bye R (1993) The role of humans in the diversification of plants in Mexico. In: Ramamoorthy TP, Bye R, Lot A, Fa J (eds) Biological diversity of Mexico. Oxford University Press, New York, pp 707–731

Cambria-Kiely JA, Gandhi PJ (2002) Aspirin resistance and genetic polymorphisms. J Thromb Thrombolysis 14:51–58

Casagrande DG (2000) Human taste and cognition in Tzeltal Maya medicinal plant use. JEA 4:57–69. https://doi.org/10.5038/2162-4593.4.1.3

Castañeda-Gómez J, Pereda-Miranda R (2011) Resin glycosides from the herbal drug jalap (*Ipomoea purga*). J Nat Prod 74(5):1148–1153. https://doi.org/10.1021/np200080k

Chaudhari N, Roper SD (2010) The cell biology of taste. J Cell Biol 190:285–296. https://doi.org/10.1083/jcb.20100314420100927c

Clayton TA, Lindon JC, Cloarec O, Antti H, Charuel C, Hanton G, Provost JP, Le Net JL, Baker D, Walley RJ, Everett JR, Nicholson JK (2006) Pharmaco-metabonomic phenotyping and personalized drug treatment. Nature 440:1073–1077. https://doi.org/10.1038/nature04648

Dal Cero M, Saller R, Weckerle CS (2014) The use of the local flora in Switzerland: a comparison of past and recent medicinal plant knowledge. J Ethnopharmacol 151:253–264. https://doi.org/10.1016/j.jep.2013.10.035

De Candolle AP (1804) Essai sur les propriétés médicales des plantes, comparées avec leurs formes extérieures et leur classification naturelle. Chez Méquignon, Paris

Dewick P (2002) Medicinal natural products. A biosynthetic approach. Wiley, Chichester

Diamond J (2002) Evolution, consequences and future of plant and animal domestication. Nature 418:700–707. https://doi.org/10.1038/nature01019

Diamond J (2005) Guns, germs, and steel. The fates of human societies. WW Norton and Company, New York/London

Efron D, Holmstedt B, Kline NL (1970) Ethnopharmacologic search for psychoactive drugs. Government printing office. Public health service publications no. 1645, Washington DC

El-Gharbaoui A, Benítez G, González-Tejero MR, Molero-Mesa J, Merzouki A (2017) Comparison of Lamiaceae medicinal uses in eastern Morocco and eastern Andalusia and in Ibn al-Baytar's compendium of simple medicaments (13th century CE). J Ethnopharmacol 202:208–224. https://doi.org/10.1016/j.jep.2017.03.014

Estrada-Reyes R, Aguirre Hernández E, García-Argáez A, Soto Hernández M, Linares E, Bye R, Heinze G, Martínez-Vázquez M (2004) Comparative chemical composition of *Agasatche mexicana* subsp. *mexicana* and *A. mexicana* subsp. *xolocotziana*. Biochem Syst Ecol 32:685–694. https://doi.org/10.1016/j.bse.2004.01.005

Etkin N (1988) Ethnopharmacology: biobehavioral approaches in the anthropological study of indigenous medicines. Annu Rev Anthropol 17:23–42

Etkin N (2006) Edible Medicines. The University of Arizona Press, Tucson, An ethnopharmacology of food

Evans WC (1998) Trease and Evans. Pharmacognosy, 14th Ed. Saunders, London

Feeny PP (1976) Plant apparency and chemical defense. Recent Adv Phytochem 10:1–40

Gaoue OG, Coe MA, Bond M, Heart G, Seyler BC, McMillen H (2017) Theories and major hypotheses in ethnobotany. Econ Bot 71:269–287. https://doi.org/10.1007/s12231-017-9389-8

Ge GB, Zhang YY, Hao DC, Hu Y, Luan HW, Liu XB, He YQ, Wang ZT, Yang L (2008) Chemotaxonomic study of medicinal *Taxus* species with fingerprint and multivariate analysis. Planta Med 74:773–779. https://doi.org/10.1055/s-2008-1074531

Gertsch J, Leonti M, Raduner S, Racz I, Chen JZ, Xie XQ, Altmann KH, Karsak M, Zimmer A (2008) Beta-caryophyllene is a dietary cannabinoid. PNAS 105:9099–9104. https://doi.org/10.1073/pnas.0803601105

Ghantous A, Sinjab A, Herceg Z, Darwiche N (2013) Parthenolide: from plant shoots to cancer roots. Drug Discov Today 18:894–905. https://doi.org/10.1016/j.drudis.2013.05.005

Goff SA, Klee HJ (2006) Plant volatile compounds: sensory cues for health and nutritional value? Science 311:815–819. https://doi.org/10.1126/science.1112614

Hänsel R, Sticher O (eds) (2007) Pharmakognosie – Phytopharmazie, 8th edn. New York, Springer, Berlin, Heidelberg

Hardy K, Buckley S, Collins MJ, Estalrrich A, Brothwell D, Copeland L, García-Tabernero A, García-Vargas S, Rasilla M, Lalueza-Fox C, Huguet R, Bastir M, Santamaría D, Madella M, Wilson J, Cortés AF, Rosas A (2012) Neanderthal medics? Evidence for food, cooking, and medicinal plants entrapped in dental calculus. Naturwissenschaften 99(8):617–626

Harlan JR (1992) Crops and man, 2nd edn. American Society of Agronomy. Inc. Crop Science Society of America, Madison

Harshberger JW (1896) The purpose of ethnobotany. Bot Gaz 21:146–154

Hart G, Gaoue OG, de la Torre L, Navarrete H, Muriel P, Macía MJ, Balslev H, León-Yánez S, Jørgensen P, Duffy DC (2017) Availability, diversification and versatility explain human selection of introduced plants in Ecuadorian traditional medicine. PLoS One 12:e0184369. https://doi.org/10.1371/journal.pone.0184369

Hawkins BA, Rodriguez MA, Weller GA (2011) Global angiosperm family richness revisited: linking ecology and evolution to climate. J Biogeogr 38:1253–1266. https://doi.org/10.1111/j.1365-2699.2011.02490.x

Heffter A (1914) Die Auffindung von Arzneimitteln. Festrede gehalten am Stiftungstage der Kaiser Wilhelms-Akademie für das Militärärtzliche Bildungswesen, 2 Dezember 1913. Verlag von August Hirschwald, Berlin

Hegnauer R (1962-1996) Chemotaxonomie der Planzen, vols.1-11b. Birkhäuser-Verlag, Basel

Heinrich M (2010) Ethnopharmacology in the 21st century – grand challenges. Front Pharmacol 1:8. https://doi.org/10.3389/fphar.2010.00008

Heinrich M (2014) Ethnopharmacology: quo vadis? Challenges for the future. Rev Bras Farmacogn 24:99–102. https://doi.org/10.1016/j.bjp.2013.11.019

Heinrich M, Barnes J, Gibbons S, Williamson EM (eds) (2004) Fundamentals of pharmacognosy and phytotherapy. Churchill Livingstone, London

Jirovetz L, Buchbauer G, Ngassoum MB, Geissler M (2002) Aroma compound analysis of *Piper nigrum* and *Piper guineense* essential oils from Cameroon using solid-phase microextraction-gas chromatography, solid-phase microextraction-gas chromatography-mass spectrometry and olfactometry. J Chromatogr A 976:265–275. https://doi.org/10.1016/S0021-9673(02)00376-X

Johns T (1990) With bitter herbs they shall eat it: chemical ecology and the origins of human diet and medicine. University of Arizona Press, Tucson

Kesselheim AS, Misono AS, Lee JL, Stedman MR, Brookhart MA, Choudhry NK, Shrank WH (2008) Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. JAMA 300:2514–2526. https://doi.org/10.1001/jama.2008.758

Kessler A, Baldwin T (2002) Plant responses to insect herbivory. The emerging molecular analysis. Annu Rev Plant Biol 53:299–328. https://doi.org/10.1146/annurev.arplant.53.100301.135207

Khoury MJ, Beaty TH, Cohen BH (1993) Fundamentals of genetic epidemiology. Oxford University Press, UK

Lawless HT, Heymann H (2010) Sensory evaluation of food. Principles and practices. Springer, New York

Lazalde-Ramos BP, Martínez-Fierro ML, Galaviz-Hernández C, Garza-Veloz I, Naranjo ME, Sosa-Macías M, Llerena A (2014) CYP2D6 gene polymorphisms and predicted phenotypes in eight indigenous groups from northwestern Mexico. Pharmacogenomics 15:339–348. https://doi.org/10.2217/pgs.13.203

Leclerc L (1877–1883) Traite des Simples d'Ibn al-Baytar 3 Vols. Institut du monde arabe, Paris

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. https://doi.org/10.1016/j.jep.2011.01.017

Leonti M, Verpoorte R (2017) Traditional Mediterranean and European herbal medicines. J Ethnopharmacol 199:161–167. https://doi.org/10.1016/j.jep.2017.01.052

Leonti M, Sticher O, Heinrich M (2002) Medicinal plants of the Popoluca, México: organoleptic properties as indigenous selection criteria. J Ethnopharmacol 81:307–315. https://doi.org/10.1016/S0378-8741(02)00078-8

Leonti M, Cabras S, Castellanos ME, Weckerle CS (2012) Reply to the commentary: regression residual vs Bayesian analysis of medicinal floras. J Ethnopharmacol 139:695–697. https://doi.org/10.1016/j.jep.2011.09.023

Leonti M, Cabras S, Castellanos ME, Challenger A, Gertsch J, Casu L (2013) Bioprospecting: evolutionary implications from a post-olmec pharmacopoeia and the relevance of widespread taxa. J Ethnopharmacol 147:92–107. https://doi.org/10.1016/j.jep.2013.02.012

Linajes A, Rico-Gray V, Carrión G (1994) Traditional production system of the root of Jalapa, *Ipomoea purga* (convolvulaceae), in Central Veracruz, Mexico. Econ Bot 48:84–89. https://doi.org/10.1007/BF02901387

Linares E, Bye RA Jr (1987) A study of four medicinal plant complexes of Mexico and adjacent United States. J Ethnopharmacol 19:153–183. https://doi.org/10.1016/0378-8741(87)90039-0

Locher C, Currie L (2010) Revisiting kinos–an Australian perspective. J Ethnopharmacol 128:259–267. https://doi.org/10.1016/j.jep.2010.01.028

Lopes AA (2019) Transnational links in rhino poaching and the black-market price of rhino horns. Aust J Agr Res Ec 63:95–115. https://doi.org/10.1111/1467-8489.12286

Mann RD (1984) Modern drug use: an enquiry on historical principles. MTP Press Limited, Lancaster

Martins DTO, Rodrigues E, Casu L, Benítez G, Leonti M (2019) The historical development of pharmacopoeias and the inclusion of exotic herbal drugs with a focus on Europe and Brazil. J Ethnopharmacol 240:111891. https://doi.org/10.1016/j.jep.2019.111891

Matthioli PA (1568) 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. Vincenzo Valgrisi, Venezia. Reprinted in Facsimile, 1967–70. Stabilimento Tipografico Julia, Rome

Meghwal M, Goswami TK (2013) *Piper nigrum* and piperine: an update. Phytother Res 27:1121–1130. https://doi.org/10.1002/ptr.4972

Miller JI (1969) The spice trade of the Roman empire 29 B.C.–A.D. 641. Clarendon Press, Oxford

Moerman DE (1979) Symbols and selectivity: a statistical analysis of native American medical ethnobotany. J Ethnopharmacol 1:111–119. https://doi.org/10.1016/0378-8741(79)90002-3

Moerman DE (2012) Commentary: regression residual vs Bayesian analysis of medicinal floras. J Ethnopharmacol 139:693–694. https://doi.org/10.1016/j.jep.2011.09.021

Moerman DE, Jonas WB (2002) Deconstructing the placebo effect and finding the meaning response. Ann Intern Med 136:471–476. https://doi.org/10.7326/0003-4819-136-6-200203190-00011

Moerman DE, Pemberton RW, Kiefer D, Berlin B (1999) A comparative analysis of five medicinal floras. J Ethnobiol 19:49–67

Moujir L, Callies O, Sousa P, Sharopov F, Seca AM (2020) Applications of sesquiterpene lactones: a review of some potential success cases. Appl Sci 10:3001. https://doi.org/10.3390/app10093001

Nicholson W, Snyder C (2007) Microeconomic theory. Basic principles and extensions. Thomson, South-Western

Nicolussi S, Viveros-Paredes JM, Gachet MS, Rau M, Flores-Soto ME, Blunder M, Gertsch J (2014) Guineensine is a novel inhibitor of endocannabinoid uptake showing cannabimimetic behavioral effects in BALB/c mice. Pharmacol Res 80:52–65. https://doi.org/10.1016/j.phrs.2013.12.010

Nievergelt A, Huonker P, Schoop R, Altmann KH, Gertsch J (2010) Identification of serotonin 5-HT1A receptor partial agonists in ginger. Bioorgan Med Chem 18:3345–3351. https://doi.org/10.1016/j.bmc.2010.02.062

Nievergelt A, Marazzi J, Schoop R, Altmann KH, Gertsch J (2011) Ginger phenylpropanoids inhibit IL-1beta and prostanoid secretion and disrupt arachidonate-phospholipid remodeling by targeting phospholipases A2. J Immunol 187:4140–4150. https://doi.org/10.4049/jimmunol.1100880

Obón C, Rivera D, Verde A, Fajardo J, Valdés A, Alcaraz F, Carvalho AM (2012) Árnica: a multivariate analysis of the botany and ethnopharmacology of a medicinal plant complex in the Iberian Peninsula and the Balearic Islands. J Ethnopharmacol 144:44–56. https://doi.org/10.1016/j.jep.2012.08.024

Pagel M, Mace R (2004) The cultural wealth of nations. Nature 428:275–278. https://doi.org/10.1038/428275a

Papageorgopoulou C, Xirotiris N, Iten PX, Baumgartner MR, Schmid M, Ruhli F (2009) Indications of embalming in Roman Greece by physical, chemical and histological analysis. J Archaeol Sci 36:35–42. https://doi.org/10.1016/j.jas.2008.07.003

Pardo-de-Santayana M, Blanco E, Morales R (2005) Plants known as té in Spain: an ethno-pharmaco-botanical review. J Ethnopharmacol 98:1–19. https://doi.org/10.1016/j.jep.2004.11.003

Pardo-de-Santayana M, Benítez G, García C, Molina M (2017) Inventario Español de los Conocimientos Tradicionales IECTB. Sustainability of traditional ecological knowledge: importance, distribution, endemicity and conservation of Spanish medicinal plants. In: Carvalho AM, Pardo de Santayana M, Bussmann R (eds) The 58th Annual Meeting of the Society for Economic Botany (SEB). Book of abstracts. Instituto Politécnico de Bragança, Centro de Investigação de Montanha & Society for Economic Botany, Bragança

Pellicer J, Saslis-Lagoudakis CH, Carrió E, Ernst M, Garnatje T, Grace OM, Gras A, Mumbrú M, Vallès J, Vitales D, Rønsted N (2018) A phylogenetic road map to antimalarial *Artemisia* species. J Ethnopharmacol 225:1–9. https://doi.org/10.1016/j.jep.2018.06.030

Pferschy-Wenzig EM, Bauer R (2015) The relevance of pharmacognosy in pharmacological research on herbal medicinal products. Epilepsy Behav 52:344–362. https://doi.org/10.1016/j.yebeh.2015.05.037

Porter RS, Kaplan JL (2011) The Merck manual of diagnosis and therapy. Merck Sharp & Dohme Corp

Prance GT (2005) The migrations of plants. In: Prance GT, Nesbitt M (eds) The cultural history of plants. Routledge, New York, pp 27–28

Prance GT, Nesbitt M (2005) The cultural history of plants. Routledge, New York

Relling MV, Evans WE (2015) Pharmacogenomics in the clinic. Nature 526:343–350. https://doi.org/10.1038/nature15817

Reynoso-Moreno I, Najar-Guerrero I, Escareño N, Flores-Soto ME, Gertsch J, Viveros-Paredes JM (2017) An endocannabinoid uptake inhibitor from black pepper exerts pronounced anti-inflammatory effects in mice. J Agr Food Chem 65:9435–9442. https://doi.org/10.1021/acs.jafc.7b02979

Rivera D, Verde A, Obón C, Alcaraz F, Moreno C, Egea T, Fajardo J, Palazón JA, Valdés A, Signorini MA, Bruschi P (2017) Is there nothing new under the sun? The influence of herbals and pharmacopoeias on ethnobotanical traditions in Albacete (Spain). J Ethnopharmacol 195:96–117. https://doi.org/10.1016/j.jep.2016.11.040

Rivlin RS (2001) Historical perspective on the use of garlic. J Nutr 131:951S–954S. https://doi.org/10.1093/jn/131.3.951S

Rizkallah MR, Saad R, Aziz RK (2010) The human microbiome project, personalized medicine and the birth of pharmacomicrobiomics. CPPM 8:182–193. https://doi.org/10.2174/187569210792246326

Rocha L, Armando L, Candido T (2016) Chapter 85 - Staranise (Illicium verum Hook) Oils. In: Preedy E (ed) Essential oils in food preservation, flavor and safety. Academic Press, pp 751–746

Santoro FR, Ferreira Júnior WS, Araújo TA, Ladio AH, Albuquerque UP (2015) Does plant species richness guarantee the resilience of local medical systems? A perspective from utilitarian redundancy. PLoS One 10:e0119826. https://doi.org/10.1371/journal.pone.0119826

Shepard G (2004) A sensory ecology of medicinal plant therapy in two Amazonian societies. Am Anthropol 106:252–266

Sherman PW, Billing J (1999) Darwinian gastronomy: why we use spices. Spices taste good because they are good for us. BioScience 49:453–463

Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS (1998) Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med 64:353–356

Siedle B, García-Piñeres AJ, Murillo R, Schulte-Mönting J, Castro V, Rüngeler P, Klaas CA, Da Costa FB, Kisiel W, Merfort I (2004) Quantitative structure-activity relationship of sesquiterpene lactones as inhibitors of the transcription factor NF-kappaB. J Med Chem 47:6042–6054. https://doi.org/10.1021/jm049937r

Soejarto DD, Addo EM, Kinghorn AD (2019) Highly sweet compounds of plant origin: from ethnobotanical observations to wide utilization. J Ethnopharmacol 243:112056. https://doi.org/10.1016/j.jep.2019.112056

Srinivasan K (2007) Black pepper and its pungent principle-piperine: a review of diverse physiological effects. Crit Rev Food Sci Nutr 47:735–748. https://doi.org/10.1080/10408390601062054

Staub PO, 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. https://doi.org/10.1016/j.phymed.2016.06.016

Stepp JR (2004) The role of weeds as sources of pharmaceuticals. J Ethnopharmacol 92:163–166. https://doi.org/10.1016/j.jep.2004.03.002

Stepp JR, Moerman DE (2001) The importance of weeds in ethnopharmacology. J Ethnopharmacol 75:19–23. https://doi.org/10.1016/S0378-8741(00)00385-8

Touwaide A, Appetiti E (2013) Knowledge of eastern materia medica (Indian and Chinese) in pre-modern Mediterranean medical traditions: a study in comparative historical ethnopharmacology. J Ethnopharmacol 148:361–378. https://doi.org/10.1016/j.jep.2013.03.068

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

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. https://doi.org/10.1016/j.jep.2014.09.036

van Gorkom BA, de Vries EG, Karrenbeld A, Kleibeuker JH (1999) Review article: anthranoid laxatives and their potential carcinogenic effects. Aliment Pharm Ther 13:443–452. https://doi.org/10.1046/j.1365-2036.1999.00468.x

Varian HR (2010) Intermediate microeconomics. A modern approach. W.W. Norton & Company, New York

Voeks RA (2004) Disturbance pharmacopoeias: medicine and myth from the humid tropics. Ann Am Assoc Geogr 94:868–888. https://doi.org/10.1111/j.1467-8306.2004.00439.x

Wagner H, Vollmar A, Bechthold A (2007) Pharmazeutische Biologie 2. Wissenschaftliche Verlagsgesellschaft, mbH, Stuttgart

Weckerle CS, Timbul V, Blumenshine P (2010) Medicinal, stimulant and ritual plant use: an ethnobotany of caffeine-containing plants. In: Hsu E, Harris S (eds) Plants, health and healing: on the Interface of Ethnobotany and medical anthropology. Epistemologies of healing 6. Berghahn Books, pp 262–301

Weckerle CS, Cabras S, Castellanos ME, Leonti M (2011) Quantitative methods in ethnobotany and ethnopharmacology: considering the overall flora–hypothesis testing for over- and underused plant families with the Bayesian approach. J Ethnopharmacol 137:837–843. https://doi.org/10.1016/j.jep.2011.07.002

Weckerle CS, Cabras S, Castellanos ME, Leonti M (2012) An imprecise probability approach for the detection of over and underused taxonomic groups with the Campania (Italy) and the Sierra Popoluca (Mexico) medicinal flora. J Ethnopharmacol 142:259–264. https://doi.org/10.1016/j.jep.2012.05.002

Wichtl M (ed) (2002) Teedrogen und Phytopharmaka: Ein Handbuch für die Praxis auf wissenschaftlicher Grundlage. Wissenschaftliche Verlagsgesellschaft, Stuttgart

Willerding U (1986) Zur Geschichte der Unkräuter Mitteleuropas. Göttinger Schriften zur Vor-und Frühgeschichte Band 22. Karl Wachholtz Verlag, Neumünster

Williamson E (2002) Major herbs of Ayurveda. Churchill Livingstone, UK

Wink M (2003) Evolution of secondary metabolites from an ecological and molecular phylogenetic perspective. Phytochemistry 64:3–19. https://doi.org/10.1016/S0031-9422(03)00300-5

Wink M, Waterman PG (1998) Chemotaxonomy in relation to molecular phylogeny of plants. Ann Plant Rev 2:300–341

Zanger UM, Schwab M (2013) Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Therapeut 138:103–141. https://doi.org/10.1016/j.pharmthera.2012.12.007

Zhu F, Qin C, Tao L, Liu X, Shi Z, Ma X, Jia J, Tan Y, Cui C, Lin J, Tan C, Jiang Y, Chen Y (2011) Clustered patterns of species origins of nature-derived drugs and clues for future bioprospecting. PNAS 108:12943–12948. https://doi.org/10.1073/pnas.1107336108

Zohary D, Hopf M (2000) Domestication of plants in the Old World: the origin and spread of cultivated plants in West Asia, Europe and the Nile Valley, 3rd edn. Oxford University Press, UK