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NATURAL PRODUCTS DERIVED FROM PLANTS THEIR DISCOVERY AND MEDICAL USES – A REVIEW

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Abstract:
Medicinal plants have historically proven their value as a source of molecules with therapeutic potential, and nowadays still represent an important pool for the identification of novel drug leads. In the past decades, pharmaceutical industry focused mainly on libraries of synthetic compounds as drug discovery source. They are comparably easy to produce and resupply, and demonstrate good compatibility with established high throughput screening (HTS) platforms. However, at the same time there has been a declining trend in the number of new drugs reaching the market, raising renewed scientific interest in drug discovery from natural sources, despite of its known challenges. In this survey, a brief outline of historical development is provided together with a comprehensive overview of used approaches and recent developments relevant to plant-derived natural product drug discovery. Associated challenges and major strengths of natural product-based drug discovery are critically discussed.

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INTRODUCTION:

This circumstance revitalized the interest in natural product-based drug discovery, despite its high complexity, which in turn necessitates broad interdisciplinary research approaches [1]. In line with this, the Austrian "Drugs from Nature Targeting Inflammation (DNTI)" consortium was formed in 2008 uniting scientists with expertise in multiple disciplines relevant for natural product-based drug discovery. The DNTI program aimed at identifying and characterizing natural products with anti-inflammatory activity by the combined and synergistic use of computational techniques, ethnopharmacological knowledge, phytochemical analysis and isolation, organic synthesis, plant biotechnology, and a broad range of *in vitro*, cell-based, and *in vivo* bioactivity models [2-4].

The first written records on medicinal applications of plants date back to 2600 BC and report the existence of a sophisticated medicinal system in Mesopotamia, comprising about 1000 plant-derived medicines. Egyptian medicine dates back to about 2900 BC, but its most useful preserved record is the "Ebers Papyrus" from about 1550 BC, containing more than 700 drugs, mainly of plant origin [5-8].

The knowledge on the medicinal application of plants in the Western world is mainly based on the Greek and Roman culture. Of particular importance are the compendia written by the Greek physician Dioscorides (1st century AD), and by the Romans Pliny the Elder (1st century AD) and Galen (2nd century AD)[9]. The Arabs preserved a large amount of the Greco-Roman knowledge during the Dark and Middle ages (i.e., 5th to 12th centuries), and complemented it with their own medicinal expertise, and with herbs from Chinese and Indian traditional medicines [9-12].

During all that time, medicinal plants were only applied on an empirical basis, without mechanistic knowledge on their pharmacological activities or active constituents. It was only in the 18th century that Anton von Störck, who investigated poisonous herbs such as aconite and colchicum, and William Withering, who studied foxglove for the treatment of edema, laid the basis for the rational clinical investigation of medicinal herbs [13].

After the discovery of penicillin (1928), an era of drug discovery from microbial sources was initiated in the 1930s, that laid the scientific and financial foundation of the modern pharmaceutical industry after World War II. At that time, the therapeutic use of extracts and partly purified natural products was increasingly replaced by the use of pure compounds [14,15]. Despite the advent of combinatorial chemistry and HTS campaigns during the last decades, the impact of natural products for drug discovery is still very high. Of the 1073 new chemical entities belonging to the group of small molecules that had been approved between 1981 and 2010, only 36% were purely synthetic, while more than the half were derived or inspired from nature [16]. A substantial number of these compounds have been discovered in higher plants [17].

The results obtained by HTS of large synthetic compound libraries, which were introduced in the 1990s [18], did not meet the expectations. Instead of introducing more drugs to the market, the approval rates of new drugs declined. Whereas 45 new drugs were approved by the US Food and Drug Administration (FDA) in 1990, only 21 were approved in 2010 [19]. While the reasons for this declining trend are complex, one important aspect is that synthetic compound libraries usually cover only a small range of the chemical diversity. Moreover, due to similar generation strategies, the HTS-compound libraries of different companies often overlap. Due to high sample numbers in such libraries, compounds to be investigated further are often selected quickly, mainly based on potency values, although a negative correlation of cell-free *in vitro* potency and favorable ADME/T (absorption, distribution, metabolism, excretion/toxicity) is likely [20].

Since natural products are made from living organisms, they possess properties that are evolutionary optimized for serving different biological functions (e.g., binding to specific target proteins or other biomolecules) [21]. Detailed analyses of structural differences between natural products and molecules generated by combinatorial synthesis found that major differences originate from the introduction of properties making combinatorial synthesis more efficient. For example, chiral separation is challenging and expensive. Therefore, creating molecules with a low number of chiral centers is favorable. Besides a much lower number of chiral centers, synthetic compounds tend to have a lower molecular weight, a higher number of freely rotatable bonds, higher chain lengths, a lower number of rings, less oxygen but more nitrogen, sulfur, and halogen atoms, a lower number of Lipinski-type H-bond acceptors and donors, and higher calculated octanol-water partition coefficients (cLogP values). Other differences are the complexity of ring systems and the degree of saturation [22-26]. These structural differences, especially the significantly lower number of chiral centers, the lower size, and the higher flexibility result in weaker and less specific activity of synthetic compounds [27]. On the contrary, natural products often have selective biological actions due to binding affinities for specific proteins relevant for

their biological functions, possess superior chemical diversity and complexity developed during biosynthesis [28], and often have more advantageous ADME/T properties.

The use of the ethnopharmacology-based approach, however, is associated with multiple challenges:

(1)Herbs that have been selected as study candidates based on ethnopharmacological data require not just detailed knowledge about their habitat, abundance, correct botanical authentication, whether they are threatened or endangered, and which permits are necessary in order to collect and investigate them, but might also provoke occasions of legal right-claims from the country of origin or from ethnical groups in which the traditional knowledge was originally generated. In this context, also access and benefit sharing issues determined in the United Nation's Convention on Biological Diversity, and in the Nagoya Protocol need to be respected (see Section 2.2). These restrictions make collection of plants on an ethnopharmacological basis more tedious and time-consuming than a mere random collection, which is regarded more feasible for the common practices of pharmaceutical industry.

(2)Some traditional systems, such as TCM and Ayurveda, involve the application of sophisticated multicomponent mixtures. The complexity of these formulations and possible synergistic effects heavily complicate the identification of active principles. On the other hand, this combinatorial approach might provide new perspectives in the treatment of multifactorial diseases, such as dementia, that might be better addressed by a multitarget-oriented, combinatorial approach.

(3)The definitions of health and disease in traditional medicine often widely deviate from the Western reductionist approach that is mainly based on anatomy, physiology, and cell and molecular biology. For example, the theory of TCM has been strongly influenced by Chinese philosophy, like the theory of *Yin* and *Yang*, emphasizing the balance of functional systems, and the theory of the Five Phases (*Wu Shing*) (fire, water, metal, wood, and earth), that are connected to five functional areas in the body (liver, heart, lung, kidney, and spleen and stomach) [29,30]. Such discrepancies to Western terminology often complicate the correct interpretation of ethnopharmacological data. Moreover, the holistic, personalized approach of these medical systems is difficult to assess by many of the bioassay systems currently used to prove pharmacological activity. However, the emerging omics- and systems biology-based technologies might be better suited to address these issues, due to their more holistic orientation.

Pharmacophore-based virtual screening constitutes another highly successful computational method. A pharmacophore model is a 3D arrangement of physicochemical features (e.g., hydrogen bond donor/acceptor, hydrophobic area, aromatic ring) that represents the key interactions between a ligand molecule and its target protein. As an example, the chemical interaction pattern that defines the interaction of magnolol with the binding site of PPARγ (PDB 3R5N) is presented in 1A [for more details about the significance of this example the reader is referred.

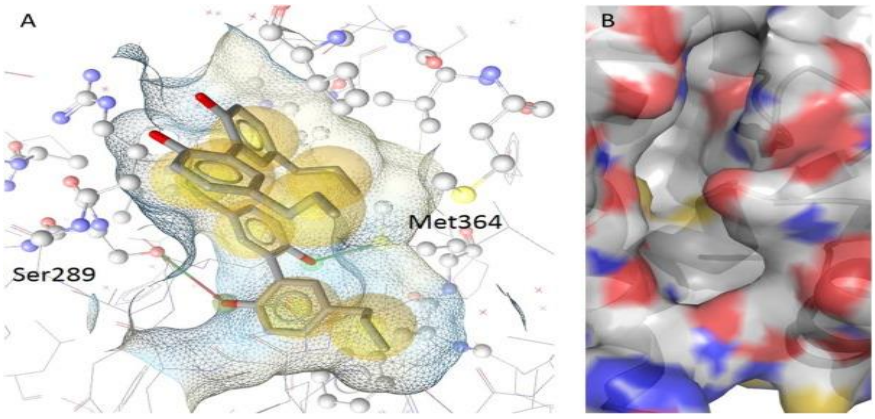
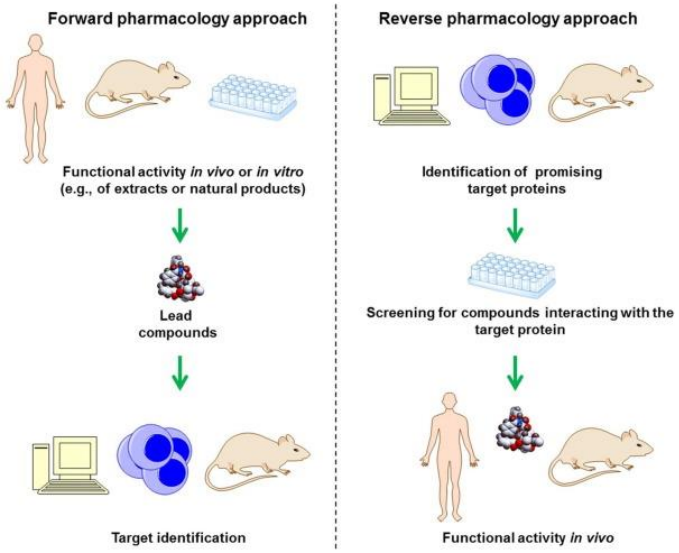


Fig. 1 A.

(A) Two molecules of magnolol concomitantly occupying the binding site of PPARγ (PDB 3R5N) are shown, with the chemical interaction pattern that defines the activity of the molecules depicted. Yellow spheres represent hydrophobic interactions, red and green arrows mark hydrogen bond acceptor and donor atoms. This interaction pattern may be converted into a structure-based pharmacophore model and used for virtual screening. (B) The empty binding pocket of PPARγ is shown, which can be used in docking simulations to place new molecules into the binding site and to calculate the binding free energy of the ligand.



Historically, the investigation of plant-derived substances was based on a forward pharmacology approach using *in vivo* animal tests, organ or tissue models, or bacterial preparations, followed by *in vitro* investigation of mechanistic underpinnings. In the more recent past, the approach of investigating plant-derived substances changed and is now usually starting with screening of large collections of plant-derived compounds ("libraries") against pre-characterized disease-relevant protein targets, with the aim to identify "hits", compounds with the desired activity that are then further studied in relevant *in vivo* models with the aim to validate them (a reverse pharmacology approach). Both the forward and the reverse pharmacology approaches use an overlapping selection of bioassays but differ in the stage when the assays are applied; [31-35]. Fig 2.

CONCLUSION:

Medicinal plants have historically been a rich source for successful drugs, and still represent an important pool for the identification of new pharmacological leads today. Renewed scientific interest in plant-derived natural product-based drug discovery is evident from the analysis of PubMed publications trends (Fig. 1). Plants are producing numerous chemically highly diverse secondary metabolites which are optimized for exerting biological functions and are still far from being exhaustively investigated. Resulting from the revived scientific interest in natural product-based drug discovery, new approaches for the identification, characterization, and resupply of natural products are being developed, that may address some of the challenges related with the development of plant-based therapeutics. One major asset of medicinal plant-based drug discovery is the existence of ethnopharmacological information providing hints for compounds therapeutically effective in humans. In order to harvest its full potential, of particular importance is the adoption of a broad interdisciplinary approach involving ethnopharmacological knowledge, botany, phytochemistry, and more relevant pharmacological testing strategies (e.g., early *in vivo* efficacy studies and compound identification strategies including metabolism and synergistic action of the plant constituents). Resupply from the original plant species is very often unfeasible to meet market demands upon commercialization of a natural product, and alternative resupply approaches are being developed that rely on biotechnological production or chemical synthesis.

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