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REVIEW

From Traditional Herbal Medicine to Rational Drug Discovery: Strategies, Challenges, and Future Perspectives

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Abstract
Plants are sources of many therapeutics used for the treatments of many complex diseases since ancient times. Plants can synthesize a plethora of natural compounds with diverse chemical structures. Despite many advances in the world, a large population of the world is still relying on the herbal system. Therefore, a holistic effort must be made for the conservation of herbal hot spots as well as also for the scientific documentation of active herbal ingredients present in a plant. A paradigm shift has taken from the herbal medicine system to modern approaches of drug design and therapy with the advancement of scientific research in the field of structural biology, genomics, proteomics, therapeutic biology, biochemistry, systems biology, and computer science. Rational approaches of drug development have made it possible to model the target, design various analogs, and dock them with the target, screen, analyze, and predict the pharmacokinetic and pharmacodynamic properties. Rational approaches have significantly reduced the cost, labor, and risk of failure in the process of drug discovery.

Keywords Computational approaches · Secondary metabolites · Pharmacognosy · Molecular modeling · Pharmacogenomics · Combination therapy

Introduction

Medicinal plants are used as sources of many therapeutics for the treatments of many complex diseases for a long time. The archeological evidence suggests the use of medicinal, poisonous, and psychoactive plants in the prehistoric past. DNA analyses of dental calculus are used to identify pathogenic bacteria present among past individuals. Thermal desorption, gas chromatography, and mass spectroscopy techniques are used for the analyses of the same dental calculus to identify the herbal compounds that were in self-use against these pathogens at that time (Hardy 2021). Paleolithic humans were familiar with the knowledge and use of medicinal plants. The knowledge and use of herbal metabolites for therapeutic use are being improved day by day due to advancements in scientific technologies.

Pharmacognosy deals with the knowledge and study of medicinal plants or other natural organisms which are the source of many metabolites that are used as a therapeutic agent for the cure of many diseases. There were many issues and challenges in exploring the world of herbal medicine, and these have been resolved by the use of molecular biology, genomics, proteomics, and genetic engineering, tissue culture, biochemistry, and biophysical techniques. In the twenty-first century, pharmacognosy has become a multidisciplinary, high-tech science of natural medicines in terms of assaying their purity, potency, and consistency, especially in its methodology of using faster and more effective analytical methods, high-throughput screening, target-based drug discovery, and *in silico* methods for virtual ligand screening (Pereda-Miranda and de Moraes Santos 2021). Molecular pharmacognosy (Alamgir 2018), genomic pharmacognosy (Yang et al. 2019b), and metabolomic pharmacognosy (Allard et al. 2018) have been contemplated as the most promising approaches of pharmacognosy research to meet emergent trends in molecular biology, biotechnology, and analytical chemistry of natural medicines. For example, nowadays, DNA barcoding represents an essential addition to the wide range

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of robust methodologies used to identify and authenticate natural drugs and their pharmaceutical products (Gesto-Borroto et al. 2021).

Many challenges and limitations of pharmacognosy have been resolved by using molecular biology techniques and approaches. Molecular pharmacognosy has provided a way to approach many challenges such as herbal and animal drug population analysis by molecular marker assay, identification of medicinal raw materials, conservation and propagation of wild resources based on knowledge of genetic diversity, mechanism of active compound biosynthesis and bioregulation, and use of genetic engineering to obtain new resources (Huang et al. 2009; Huang et al. 2010). Metabolome profiling provides the biological understanding of metabolic functional states in response to environmental factors. A vast amount of metabolome data on herbal plant metabolites can be produced using high-throughput analytical techniques such as mass spectroscopy and NMR-based analytical techniques. Databases and informatics analysis tools such as data processing, statistical analysis, and data mining can provide useful metabolomics information, *e.g.*, the chemical structures, mass spectrum patterns, metabolite profiles, functions, dynamic metabolite changes, and biochemical transformations (Kusonmano et al. 2016). Due to the high consumption of herbal products and their derivatives, an increase of adulterant materials in these herbal products has been noticed. Adulteration reduces the concentration of bioactive metabolites, and an adulterant may have a toxic compound. To avoid these instances, DNA mini-barcoding, metabarcoding, and bar-HRM technologies can be used to properly authenticate and identify medicinal plants (Gesto-Borroto et al. 2021). A potential DNA barcode (ITS2) is used to confirm the identities of herbal materials and ensure their safe application (Pang et al. 2013). Countries with high consumption of herbal drugs and products must apply DNA barcoding to provide safe and effective treatment.

Search Strategy

This review represents the significance of structurally diverse natural metabolites synthesized in plants by various synthetic pathways. These natural compounds have medicinal value known traditionally as well as also serve as lead molecules for the design and development of potential drugs against various diseases. A vast set of research and review articles are available that cover a broad dimension of pharmacognosy, pharmacology, tissue culture and metabolite production, plant genomics, and profiling, rational drug designing, pharmacokinetics, pharmacodynamics, pharmacogenomics, etc. Here, we searched the literature using various platforms such as PubMed, Google Scholar, Springer, Elsevier, and databases to point out the shift from the herbal medicine system to rational approaches, challenges, opportunities, and future perspectives in the herbal medicine system. We also discussed the need for strategies for conservation and propagation of herbal plants, issues, and challenges in decoding transcriptional profiling and synthetic pathway of herbal metabolites, and molecular basis of herb-herb or herb-drug interaction to avoid toxic instances (Fig. 1).

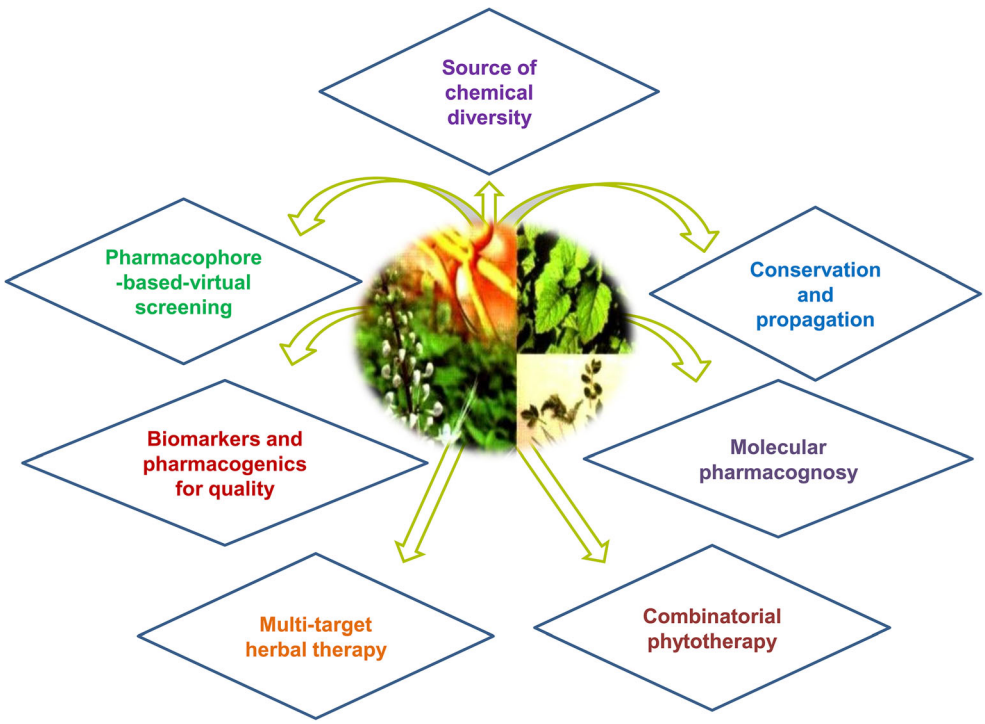


Fig. 1 Important challenges and opportunities related to the field of traditional herbal medicine for drug design

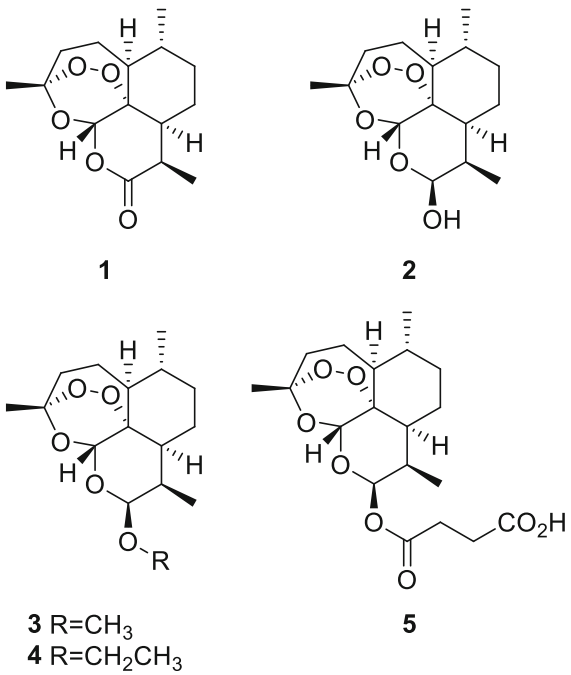
Discussion

Significance of Herbal Medicine System

Herbs are an important source of different bioactive metabolites, which possess the capability to modulate the natural targets in host and pathogen and also generate the therapeutic response. The different parts of the plants produce thousands of natural compounds with diverse chemical structures, which provide the pharmacophoric skeleton for designing potential drug candidates (Schmidt et al. 2008; Moreira et al. 2014; Gao et al. 2018; Behl et al. 2021). In Europe, 90% of medicinal plants are harvested from wild resources. Despite having so many advances in the modern medicine system, 80% of the population in developing countries relies on traditional herbs for their primary health care (Chen et al. 2016). The demand for herbal medicine and herbal products is increasing rapidly throughout the entire world. About 35% of the prescribed drugs are derived from natural sources or the design of their chemical structure was inspired by the herbal compounds (Dias et al. 2012). China and India are the well-known medicinal hot spots with 11,146 and 7500 species, respectively, followed by Brazil, Colombia, South Africa, and the USA (Chen et al. 2016). Certain plant families have a higher number of threatened medicinal plant species than others, which need to be conserved and propagated using modern approaches of biotechnology (Chokheli et al. 2020).

In traditional systems, herbal formulae are prepared in standardized ways using different parts of the medicinal plants. Herbal preparation methods include infusions, decoctions, tinctures, macerations, hot baths, inhalation of powdered herbs or smokes, and steam inhalation of plant parts in hot water (Zhang et al. 2018). Hot spots related to medicinal plants are not uniformly distributed across the globe. The therapeutic knowledge related to an herb and its way of application against disease is traditionally validated by the use of many people for a long time, which may be discovered by the accidental use of an herb from a part of the plant or may be derived by trial and hit approaches (Petrovska 2012; Sofowora et al. 2013; Leonti et al. 2020).

Artemisinin combination therapies (ACTs) have been used as the first-line treatments against *Plasmodium falciparum* malaria for decades. As malaria has been present throughout human history, it is no surprise that over 1200 plant species have been utilized in traditional medicine to treat malaria, including the leaves of *Artemisia annua* L., Asteraceae, or sweet wormwood. The use of sweet wormwood for the treatment of malaria comes from traditional Chinese medicine as first described in "A Handbook of Formulas for Emergencies" by Ge Hong (283–363 CE). The active compound artemisinin (**1**) has been a key molecule in the treatment of malaria and the first antimalarial of the endoperoxide class, owing to the presence of a peroxide containing 1,2,4-trioxane ring presumed to act as the pharmacophore group of the molecule. However, issues with solubility and extensive first-pass metabolism make artemisinin somewhat unsuitable as a therapeutic medicine. The first generation of semi-synthetic ARTs, dihydroartemisinin (DHA, **2**), artemether (**3**), artemether (**4**), and artesunate (**5**), were designed with clinical use (Woodley et al. 2021). However, poor solubility of the ART-ethers necessitates administration by intramuscular injection or oral routes which are not ideal for the rapid systemic exposure required for clearing parasite burden in severe malaria. Artesunate (**5**) is the succinic ester of DHA displaying greatly improved aqueous solubility which enables administration by intravenous (IV) infusion allowing for effective treatment of severe malaria.



Semi-synthetic artemisinin (ARTs) causes promiscuous alkylation of parasite proteins (Fig. 2). Due to resistance and the synthetic limitations of ART, fully synthetic endoperoxide-based antimalarials have been developed using various endoperoxide warheads including 1,2-dioxanes, 1,2,4-trioxanes, 1,2,4-trioxolanes, and 1,2,4,5-tetraoxanes, as a second generation of antimalarials (Woodley et al. 2021).

There are several case studies in literature where most of the drug development strategies are based on the herbal metabolite or inspired by the core of an active compound possessing pharmacological activity. Traditional Chinese medicine represents a vast set of diverse compounds for drug discovery, and most of them are still untapped. TCM-derived medicines have already contributed to modern medicine. In recent years, the application of Chinese medicine–derived

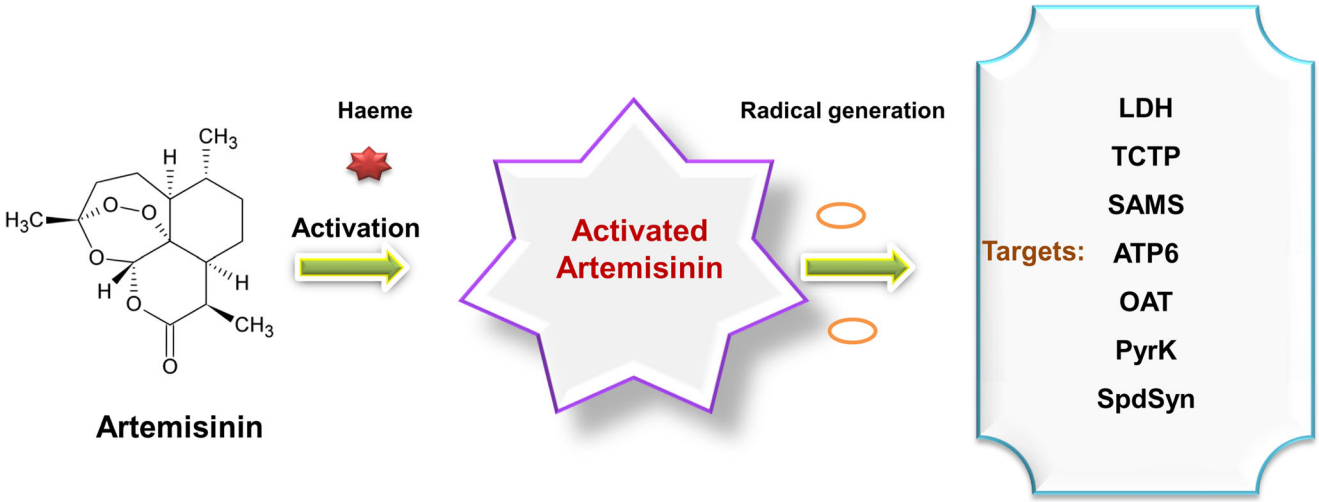
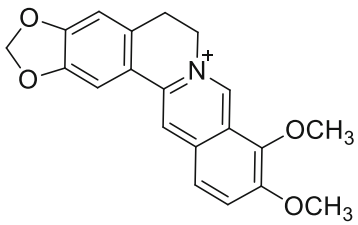


Fig. 2 The proposed mechanism of action of artemisinin for its antimalaria effects. Artemisinin is activated by haem, a precursor to hemoglobin, which is necessary to bind oxygen in the bloodstream, which is released during hemoglobin digestion by the malaria parasite. This generates reactive radicals which alkylate a range of parasite proteins, eventually killing the parasite: Ca^{2+}-ATPase (ATP6), the translationally controlled tumour protein (TCTP), ornithine aminotransferase (OAT), pyruvate kinase (PyrK), L-lactate dehydrogenase (LDH), spermidine synthase (SpdSyn), and S-adenosylmethionine synthetase (SAMS). Adapted from Wang et al. 2018

herbs and formulations for evidence-based therapy has increased significantly. The molecular basis of action and clinical impact of several derived medicines such as artemisinin (**1**), arsenic trioxide (As_2O_3), berberine (**6**) (Khashayar et al. 2021), and *Salvia miltiorrhiza* Bunge, Lamiaceae, has been studied well, which can provide potential avenues for further research (Wang et al. 2018).



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Molecular and Genetic Study Levels

There is some ancient literature that provides documentation on the therapeutic use of many herbs, but still, there is a need to explore, document, and catalog the traditional knowledge of herbal medicine. The modern genomics, proteomics, bioinformatics, and metabolomics approaches can explore the genes encoding for metabolites and bioactivities, screening of a particular plant metabolite and evaluation of its therapeutic efficacy, the interaction of a plant bioactive with a drug target in the human body and its impact on related biological pathways, and disease-modifying potential and related toxic effects (Rinschen et al. 2019; Salem et al. 2020). Researchers are trying to validate the traditional knowledge of herbal medicine and its known impact on disease using these modern approaches. Many genome sequencing projects and transcriptional profiling experiments related to herbal plants are in the way, which can provide genetic- and molecular-level information for profiling of metabolites and exploring the possibilities about the synthetic pathway related to a plant product (Pathak et al. 2020).

Molecular Pharmacognosy

Molecular pharmacognosy studies the classification, identification, cultivation, and protection of crude drugs, as well as the production of effective elements at the molecular level. (a) Discerning the false from the genuine to settle the problem of variety confusion: due to the rise in the scope of use and dosage of medicines, there are increasing numbers of plant and animal homonyms and materials with similar appearances; these can be taken as the same drugs in different regions, thus leading to variety confusion. As such, it is necessary to discern the false from the genuine in terms of their origins and distribution areas. Only in this way can quality be guaranteed. (b) Quality assessment: a systematic study should be conducted on crude drugs with multiple origins and genuine quality, including the place of origin, harvesting, processing, storage, and the influence of transportation upon active ingredients, to confirm high-quality varieties and the factors that may have effects on them. More than that, excellent varieties should be researched and cultured to achieve fast growth, high-quality, and high yield to meet the increasing demand for medication.

In recent years, DNA barcoding technologies have been applied to a variety of herbal and animal drugs, such as *Panax ginseng* C.A.Mey, Araliaceae, *Bupleurum chinense*

DC., Apiaceae, and *Dendrobium catenatum* Lindl., Orchidaceae, *inter alia*. The accurate and fast scientific identification of the herbal plant is necessary to avoid adulteration and toxic instances (Gesto-Borroto et al. 2021). Taxonomy-based identification of plant species is orthodox, time-consuming, and could be inaccurate whereas the modern DNA barcode approach is rapid and precise. DNA barcodes such as matK, rbcL, trnH-psbA, ITS, trnL-F, 5S-rRNA, and 18S-rRNA are being used for the identification of herbal plants (Mishra et al. 2016).

DNA barcoding along with metabolomics, transcriptomics, and proteomics can be used for the effective authentication of herbal products. Many plant species of the Lamiaceae family are the primary source of bioactive materials and metabolites. Products of these species are often adulterated due to the scarcity of raw plants. For identification of different species of Lamiaceae, proposed DNA barcode loci (matK, trnH-psbA, and trnL) were investigated for their PCR amplification, and it was observed that matK locus accurately distinguishes all the chosen species followed by trnH-psbA and trnL (Thakur et al. 2021). DNA barcode–based authentication for medicinal species of *Mentha*, *Ocimum*, and *Plectranthus* may reduce the related unfair trades and adulterations.

Recently, a precise species detection of a traditional multi-ingredient herbal Chinese medicine was performed by shotgun metagenomic sequencing as a complementary method for microscopy, thin-layer chromatography, and high-performance liquid chromatography to address the quality, efficacy, and safety issues associated with medicinal plants (Xin et al. 2018). Longdan Xiegan Wan (LDXGW), a traditional Chinese medicine derived from an herbal prescription from the Qing Dynasty (seventeenth century), is composed of ten herbal crude materials, including *Gentiana crassa* subsp. *Rigescens* (Franch. ex Hemsl.) Halda, Gentianaceae (roots); *Bupleurum chinense* DC., Apiacea (roots); *Akebia trifoliata* (Thunb.) Koidz., Lardizabalaceae (stem); *Alisma plantago-aquatica* subsp. *orientale* (Sam.) Sam., Alismataceae (rhizoma and roots); *Plantago asiatica* L., Plantaginaceae (stir-fried seeds with salt solution); *Angelica sinensis* (Oliv.) Diels, Apiaceae (stir-fried roots with yellow rice wine); *Scutellaria baicalensis* Georgi, Lamiaceae (roots); *Gardenia jasminoides* J.Ellis, Rubiaceae (stir-fried fruits); *Rehmannia glutinosa* (Gaertn.) DC., Plantaginaceae (roots); and *Glycyrrhiza uralensis* Fisch., Fabaceae (roots stir-fried with honey). Some of the herbal materials are derived from multiple species and have some adulterants; for example, the incorrect substitution of plant stems of *Clematis armandii* Franch. Ranunculacea, *Aristolochia manshuriensis* Kom., and *A. fangchi* Y.C.Wu ex L.D.Chow &; S.M. Hwang, Aristolochiaceae, for *A. trifoliata* illustrates potential toxicity. Bioinformatics analysis indicated that the ITS2 region, as a DNA barcode, showed the highest identification efficiency. It could successfully detect all prescribed species, including the adulterants, in lab-made sample references of plant mixture. The metagenomic sequencing detected the substitution of *A. trifoliata* in the commercial samples, while the thin-layer chromatography analyses of the herbal mixtures could not distinguish them (Fig. 3).

Combination Therapy

Herbal extracts from a plant part do not include a single metabolite or class of compounds. However, it is a complex mixture of different bioactive agents. Therefore, it becomes necessary to explore the main constituents in the mixture which generate a therapeutic response. The therapeutic knowledge about each bioactive metabolite in an herbal mixture will improve our understanding regarding therapeutic efficacy and will also reduce the risk of side effect generated due to the presence of other bioactive specialized compounds (Sasidharan et al. 2011). It is believed that herbal medicines are safe and have fewer side effects as compared to synthetic drugs. Nonetheless, it may also be lethal if taken without prescription and in an undesired combination. It is expected that once the genomic and proteomic data of most of the herbal plants will be explored and made available in biological databases, then it will be easy to find a synthetic pathway related to a bioactive using comparative genomics (Ekor 2014, Karimi et al. 2015).

People have had a strong belief in the traditional herbal system for a long time. Clinical trials related to herbal medicine should be conducted to assess safety and efficacy. The World Health Organization also supports the clinical trials of herbal medicine and issued the guidelines regarding these examinations. Many examples suggest that an herb in combination with another herb may generate a synergistic effect against the disease, and support the concept of combination therapy (Ventola 2010). Herb may also have a toxic effect when taken in combination with another herb or drug due to herb-herb or herb-drug interaction. Herbal medicines also have different efficacy to diverse persons or populations. Therefore, the principles of pharmacogenomics should be applied uniformly for both herbal medicines and their phytopharmaceutical products. Herbal medicines contain many complex and diverse compounds, and their composition depends on the species, plant part used, time of harvesting, and adulteration with microbes and other contaminants. But high-throughput screening and modern biotechnology tools have made it possible to assess and recommend herbal medicine after clinical analysis.

China and India have a long history in the therapeutic application of botanical drugs in traditional medicine. Traditional Chinese medicine (TCM) and Ayurveda are considered two of the most ancient systems of medicine, with a history of more than two millennia, and both systems have many common medicinal materials. Medicinal

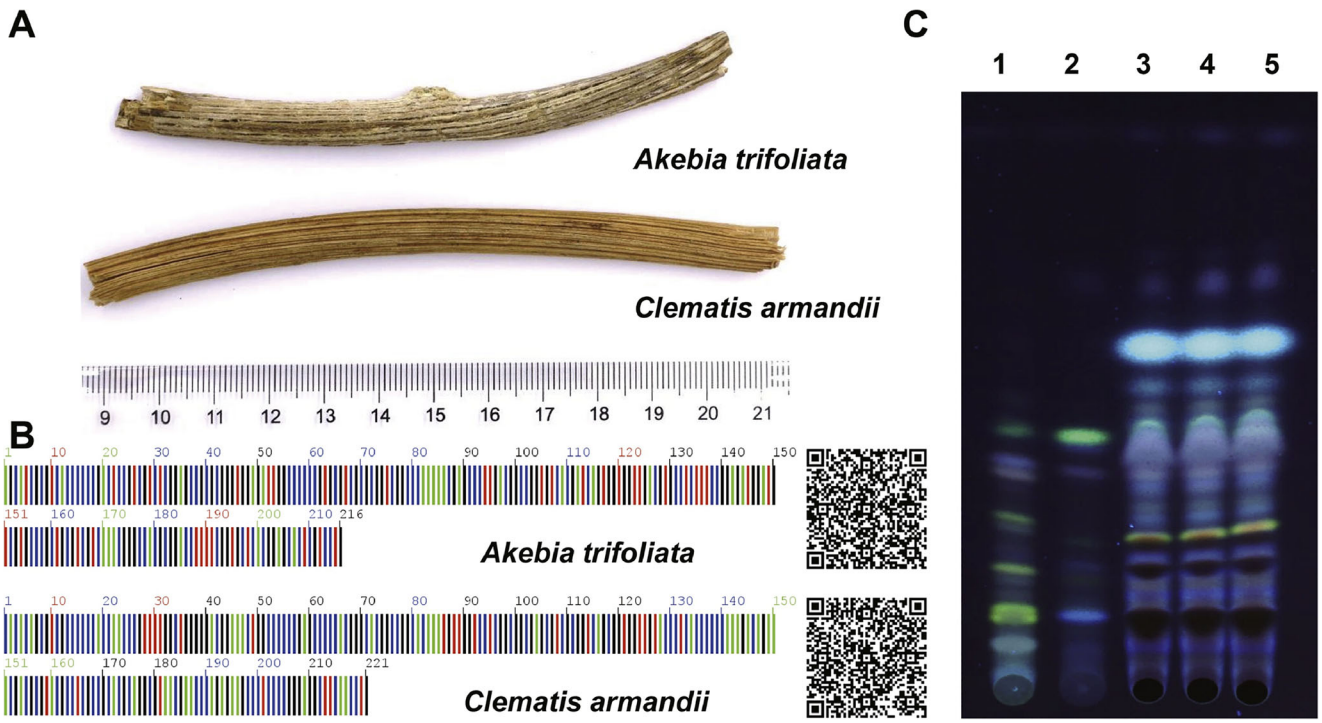

Fig. 3 Morphological characteristics, DNA barcodes, and the TLC identification of *Akebia trifoliata* and *Clematis armandii*. **A** Morphological characteristics of plant stems. **B** DNA barcodes (ITS2) of *Akebia trifoliata* and *Clematis armand*ii. **C** TLC chromatogram: line 1, *Akebia trifoliata*; line 2, *Clematis armandii*; line 3, lab-made Longdan Xiegan Wan (LDXGW) without *Akebia trifoliata* and *Clematis armandii*; line 4, lab-made LDXGW with *Akebia trifoliata*; line 5, lab-made LDXGW with *Clematis armandii*. Reproduced from Xin et al. 2018

plants are the principal medicinal materials used in both these systems. In India, people have traditional knowledge about herbal plants and their applications for the cure of many skin diseases. Ayurvedic and Unani medicine system also recommends many such herbal therapies for the cure of various diseases. For example, 119 herbal plants are available only for the treatment of 39 skin diseases in India (Anand et al. 2021). Ayurveda and TCM provide the drug processing strategies used for many herbal plants, and further exploratory study on herbal extracts and their processing is required for extensive utilization of traditional knowledge (Jaiswal et al. 2016).

There is also a need to search for similar plant species which can be used as alternative sources of herbal extract for endangered or high-cost species. In the traditional medicine system, there are several examples of herbal formula preparation which involves extract from many herbal plants. One herb compound/drug in presence of another herb compound/drug may synergistically improve the therapeutic response. For example, Xiaozhang Tie is an herbal compound-based formula used for the treatment of cirrhosis-associated ascites. Several proteomic, biochemical, histopathological, and immunohistochemical techniques were used to identify the therapeutic targets associated with this herbal formula (Zhang et al. 2019). Xiaozhang Tie elevates the arginine levels and reduces the serum nitric oxide levels by interacting with L-arginine and nitric oxide pathways.

Conservation and Propagation Strategies

Studies have shown that plant species are disappearing at a very higher extinction rate than expected. If this rate continues, then we will lose many important medicinal herbs in the future (Chen et al. 2016). As per the International Union for Conservation of Nature and the World Wildlife data, 50,000 and 80,000 flowering plant species are used for medicinal purposes. About 15,000 plants are threatened with extinction due to their natural habitat destruction by the human population, overconsumption of plant species, and unfavorable climatic changes (Chen et al. 2016). In China, India, Kenya, and Nepal, habitat destruction is one of the main reasons behind the extinction of medicinal plants.

Many guidelines and recommendations have been suggested for the conservation, propagation, inventorying, and status monitoring of medicinal plants. Sustainable use of wild resources can help reduce the extinction rate of medicinal herbs around the globe. In some countries like Brazil, China, India, and South Africa, the high demand for the increasing population is one of the causes behind the loss of flora and fauna. Plant tissue culture, micropropagation, and synthetic seed development approaches are very useful in improving the yield, quality, and potency of medicinal products (Chen et al. 2016; Chokheli et al. 2020). Tissue culture and fermentation of medicinal plants can produce desirable bioactive agents on a large scale. Tissue culture can also be utilized to

propagate rare medicinal plants at a higher rate, as well as to produce many secondary metabolites. When normal seeds are unable to germinate, synthetic seed technology can be useful to cultivate the herbal plant *in vitro* or *ex vitro*. Genetic manipulation in the desired herbal plant may be carried out to reduce the breeding time for large-scale production (Hussain et al. 2012; Chandran et al. 2020).

The exploratory studies on medicinal plants and identification of new bioactive agents are required to characterize and validate potential lead compounds for drug discovery. Plant cell cultures, heterologous biosynthesis, and synthetic biotechnology approaches are in practice for large-scale and cost-efficient production of secondary metabolites (Kayser 2018). A better understanding of the genetic regulation of pathways and protein expression is required for the functional expression of biosynthetic cascades from plants. For *de novo* biosynthesis of a plant metabolite, basic knowledge of pathway reconstruction and the multitude of genes involved in synthesis are required.

There are many successful studies related to the *in vitro* culture of medicinal plants using micropropagation, and efficient protocols for micropropagation of various medicinal plants are available. *In vitro*, culture techniques are important for enhanced production of secondary metabolites and conservation of endangered, rare, and threatened medicinal plant species. Efficient protocols have been developed for the propagation of various medicinal plants such as *Aloe vera* (L.) Burm.f., Xanthorrhoeaceae; *Artemisia annua* L., Asteraceae; *Catharanthus roseus* (L.) G.Don, Apocynaceae; *Withania somnifera* (L.) Dunal, Solanaceae; and *Rauvolfia serpentina* Benth. ex Kurz, Apocynaceae (Singh and Singh 2021). Secondary metabolites from medicinal plants are produced *in vitro* by callus induction and growth, shoot proliferation, cell culture, and the inducing hairy roots using transgenic techniques (*Agrobacterium rhizogenes*), for example, shikonin from cell cultures of *Lithospermum erythrorhizon* Siebold & Zucc., Boraginaceae; berberine from *Coptis japonica* (Thunb.) Makino, Ranunculaceae; and sanguinarine from *Papaver somniferum* L., Papaveraceae.

Tissue culture techniques have been used for the conservation of medicinal plants such as *Saussurea costus* (Falc.) Lipsch., Asteraceae; *Ginkgo biloba* L., Ginkgoaceae; *Gymnema sylvestre* (Retz.) R.Br. ex Sm., Apocynaceae; *Tinospora sinensis* (Lour.) Merr., Menispermaceae; and *Oroxylum indicum* (L.) Kurz, Bignoniaceae, among others (Singh and Singh 2021). Normally, a plant produces secondary metabolites under various climatic and unfavorable stress conditions such as lack of nutrients, predation, and pathogenic interaction. Tissue culture is one of the important, eco-friendly, and significant approaches to conserve medicinal plants and their germplasm. It is a method of plant secondary metabolite production (Patil and Shahnawaz 2022).

Pharmacogenomics

Many herbs are used as spices and condiments in our regular diet, and they require no medical supervision as they are being used for a long time. Herbal medicines should also meet some regulatory specifications before approval and marketing authorization. The practices related to unlicensed herbal remedies should be banned to avoid the case of toxicity and serious health issues (Corns 2003; Prasad and Aggarwal 2011).

Adverse effects due to herb-herb interaction and herb-drug interaction are an important safety issue in the case of the conventional use of herbs. An herbal mixture contains many chemical compounds, and these compounds may target different enzymes, receptors, hormones, and other molecules in our body system, which may generate a diverse pharmacological response (Rosenkranz et al. 2012; Borse et al. 2019). The adverse effect due to these interactions takes place when an herb possesses the capability to affect the absorption, distribution, metabolism, and excretion of concomitantly used herb or drugs.

Pharmacogenomics is the study of how genes affect a person's response to drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective and safe medications and doses that will be tailored to a person's genetic makeup. The application of pharmacogenomics can predict the potential side effects associated with herb-drug interaction based on the absorption, distribution, metabolism, and excretion profile of individuals (Borse et al. 2019; Thomford et al. 2015).

For the safe use of herbal medicines, a better understanding of herb-drug interaction along with the genetic variations is required. Herbs interact with the CYP450 enzymes such as CYP3A4, CYP1A2, CYP2C9, and CYP2C19, and positively or negatively influence the metabolism of a drug by herb-drug interaction (Liu et al. 2015). Several polymorphisms related to different CYP450 enzymes have been reported in the human population. Some individuals may be poor metabolizers and some of them may be extensive metabolizers. If an herb negatively influences the metabolism of a drug, then a poor metabolizer can have some toxic effect due to poor excretion of the drug. Similarly, the positive influence of an herb on drug metabolism can reduce the therapeutic response. For example, grapefruit juice is a potent inhibitor of the cytochrome P450 CYP3A4 enzyme. Grapefruit juice increases the bioavailability of drugs by affecting the drug metabolism whereas in some cases, its interaction with drugs like astemizole or terfenadine may have a fatal effect (Gervasini et al. 2006). The incidence of herb-drug interactions is increasing; still, the mechanism of herb-drug interactions in different genotypes for many herbs is not clear.

The fundamental genetic basis behind the varying response of the drugs in different genotypes must be explored for better

and effective treatment. Herbs also interact with the transporters in the pharmacokinetic pathways and different polymorphisms related to the transporter gene (Liu et al. 2015). For example, the metabolism of warfarin is induced by the herbal Danshen-Gegen formula (DGF) in CYP1A1 and CYP2B1 genotype, which causes an increase in intestinal absorption of warfarin as a result of binding of warfarin to plasma protein binding to get reduced (Zhang et al. 2014). Another example is berberine (**6**), which can be easily obtained from medicinal plants from different families of plants, mainly growing in high-altitude regions, such as Annonaceae (*e.g.*, *Xylopia* L.), Berberidaceae (*e.g.*, *Berberis* L.), Menispermaceae (*e.g.*, *Tinospora* Miers), Papaveraceae (*e.g.*, *Argemone* L.), Ranunculaceae (*e.g.*, *Coptis* Salisb.), and Rutaceae (*e.g.*, *Zanthoxylum* L.), some of them used for the treatment of diabetes (hyperglycemia), high levels of cholesterol or other lipids in the blood (hyperlipidemia), and high blood pressure in several traditional folklore formulations in Ayurvedic and Chinese medicine. Due to inhibition of the CYP3A4 enzyme, berberine can adversely interact with cyclosporine A and increase its bioavailability, which necessitates a lower dosage. Furthermore, berberine can adversely interact with warfarin, thiopental, and tolbutamide, increasing blood toxicity. Macrolide antibiotics such as azithromycin and clarithromycin may also interact with berberine and may result in heart complications (Khashayar et al. 2021).

Computational Resources for Drug Discovery

In the past few years, considerable technological advancement has occurred in the field of computational hardware, software, and algorithm development. These efforts have greatly affected the computer-aided drug discovery process and the development of biogenic and synthetic drug–like compound databases (Stanzione et al. 2021). There are many databases such as PubChem, ChEMBL, and ZINC, which contain information about thousands of chemical compounds derived from different herbs or natural sources (Zhao et al. 2020). Detailed information about herbal compounds such as compound name and its source, IUPAC name, chemical composition, 2D and 3D structural file, molecular weight, lipophilicity, hydrogen bond donor and acceptor, biological targets, bioactivity assay, efficacy, toxicity, related literature, and other datasets are systematically cataloged and stored in these databases which can be accessed freely for the research purpose (Ramsay et al. 2018; Rifaioglu et al. 2019). These plant metabolites can be used as a lead molecule for drug design against a known therapeutic target.

Herbs or drug molecules generate therapeutic effects by targeting enzymes, receptors, hormones, DNA, RNA, lipids, or carbohydrate molecules. In most cases, proteins are used as a potential drug target (Schenone et al. 2013). Traditional knowledge of herbs and their pharmacological applications are very helpful in rational drug design. Computational tools and algorithms have played a very significant role in the process of drug designing. Now, various software tools and servers are available for modeling and validation of the 3D structure of the target protein (Gupta et al. 2021). The area and composition of the binding site or cavity in the target protein can be determined using theoretical computation. The analog of a substrate molecule can also be used for targeting the protein. The protein-ligand complex information for many proteins is stored in the PDB database, which can be analyzed to find the binding-related information of substrate, cofactor, previously known inhibitor, or antibody (Sliwoski et al. 2014; Burley et al. 2021).

Herbal compounds have a vast set of structural diversity, which can be used as lead molecules to proceed for drug designing. Most of the lead compounds are natural in origin. Lead compounds may have some therapeutic efficacy against disease, but they do not qualify the parameters of drugs (Thomford et al. 2018; Batool et al. 2019). Traditionally known herbal compounds can also be used as a lead for drug development. Binding interaction, specificity, selectivity, absorption, distribution, metabolism, toxicity, and many other parameters of herbal lead compounds need to be optimized. During the process of lead optimization, a lead molecule undergoes a series of chemical modifications to satisfy the different criteria to serve as a candidate drug (Thomford et al. 2018). For example, if a plant compound has very good absorption and distribution and binding affinity for the drug target, but it possesses poor metabolism and toxic substructure, then, there is a need to bring some chemical modification in the herbal compound so that it can be easily metabolized by liver enzymes.

The toxicity of herbal compounds can be minimized by removing toxic groups or replacing them with other groups (Gertsch 2011; Singh and Pathak 2020). Lumiracoxib is an anti-inflammatory drug and possesses severe liver toxicity. Another safe and effective drug, diclofenac, was developed from the lumiracoxib by replacing the fluorine with chlorine and removing the methyl at the meta position of phenylacetic acid (Selg et al. 2007). During the drug discovery process, the addition of toxic groups such as aromatic nitro, aromatic amines, bromoarenes, hydrazines, polyhalogenated groups, and hydroxylamine is avoided in candidate drugs, and these groups are removed if they are already present in the starting lead compounds. Many theoretical rules related to structure-property and structure-activity are available, which guides us about the changes that are required in the lead molecule to achieve better efficacy, pharmacokinetics, and pharmacodynamics (Singh and Pathak 2020). Molecular docking software is very helpful in screening some potential compounds against a target from a vast set of compounds based on the binding energy of the docked complex (Pathak et al. 2018). Docking and structure visualization tools have made it possible to predict the

binding pose of the compound and related interaction with amino acids of the target protein (Fig. 4). Pharmaceutical companies are using this approach for drug development, and there are many successful stories of computer-aided drug designing (Agnihotry et al. 2020; Pathak et al. 2020; Rai et al. 2021). Some drugs such as captopril for the target angiotensin-converting enzyme (hypertension), dorzolamide for the target carbonic anhydrase (glaucoma), saquinavir for the target HIV-1 and HIV-2 protease (AIDS), zanamivir for the target neuraminidase (influenza), and aliskiren for the target renin (hypertension, high blood pressure) are examples of a drug developed by computational approaches (Pathak et al. 2020).

The entire structure of a plant compound is not responsible for therapeutic response, and the skeleton in the entire structure which governs the biological response is known as pharmacophore (Rubió et al. 2013; Singh and Singh 2020). If different herbal compounds possess the same therapeutic role against a particular target, then it can be concluded that all compounds share some common substructure, and that is why it generates a similar biological response against a disease (Ji et al. 2009; Singh and Pathak 2020). Pharmacophore modeling tools have made it possible to find the pharmacophore in a plant compound, which can be used as the main structure for designing different analogs. During drug designing, we do not bring any change in the basic pharmacophore structure, but we grow the desired substructure or groups on different positions of pharmacophore to achieve better potency, efficacy, and selectivity. Computational models have been designed to search a vast set of compounds that possess a particular pharmacophore based on input data (Singh and Pathak 2020; Swaminathan 2020). For example, sirtuins catalyze the reversible deacetylation of lysine residues in the histones or non-histone substrates, and inhibitors of SIRT2 can be used as a therapeutic candidate to cure cancer and metabolic and neurodegenerative disorders. The pharmacophore-based virtual screening was performed to identify a set of compounds that can serve as a lead (Eren et al. 2019). After the pharmacophore-based screening, a total of 31 compounds were taken for evaluation of *in vitro* inhibition, and finally, two compounds with better potency were chosen for *in vitro* cytotoxic assays in cancer cell lines.

Molecular dynamics simulations of the protein-drug complex have made it possible to understand and investigate the dynamic behaviors of protein-drug interaction under the physiological conditions of the real system (Singh and Singh 2020; Shukla and Tripathi 2020). This computational study includes different parameters such as temperature, pH, water, Na+, and Cl− ion concentration, cofactor, presence of other molecules in simulation for drug binding interaction. Computational tools for quantitative structure-activity relationship (QSAR) analysis have been developed, which can generate a regression model between physicochemical or structural property and biological activity based on the correlation between structure and activity of previously known compounds for that target. Once the quantitative structure-activity relationship model is generated, then it can be used to predict the biological activity of a compound based on its structural properties (Gupta et al. 2020). For example, acetylcholinesterase is a potential drug target for designing inhibitors against Alzheimer's disease. A series of *N*-benzylpyrrolidine derivatives with known inhibition activity for acetylcholinesterase were used for developing 3D-QSAR models based on CoMFA and CoMSIA approaches (El Khatabi et al. 2021). These models are statistically validated by comparing the predicted *vs.* observed activity of inhibitors in the training and test

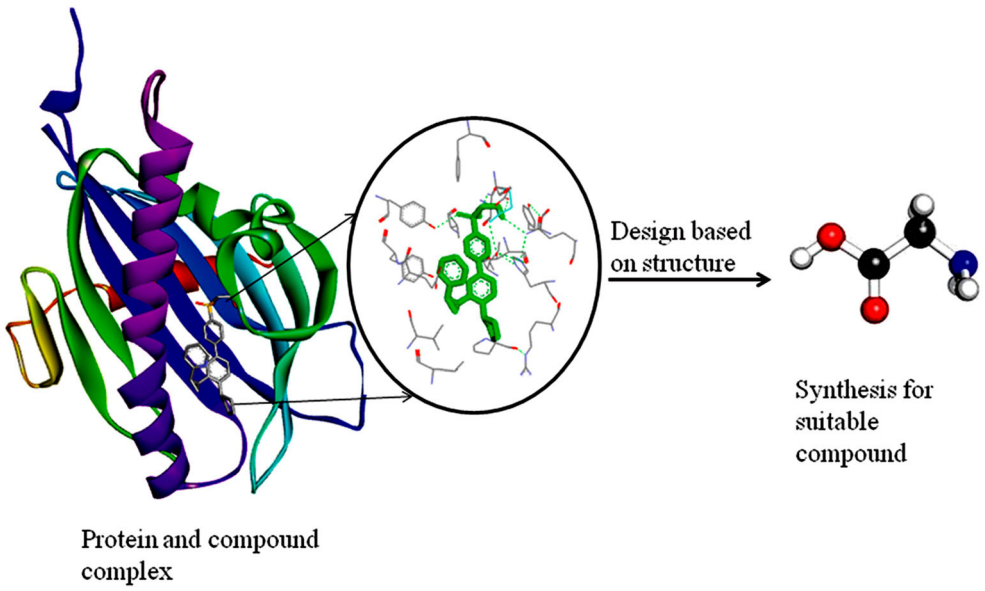

Fig. 4 Structure-based drug design. Molecular docking guides the process of drug designing based on target binding site of the compound and related interaction with amino acids of the target protein. Reproduced from Agnihotry et al. 2020

set, and good predictability was found for both models. The 3D-QSAR model provided a better understanding of the structural features required for acetylcholinesterase inhibition. Finally, six acetylcholinesterase inhibitors were designed based on QSAR knowledge, and one inhibitor with the highest predicted activity was used for molecular docking and molecular dynamics (MD) simulation study.

Now, many researchers have developed computational models of absorption, distribution, metabolism, and toxicity predictions which are very helpful in predicting the suitability of a compound to serve as a drug (Lipinski et al. 2001; Yang et al. 2019a). These predictions reduce the risk of failure for drugs during clinical trials as they predict the ADMET profile of drugs during the stage of the drug development process. Advances in the field of genomics, proteomics, metabolomics, microarray technologies, pharmacogenomics, and computer science have made a paradigm shift from traditional herbal systems to modern drug discovery.

Perspectives and Future Directions

In recent years, a lot of research have been conducted in the field of herbal medicine; still, several herbal plants and their therapeutic potential have not been explored well. Plant tissue culture, metabolite production, and processing techniques have opened a new door for the large-scale propagation of herbal plants and the production of biologically active metabolites. Herb-drug interaction studies for most frequently used herbs and drugs must be promoted to avoid the toxic/fatal responses. Synthetic cascade/pathways related to the synthesis of the herbal metabolites in plants are being explored which can be used for large-scale production of metabolites using genetic engineering and manipulation techniques. Plants are providing a vast set of lead compounds for drug discovery. The US National Institutes of Health (NIH) and some other organizations have paid more attention to the scientific investigation of herbal medicines. Compounds with toxicity *in vitro* assays should be further investigated to find the information about the toxic groups and changes required in the existing molecules. Several approaches to computer-aided drug designing are playing a significant role in reducing the cost, time, and complexity in the drug discovery process.

Conclusions

Plant metabolites provide a vast source of structural diversity for the process of drug discovery. A lot of undocumented, scientifically unproven traditional knowledge related to sources, herbal processing, combination, and therapeutic use of medicinal herbs are available. There is a need to explore herbal species, scientific document them, and develop strategies for their propagation, conservation, and large-scale metabolite production. Mechanism of action related to the herbal metabolites/drug, herb-drug interaction, combination therapy and its impact, pharmacogenomics knowledge of drug, and related polymorphism is a very important aspect that must be covered for the safe and effective medication. Computational approaches have made it possible to search, design, and screen the drug candidate; understand and analyze the drug-target binding affinity and interactions, pharmacokinetics, and pharmacodynamics; and do many other predictions related to a candidate drug.

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Author Contribution DBS developed the idea for this review article and its coverage. DBS and RKP drafted the article, and DR critically revised the work. All authors have read the final manuscript and approved the submission.

Declarations

Conflict of Interest The authors declare no competing interests.

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