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Ethnopharmacology of Medicinal Plants

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ABSTRACT: Ethnopharmacology is an evolutionary process to discover plant-based drugs or new techniques for semi-synthetic drugs. Often, the crucial role in this process plays the lack of scientific data to support therapeutic uses. Ethnopharmacology, through the description of the beneficial effects of plants, has provided an early framework for the therapeutic use of natural compounds. Natural products, either in their native form or after crude extraction of their active ingredients, have long been used by different populations and explored as invaluable sources for drug design. The transition from traditional ethnopharmacology to drug discovery has followed a straightforward path, assisted by the evolution of isolation and characterization methods, the increase in computational power, and the development of specific chemoinformatic methods.

KEYWORDS: ethnopharmacology, plant, drugs, medicines, discover

I. INTRODUCTION

The deriving extensive exploitation of the natural product chemical space has led to the discovery of novel compounds with pharmaceutical properties, although this was not followed by an analogous increase in novel drugs. In this work, we discuss the evolution of ideas and methods, from traditional ethnopharmacology to in silico drug discovery, applied to natural products. We point out that, in the past, the starting point was the plant itself, identified by sustained ethnopharmacological research, with the active compound deriving after extensive analysis and testing. In contrast, in recent years, the active substance has been pinpointed by computational methods (in silico docking and molecular dynamics, network pharmacology), [1,2,3]followed by the identification of the plant(s) containing the active ingredient, identified by existing or putative ethnopharmacological information. We further stress the potential pitfalls of recent in silico methods and discuss the absolute need for in vitro and in vivo validation as an absolute requirement. Finally, we present our contribution to natural products' drug discovery by discussing specific examples, applying the whole continuum of this rapidly evolving field. In detail, we report the isolation of novel antiviral compounds, based on natural products active against influenza and SARS-CoV-2 and novel substances active on a specific GPCR, OXER1. Humans possess discrete pharmacological knowledge of the therapeutic properties of plants from the beginning of their evolutionary history, leaving imprints in prehistoric and later cultural heritage [1,2]. However, this knowledge, accumulated in traditional medicine and ethnopharmacology, is declining. Nevertheless, elements of ethnopharmacological knowledge and practice, exercised either in parallel or supplementing the official treatment of diseases, create significant pressure on the scientific community to provide data related to the safety and effectiveness of the natural extracts. This element remains partially unfulfilled until now.

The use of plant extracts, containing hundreds of chemicals as pharmaceutical agents, is no longer a black box or the primary obstacle to understanding their mechanisms of action and/or the contained "active compound(s)". [4,5,6]This is powered by the significant increase in the detection and precision limits of analytical methods, the significant multiplication in computational power, and the construction of large public libraries of chemical (and natural) compounds (Figure 1, upper part). Indeed, many circulating drugs derive from natural products, and many emblematic drugs, such as taxol [3,4,5], vinblastine [6,7], quinine [8,9], and artemisinin [10], are rooted in traditional medicine and ethnopharmacology [11]; nevertheless, at a later stage, these drugs have been synthesized by modern chemistry and re-evaluated with modern analytical and pharmacological methods. Taxol (known as paclitaxel) is a nitrogen-containing diterpenoid isolated from the bark of Taxus brevifolia Nutt., which acts as a tubulin stabilizer and leads to cell cycle arrest, acting as an anticancer agent. Vinblastine and vincristine are closely related indole dihydroindole dimers (bisindole alkaloids), isolated from Catharanthus roseus (L.) G. Don (formerly known as Vinca rosea L.), the Madagascar periwinkle. Both of these anticancer agents, known as vinca alkaloids in the medical literature, are specific binders of tubulin, leading to tubulin depolymerization and cell cycle arrest in the metaphase stage. Quinine is an alkaloid obtained from Cinchona spp. It was the first antimalarial drug and served as an effective remedy for this potentially lethal infectious disease in colonial times, making possible European settlement in many tropical and subtropical parts of the world. Finally, artemisinin is a sesquiterpene lactone antimalarial compound with an endoperoxide group, discovered as a constituent of Artemisia annua L., with a unique mechanism of action[7,8,9] on the heme complex.

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In recent years, innovative extraction technologies, including semi-bionic extraction; supercritical fluid extraction; microwave-assisted, ultrasonic-assisted, and enzyme-assisted extraction; molecular distillation methods; membrane separation technology; and sophisticated new methodologies and instrumentation such as HPLC-MS, LC-MS, GC-MS, NMR, and crystallography, in parallel with the development of biology and clinical and experimental medicine, have allowed the re-evaluation of the corpus of traditional knowledge, the determination of chemical components of plant extracts, the identification of "active compound(s)", and the development of novel drugs [12,13]. Galantamine [14], an Amaryllidaceae-type alkaloid from Galanthus woronowii Losinsk and other species of this genus, which has been recently approved for the treatment of early-onset Alzheimer's disease, is an example of a recent achievement. A detailed presentation of plant-derived drug discovery in the last 30 years has been extensively reviewed and discussed in a recent series of publications [13,15,16,17].

Plants synthesize an immensely rich diversity of specialized secondary metabolites comprising an enormous number of active or complementary compounds [18,19]. This is due to several reasons, including (1) the high plant biodiversity in many areas of the world; (2) their significant ecological role in plant physiology, which is related to the high variability of problems that the plants have to face (protection from herbivores, pathogens, stress (including UV protection), other plant–plant and plant–animal interactions, etc); (3) the fact that, for the same problem, different evolutionary solutions have appeared in divergent plant lineages, with identical or similar pharmacological action [18,20]; and (4) the fact that different parts of the plant and different extraction methods of the same plant may result in a different collection of active compounds, with sometimes opposing biological effects [21]. Therefore, the validating process of ethnopharmacological knowledge is a laborious, and usually partially successful, enterprise [11], taking into account that only 1/10,000 tested compounds may lead to a successful drug in a time frame of almost ten years [10]

The exponential increase in computational power and data storage capabilities in recent decades has led to faster and, in some cases, economically sustainable solutions for drug discovery. The development of chemical libraries with billions of compounds and specific libraries of existing or putative natural compounds, with hundreds or thousands of molecules, together with the development of novel computational approaches (in silico docking methods, assisted by molecular dynamics, quantitative structure–activity relationships (QSARs), in silico evaluation of absorption–distribution–metabolism (ADMET), etc.), have been advanced as promising methods for the initial screening of the natural compound chemical space for a given disease (Figure 1, lower part) [23,24]. Computational high-throughput virtual screening has advanced as a cost-effective and less time-consuming method for drug discovery [22], as compounds from different chemical libraries have been subjected to high-throughput screening against a valid or presumed pathophysiological disease-related target. The first success of this approach was obtained in 1990, with the discovery of a dopamine D2 agonist [25]. Since then, the computational approach and virtual screening have been combined with network pharmacology (construction of signaling and interacting cellular networks, based on the observed or deducted interaction of compounds with cellular mechanisms). This has helped and accelerated drug discovery and development, positioning network pharmacology [26] as a paradigm shift in a newly emerged methodology, targeting all critical networks involved or perturbed in a disease. This approach complements the genomic, genetic, gene-related, and pathophysiological approach to disease. However, although computational chemistry has revolutionized the process of drug discovery, some limitations still exist, inherent to the accuracy of the computer programs used and the possible overfitting, induced by in silico methods, necessitating proper experimental validation.

Here, we discuss in brief the different steps in drug discovery, from ethnopharmacological observation to modern, high-throughput virtual screening, in an attempt to follow the rapid evolution of ideas in the field. Although a detailed review of all these topics is out of the scope of the current work, we review and discuss the progress and experimental approaches, applied to natural products, as depicted in Figure 1. We point out that in the past, the starting point was the plant itself, highlighted by sustained ethnopharmacological research, with the active compound deriving after extensive analysis and testing. In contrast, in the current state of scientific knowledge, the active substance is pinpointed by computational methods (in silico docking and molecular dynamics, quantitative structure–activity relationship (QSAR), network pharmacology, ADMET), followed by the identification of the plant(s) containing the active ingredient, seeking existing or possible ethnopharmacological information and relationships. We further stress the potential pitfalls of recent in silico methods and discuss the absolute need for in vitro and in vivo verification as a future recommendation. In addition, we present our contribution to this process, through specific examples of novel drug discovery. We further stress the potential pitfalls of recent in silico methods and discuss the absolute need for in vitro and in vivo verification of computer-generated data.[9,10]

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II. DISCUSSION

Ethnopharmacology is the scientific study of traditional medicines, which continue to provide new drugs and lead molecules for the pharmaceutical industry. The recent introduction of artemisinin as an effective antimalarial is a good example of this as the source of this compound, Artemisia annua, was used to treat fevers and malaria-like symptoms in traditional Chinese medicine. A large amount of information still awaits disclosure to the scientific community and this book is an attempt to do this for plants of Asia and the Pacific.

As might be expected for such a vast area with a large number of species, this comparatively small volume cannot be expected to cover anything except a small proportion of the interesting plants which are found in the region. Unfortunately, it does this rather inadequately, claiming to be the first book to do this and ignoring the much more scholarly works of Perry and Metzger (Medicinal Plants of South-east Asia), Burkhill (Economic Products of the Malay Peninsula) and others. It concentrates on three therapeutic categories only, i.e. anti-inflammatories, the CNS and cancer, whilst neglecting the many other diseases for which the plants are used. Even with the categories dealt with, some recent work is not mentioned.

In addition, ethnopharmacology should take into account the philosophical framework for the practice of medicine of any group, since this influences both diagnosis and treatment of diseases. The remit of this book includes China, which has a very well-developed approach in this respect, but such aspects are hardly covered.

Illustrations of plants are mainly line drawings, which are clear, but possibly not very relevant to a serious researcher looking for information leading to experimental work. The structures drawn do not appear to have been thoroughly checked, since some are completely wrong, e.g. hypericin p. 19, ibogaine p. 72, while others are not drawn conventionally and/or have names misspelt, e.g. genistein p. 210. Valerenic acid p. 90 has a pentavalent carbon!

Ethnopharmacology can be basically defined as “the interdisciplinary scientific exploration of the biologically active agents that are traditionally employed”. Therefore, the ethnopharmacological approach is based on a body of work that spans several disciplines such as botany, chemistry, and pharmacology. This includes field observations, descriptions of the utilization and bioactivities of folk remedies, botanical identification of the plant material as well as phytochemical and pharmacological research. Investigations of the indigenous remedies and their possible effects have attracted attention of many researchers for ages. Drug discovery from natural sources in the light of ethnopharmacological studies has an important role in the development of current therapeutic systems. Plants, animals and minerals are among the natural products that have been the basis in the treatment of many diseases for centuries. Recently, much attention has been paid to pharmacognostical, phytochemical and pharmacological studies of traditional medicinal plants. Moreover, biological activity potential of natural medicines has been investigated in many preclinical and clinical studies, revealing diverse biological effects of a wide range of plant derived compounds in various classes of chemical groups. The majority of the natural sources whose active compounds are currently employed actually has an ethnomedical use. Therefore, recently, many of the pharmaceutical companies have renewed their strategies in the field of natural product research in order to bring out potential sources and new molecules for the drug development. For the discovery and development of novel, safe and affordable medicines, the ethnopharmacological knowledge could be beneficial thanks to its approach [6,7,8]that could be supported by experimental base. In the present study, ethnopharmacological aspects of herbal medicine and plant-based drug discovery process will be emphasized and important issues in their use as complementary medicine will be mentioned.

III. RESULTS

Throughout centuries, traditional herbal medicine and the employment of medicinal plants have constituted an important tool for the treatment and prevention of numerous diseases. The present study focuses on the collection of ethnopharmacological data regarding the uses of medicinal plants for the treatment of dermatological ailments in various villages of Mount Pelion, Greece. More specifically, the study area is represented by the city of Volos and villages located in Central West Pelion and has not been investigated up to now. The information on the medicinal uses of the various species was obtained through extensive semi-structured interviews or the completion of specific questionnaires by the informants. Although the Covid-19 pandemic caused difficulties and obstacles in carrying out this research procedure, 60 informants were recruited and interviewed (36 women and 24 men). Their age range was between 31 and 97 years and their educational level was characterized by great diversity (primary, secondary, and higher education). The elaboration of the gathered information included the calculation of some quantitative indices, such as Fidelity Level (FL), and Informant Consensus Factor (FIC). Moreover, [2,3,4]the relative importance of each reported species was identified by calculating the Use Value (UV). The interviews revealed 38 plant taxa belonging to

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27 plant families reported to be used in the study area exclusively against skin diseases. The plant family mostly mentioned by the informants was Hypericaceae, followed by Plantaginaceae and Amaryllidaceae, while among the most popular methods of application are cataplasms, compresses, and topical application of decoction or raw plant material. Some of the most cited species are Hypericum perforatum L., Quercus coccifera L., and Plantago sp., traditionally used to treat skin problems such as eczema, wounds, and insect stings. The present ethnopharmacological study is the first documentation of ethnobotanical knowledge of this area that points out the traditional uses of medicinal plants against skin ailments.

Ever since the development of mankind and advanced civilizations, the healing activities of a great number of medicinal plants were evidenced, reported, and communicated to successive generations, highlighting the importance of the dissemination of ethnopharmacological knowledge (Petrovska, 2012). The uses of plant species in folk medicine demonstrate the strong connection between human communities and nature and constitute a cultural heritage that tends to vanish due to socio-economic and land use changes (Danna et al., 2019). In Greece, medicinal plants' use to treat several illnesses including skin diseases dates back to ancient times, when Hippocrates (fifth century BC) and Dioscorides (first century AD) established the scientific aspect of medicine based on the healing properties of different plant species (Hanlidou et al., 2004). In Greek mythology, Cheiron was a centaur renowned for his skills in prophecy, astrology, botany, pharmacy, and mainly in the science of herbs and medicine. The forested slopes of Pelion are where, according to tradition, Cheiron the centaur practiced the art of healing with herbs (Lietava, 1992). [5,6,7]The traditional knowledge was preserved through centuries in the study area and represents an important pillar not only of traditional cultural and folkloristic heritage, but also of Greek traditional medicine. The Mediterranean basin is one of the richest biodiversity hotspots due to its intricate topographical, geographical, and climatic factors (Kougioumoutzis et al., 2019). Greece hosts 7,043 native plant taxa, 1435 of which are Greek endemics (Dimopoulos et al., 2016). In Greece, the number of ethnobotanical studies on traditional uses of medicinal plants is scarce. The recent surveys concerning the knowledge of medicinal plants of Greece were carried out in the regions of Zagori (Malamas and Marselos, 1992; Vokou et al., 1993), Thessaloniki (Kleftoyanni and Kokkini, 2003; Hanlidou et al., 2004; Karousou et al., 2007), Crete (Skoula et al., 2009), Mt. Pelion (Brussell, 2004), Greek Islands of North Aegean (Axiotis et al., 2018), Central Macedonia (Tsioutsiou et al., 2019), Lemnos island (Papageorgiou et al., 2019), Peloponnesus (Petrakou et al., 2019), and more recently on Milos island (Cyclades) (Perouli and Bareka, 2019). More specifically, near the study area only one ethnobotanical study was conducted in the past, including general information on the traditional uses of plants, but not exclusively for medicinal purposes. Even though very few ethnobotanical studies have been conducted in Greece, none of them was exclusively focused on the use of plant species against a specific category of pathological conditions such as skin diseases, that represent one[7,8,9] of the most common categories of ailments in the history of medicine. Nowadays, skin disorders are a public health problem in many parts of the world, while dermatological disease treatment is a global concern, especially in the case of chronic wounds, where despite scientific progress their comprehensive treatment remains still a challenge (Posnett et al., 2009). Skin diseases are numerous and harmful in many ways, and they affect people of all ages from neonates to the elderly. Some skin pathological conditions such as eczema, wounds, psoriasis, and impetigo are among the top 50 most prevalent diseases globally. Moreover, skin diseases are the fourth leading cause of the non-fatal disease burden, highlighting the need for finding ways to manage them (Seth et al., 2017). Considering the scarcity of published ethnopharmacological information along with the significant floristic diversity of the region of Thessaly and in particular of Mount Pelion, our aim is to survey medicinal plants and their traditional uses for the treatment of different skin diseases, which are undoubtfully a common health difficulty.

IV. CONCLUSION

Finally, this is the first quantitative ethnomedicinal study of therapeutic herbs utilized against skin diseases intended for the discovery of bioactive natural products for their treatment, as well as their inclusion in future global strategies, in order to improve the health of the affected populations worldwide (Hay et al., 2014).[10]

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