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REVIEW

Exploring Medicinal Plant Legacy for Drug Discovery in Post-genomic Era

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Abstract Plants are a valuable source of pharmacologically important compounds since these are traditionally important in medicinal systems. Medicinal plant-based ancient wisdom could serve as a powerful tool to facilitate focused research on natural compounds for the drug discovery process. Medicinal plants are more important sources for drug discovery, specifically lead molecules as these offer several advantages over the synthetic molecules. Since in post genomic era, molecular targets for most diseases are known, conventional bioscreening strategies for medicinal plants are not sufficient to fulfill the present demand. It makes the role of medicinal plants more significant than ever before. The rich heritage of Indian medicinal plants can be explored utilizing various computational approaches for bioprospecting in the post-genomic era. In this review, the authors explore how Indian medicinal plant legacy can be utilized in post-genomic era utilizing the computational, bioinformatics, chemo-informatics, genomics and systems biology approaches. This approach shall make possible the systematic analysis integrating traditional and modern data in order to validate medicinal plant based knowledge.

Keywords Indian medicinal plants · Bioprospecting · Genomic · Reverse pharmacology · Computational approaches

Significance statement This review provides a basic discussion platform for integration of different modern biological, chemical and computational techniques of Genomics, Proteomics and Systems biology to reduce the cost and time for drug discovery projects.

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Introduction

Plants are a valuable source of food, feed, fiber, furniture, fuel spices and medicines [1]. The medicinal use of plants dates back to the ancient civilization. Plant-based drugs and lead molecules constitute a well-known systems of health in India like Ayurveda, Yoga, Siddha, Unani, Naturopathy and Homeopathy [2]. Plant based medications constitute the major role in health care system of the world. According to the World Health Organization (WHO), around 80% of the world's population is dependent on traditional plant based medicine system. Indian medicinal plants are the very rich source for a huge variety of bioactive compounds. Medicinal plant families like Solanaceae, Asteraceae, Caesalpiniaceae, Liliaceae, Apocynaceae, Piperaceae, Rutaceae and Sapotaceae are the major source of many plant products including alkaloids, flavonoids, coumarins, fatty acids, cucurbitacins, diarylheptanoids, iridoids, lignans, limonoids, physalins oligorhamnosides, naphthoquinones, and phenanthrene derivatives [3]. Rapid advancement in sequencing technology has allowed much faster completion of genome projects for various medicinal plants, microorganisms, pathogens and animals. Computational biology approaches have also accelerated the process of structural and functional annotation leading to identification and prediction of a large number of drug targets. This created the demand to explore new sources for the identification of novel drug molecule for the identified drug targets. Due to multiple resistance, the necessity of novel chemical compounds to treat human diseases is continually increasing. There is also need for determining new pharmacologically significant compounds i.e. rational drug design, where the drug is purposefully personalized towards a specific target in the microbial cell [4].

Drug discovery is a long process involving the application of various scientific disciplines including Biology, Physiology, Biochemistry, Chemistry, Pharmacology, Pharmacognosy, Microbiology, Molecular modeling and Combinatorial chemistry that contributes to natural product discovery. The approaches to new drug development through natural products are the single most successful strategy. Medicinal plant-based drug discovery offers several advantages over synthesis based conventional drug discovery. For example, medicinal plant-based drugs are safe, cheap, nontoxic, minimum side effect, have better ADME compliance and most importantly they can resist the development of drug resistance by pathogens [5]. In this review, the significance of Indian medicinal plants is explored to meet the demand of post-genomic era and how computational approaches can be best utilized. The relationship between Indian medicinal plant legacy, post-genomic era, and computational approaches is discussed.

Indian Medicinal Plant Legacy Medicinal systems in India begins with the development of agricultural-based Indus Valley civilization around 4500 BC. India is a mega biodiversity center with 45,000 plant species. India has rich floral diversity due to the 16 different agroclimatic zones, 10 vegetative zones, and 15 biotic provinces. India has also 2 of the 4 mega biological diversity areas of the world. Gangetic plains, forests of Himachal Pradesh, and Western Ghats, are some of the hotspot areas of mega-diversity. The Indian subcontinent is a rich resource of medicinal plants that are used for the treatment of a number of diseases since a long time, forming a rich source of knowledge [3]. Total number of medicinal plant species in India ranges from 3000 to 8000. The Botanical Survey of India reports over 15,000 plant species in the country, of which approximately 7500 species are used as source of herbal medicine. Diversity of medicinal plants in India distributed in different states due to favorable climatic conditions at these locations.

Plants have been the part of traditional medicinal system, being used for thousands of years. Plant based medicine system is playing very major role in health care. World Health Organization (WHO) reports state that approximately 80% of the world's population depends on knowledge of traditional medicines for primary health care. Modern drug discovery includes the identification and validation of drug target, identification of potential hits, and optimization of compounds to increase the affinity, selectivity, potency, metabolic stability and oral bioavailability. A metabolites is isolated from a particular anatomical part such as root, leaves and flower of the plant, and the knowledge of botany and chemistry is important for the efficient isolation and identification of bioactive compounds from a plant. In India, keeping in mind the importance of medicinal plants, the Government of India has established a separate division AYUSH under the Ministry of Health and Family Welfare. The National Medicinal Plants Board was also established in the year 2000 by the Govt. of India to explore and utilize the knowledge of medical plants. The traditional system of medicine is basically based on non-systematic and systematic systems. Non-systematic is mainly local/folk/tribal stream, which is generally transferred orally from person to person and its knowledge and use is limited to a group of people living in a particular area. The systematic system of traditional medicine is well documented in the literature, and developed as a result of accumulation of knowledge over hundreds of years. They are Ayurveda, Siddha (South of India) and Unani (Muslim community). Ayurveda, Siddha and Unani are also officially recognized for the purposes of national health services along with modern allopathy system.

In Indian culture, functional foods and spices are normally used not only to meet the dietary requirements but also to prevent or treat various diseases. These are also named as nutraceuticals. Food ingredients such as vitamins, essential fatty acids, dietary fibers, oligosaccharide, minerals, antioxidants, lactic acid bacteria cultures and lignins enhance the value of food and make it functional. Indian medicine system believes that complex diseases can be cured with the complex combination of herbal compounds whereas Western system believes that a single component drug can be more effective against a disease. In India, whole food is used as functional foods rather than supplements. In India, some medicinal plants such as onion, garlic, black pepper, mustard, saffron, red cinnamon, chili, clove, curry leaf, turmeric, fenugreek and ginger are used as regular dietary supplement. The general herbal drug discovery process includes selection of plant part, crude extract preparation, screening of biological activity, investigations of chemo-pharmacological properties, study of toxicological and clinical outcome, and use of active component for lead optimization.

Nature is the best combinatorial chemist as it provides a vast diversity of compounds and till now many natural products and their analogues have been transformed into a drug. Herbal drugs are less toxic due to their natural origin. Compounds derived from the medicinal plants can be used as a new drug themselves and can also be utilized as a lead for further optimization. During drug discovery, if new chemical moieties are not available, compounds with some known biological activity against the disease can be used as a lead compound (Fig. 1). The important step in drug discovery is to determine the 3-D structure and validate the drug target. Computer aided drug designing can be categorized into two types: (1) structure based drug designing and (2) ligand based drug designing. Virtual screening and molecular docking approaches provide the correct binding pose information of a compounds in the binding site of a drug target. Defining the position of correct binding site during docking is also a challenging task. There are many computational tools available for binding site prediction and validation. During drug discovery process, the potency, selectivity and binding affinity of leads can be optimized by a series of chemical modifications. Nature provides a vast diversity of chemical compounds that can have some therapeutic applications. Therapeutic potential of natural plants should be explored well and utilized in a systematic manner to achieve the highest therapeutic response against a disease. The WHO has also acknowledged the role of traditional medicine and has suggested some useful strategies, guidelines and standards for the use of herbal medicines.

Genomics for Reverse Pharmacology

Traditional knowledge on Indian medicinal plants guides a researcher to start the drug discovery process from a well-known, tested and safe compound, and offers different advantages during testing. Reverse pharmacology integrates the documented clinical or experiential hits into leads and further optimize these leads into drug candidates. With the help of reverse pharmacology, drug discovery process from laboratories to clinics, actually reversibly directed from clinics to laboratories. Observations and data from clinical experiments serve as a starting point in reverse pharmacology. Reverse pharmacology may be more effective approach of drug discovery in those countries where health care system, clinical and laboratory documentation facilities are highly developed. India has enormous potential for reverse pharmacology as here exists vast experience-based evidence practiced in Ayurveda, Siddha, and Unani. A golden triangle search engine consisting of Indian medicinal plant, post-genomic era information and computational biology/chemoinformatics approaches will converge to form a novel drug discovery process for effective, safe and personalized medicines (Fig. 2).

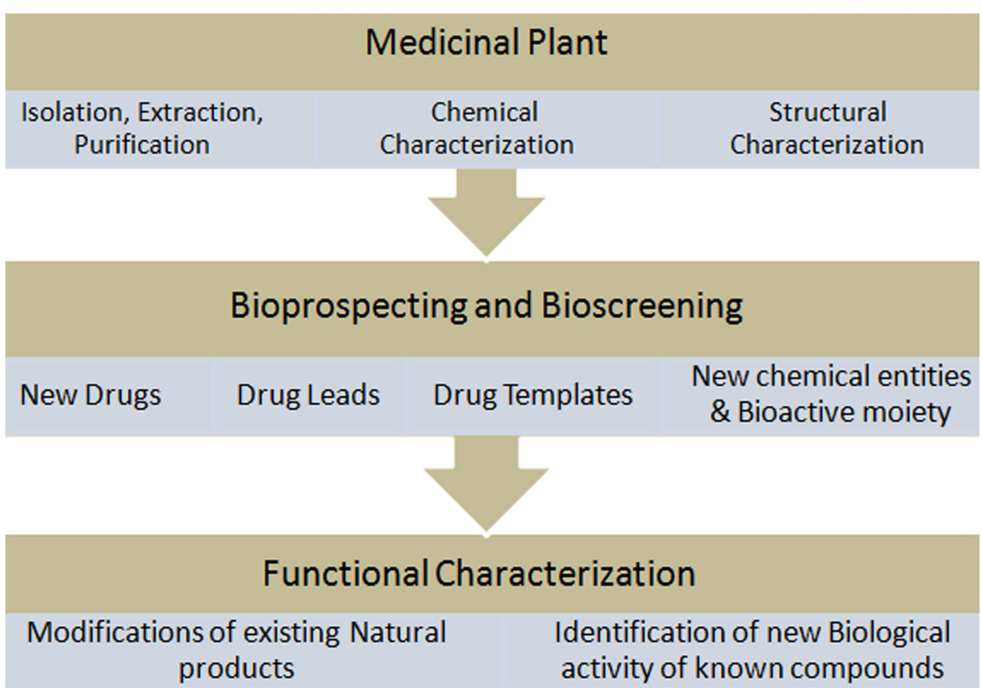

Fig. 1 Components of medicinal plants used for drug discovery. A diagrammatic route from isolation to functional characterization

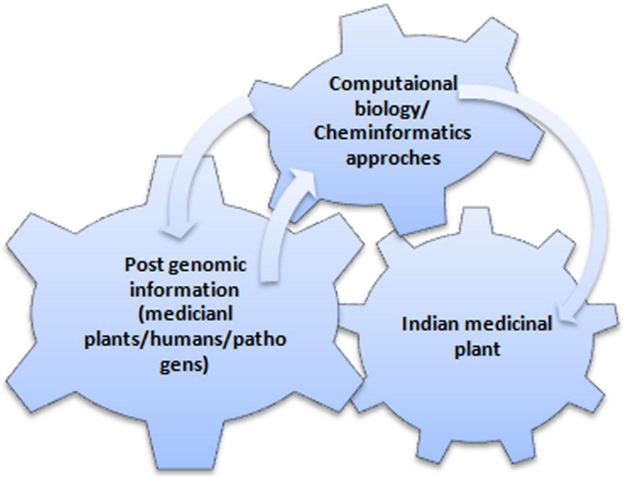

Fig. 2 Drug discovery search engine combining post genomic information and computational tools leading to Indian medicinal plants as potential sources

Emergence of Omics

In recent years, a vast amount of genomic/proteomic data has been generated with the application of next- generation sequencing (NGS) technology. However, very few studies were based on genomics of medicinal plants. In comparison to important crops, medicinal genome projects are still in its emerging stage. The completion of the sequencing of the large number of genome projects including human genome, and those of other organisms, is expected to give many potential new drug targets involved in various diseases and metabolic pathways [6]. Thus, genomics has created a new platform for the identification of thousands of novel drug targets in humans, pathogens, animals, and insects. Genomic-led revolution transformed the drug discovery process into a stage of many drug targets with a small number of available leads. With the application of NGS technology, the genome sequencing of medicinal plants became feasible due to the reduced cost and time for the projects. The genome projects of various medicinal plants are going on. These works give the opportunity for analysis of functional genomics studies on unique biosynthetic pathways of a secondary metabolite, genome annotation and data mining. Thus, it will help in the development of the therapeutics and the selection of cultivars with good agricultural traits (yield, nutritional content, fruit size, abiotic stresses tolerance and resistance to multiple diseases) [7].

The genomes of medicinal plants can describe evolutionary and comparative genomic relationships of medicinal plants. Genomic information can be more helpful in understanding the evolution of secondary metabolites and also in predicting the structure and function of the new genes. Secondary metabolites are the biosynthetic products of the primary metabolites and are the key agents for the medicinal properties of the plants. Development in genomics-based research will also help in finding certain medicinal plants having hidden set of genes that can yield more secondary metabolites. Although, in the post-genomic era, more genome specific information and supporting HTS systems are available but still, the new strategies for drug discovery have not been employed effectively. New informational paradigm into drug discovery process has been represented by the application of genomics. Sequencing of the human genome has revealed so many new drug targets that can be important in treatment of diseases.

Better understanding of the human genome explains the genomic basis of individual variation. Pharmacogenomics, which deals with drug development process based on information generated though human genome project can be used for the discovery of more predictive, individual and customized therapy. Pharmacogenomics evaluates the inherited variations in genes and relates it with drug response. These variations can be used to predict the good, moderate, bad or no response of a drug in different individuals. Medicinal genome projects will provide a basis for comparative genomics, metabolic engineering and transgenic approaches to explore the complete synthetic pathways, so that analysis of various medicinally significant traits during genome evolution can be performed.

Computational Approaches for Drug Discovery

The volume of data generated through various genome projects are increasing day by day with a very high rate. The entire process of drug discovery involves several steps like identification and optimization of drug target, identification and optimization of lead compounds, development of lead into drug molecule, prediction of ADME parameters etc. Many of these steps are very complex and time taking if the conventional approaches are used for drug discovery. This limitation can be overcome with the application of various computational approaches. Computational approaches have speed up the process of drug design [8]. Major computational approaches includes chemo-informatics, genomics, bioinformatics, and system biology. Computational tools easily analyze and interpret the data generated from natural products and also thus integrating traditional and modern data to infer knowledge (Fig. 3). There is a huge potential that could be exploited from the biodiversity within the plant kingdom. Bioprospecting and bioscreening of plant metabolites provides an approach for discovery of potential drugs. Computational approaches can be employed to identify new bioactive constituents from plants, as well as to uncover patterns

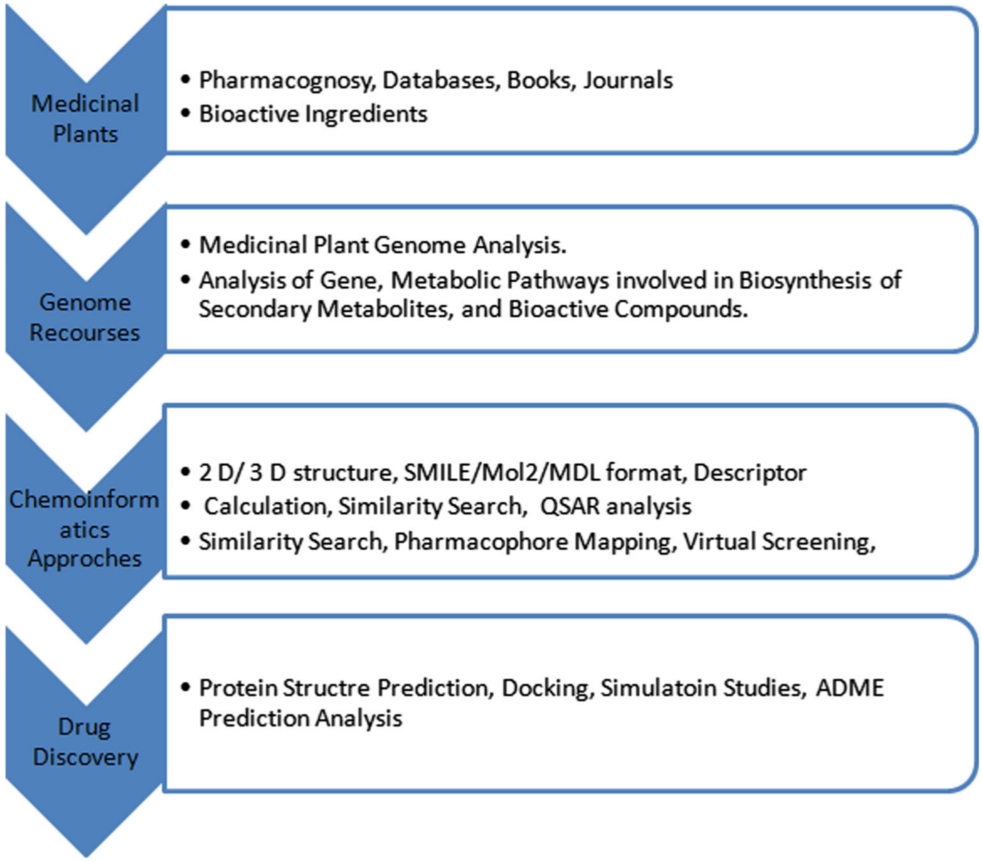

Fig. 3 Drug discovery process using computational/ chemoinformatics approaches

in phytochemical data. Chemical constituents and their respective bioactivities need to be characterized for the standardization of herbal therapeutic approaches. Computational approaches can be useful in optimization of herbal mixtures. Biological activities of different components in a herbal product need to be evaluated. The correlation between chemical composition of a compound and its biological activity can be assessed to build a predictive model.

Computational approaches can be used to discover and optimize drug candidates inspired by nature. New pharmacophores may guide some new drug targets as well as increase the possibility for combinatorial chemistry. Another important computation approach is phylogenetic analysis. Phylogeny has provided an explanation to many scientific fields but has been overlooked in medicinal plant-based studies. Phylogeny and phytochemical studies are built upon the premise that the plant species belonging to the same family may have similar biochemical pathways. The distribution of medicinal properties of the plant follows the phylogenetic pattern. This approach can be used to find potential candidates in new plants based on chemical similarities. Medicinal properties of plants are not randomly distributed in plant kingdom, and phylogeny shapes the ethnobotanical use of plants. Phylogeny can be used to evaluate the significance of phylogenetic signal of medicinal properties in plants. Application of phylogeny approaches have shown that similar ethnobotanical use of a plant occur in different areas where related medicinal plants are available.

Secondary metabolites are produced in response to external stimuli such as nutritional changes or foreign infection. Most bioactive natural products have the ability to target specific protein coded by essential gene [9]. Ethnobotanical knowledge has provided sufficient basis for further investigation of outdated plant for medicinal properties. A large potential of plant is required to produce sufficient amounts of the bioactive compounds for medical use. Plant associated microorganisms have been found to produce novel bioactive metabolites with wide ranging medicinal uses such as antibiotics, immunosuppressants, antiparasites and anticancer agents [10]. Therapeutic importance of different medicinal plant is based on the characteristic of bioactive secondary metabolites. However, the therapeutic efficacy of a herb depends on the identification of correct plants source. The correct source plant must be utilized to avoid poisoning. Some time, only physical characterization of a medicinal plant may guide the wrong selection of source plant. To avoid poisoning, death and other instances, a more reliable method for characterization of source plant is required. DNA-based markers may be used for the efficient and reliable identification of plant species. DNA barcodes of medicinal plants can be built to differentiate the one species from others in the same plant kingdom. Potential drugs can be mined using structure-based virtual screening of plant based chemical libraries. Virtual screening methods have some limitation due to vast number of phytochemical, large number of conformation due to rotatable bonds and difficulties in calculation of binding affinities.

Bioinformatics approaches can be used for identification of novel drugs by evaluating the patterns among phytochemical data. Some of the key disciplines are data mining, machine-learning methods for developing computational models, QSAR, system biology. New disciplines like clinical bioinformatics, translational bioinformatics, medical informatics and health informatics can also be incorporated in discovery process. Medicinal plant genome research and bioinformatics approaches also facilitate the understanding of cellular processes associated with plants, their metabolic pathway, genes, enzymes related with synthesis of secondary and primary metabolite or bioactive compound. Bioassay-based fractionation of the plant may produce standardized extract or bioactive compound [11]. One of the most important need today is the designing of software for prediction of synergistic effect of combination of bioactive components, so that mixture of plant extracts could be used directly without isolation or purification of individual components.

Medicinal Plant Databases

There is a need of common platform for integrated access of information available on medicinal plants over the ages and those being explored by modern approaches. Several databases are available for cataloguing information related to one or more aspects of medicinal plants, such as ethnobotany, bioactive metabolites and their pharmacology, targets of active constituents, genomic or transcript-based information. There are various national and international databases dealing with different aspects of medicinal plants. Some of the important international databases include National Center for Biotechnology Information (NCBI), Kyoto Encyclopedia of Genes and Genomes (KEGG), Traditional Chinese Medicine Information Database (TCM-ID), Herb Ingredient's Target (HIT), and Therapeutic Target Database (TTD). The NCBI at the United States National Library of Medicine hosts 'Plant Genome Central'. A remarkable effort has been made for developing the Medicinal Plants Genomics Resource (MPGR: http://medicinalplantgenomics.msu.edu/). These databases provide complete information about the therapeutic targets, prescriptions, herbal constituents and functional role of active ingredients, molecular structure, clinical indications, therapeutic and toxic response. Food and Agriculture Organization of United Nation is maintaining, medicinal plant information databases, a source for information relating to medicinal plants. In addition, there are some regional databases like Raintree's (http://rain-tree.com/ethnic.htm), which provides information about ethnic and therapeutic role of plants from Amazon rainforest. This database contains data and information related to taxonomy, photochemistry, ethnobotany and clinical abstracts.

For thousands of years, Indian medicinal plants hold significant role in diagnosis and treatments of many diseases. However, due to lack of proper investigation, documentation and poor understanding of Indian medicinal plant ingredients, this prosperity of natural resource has not been utilized. Recently, effort has been made for studying Indian medicinal plants, from which a large number of bioactive ingredients have been identified, isolated and scientifically studied. There are various databases in India giving information related to Indian medicinal plants. Some of these important databases include Indian medicinal Plant Database (http://www.medicinalplants.in/), Database on Medicinal Plants (http://nmpb-mpdb.nic.in/user/index) and FRLHT-Encyclopedia on Indian Medicinal Plants (http://envis.frlht.org/indian-medicinal-plants-database.php), and Encyclopedia of Medicinal Plants (http://herbs.indianmedicinalplants.info/). There are other databases, which are very specific, including NPACT: Naturally Occurring Plant-based Anticancer Compound-Activity-Target database [12], InDiaMed: A Comprehensive Database of Indian Medicinal plants for Diabetes (http://www.indiamed.info). However, these databases are providing general information about sources of medicinal plants, traditional usage, processing guidelines and storage procedures. The information on the constituents of Indian medicinal plant is not well organized.

But surprisingly there is no comprehensive Indian medicinal plant database that contains three-dimensional structural/molecular information of Indian medicinal plant constituents, which can be used for computational operations like molecular descriptor calculation, similarity/dissimilarity search, pharmacophores mapping, molecular docking simulation and virtual screening for drug discovery [13]. Hence, there is an urgent need to build a comprehensive medicinal database resource for integrating Indian medicinal plant legacy with existing knowledge and with genomic data information to facilitate the drug discovery process. The exploration of compound databases comprising a vast diversity of drug-like compounds and databases on target genes, proteins and pathways, will guide the design of new candidate drugs for pharmacological evaluation.

Advantages of Medicinal Plant-Based Approaches

Every medicinal system or therapy has certain advantages and limitations. Modern medicine has also certain limitations. Some significant issue with the modern medicine is the emergence of drug-resistant microorganisms, adverse side effects, new emerging diseases, and their high cost of therapy have focused interest in medicinal plants. Plants and their products are part of daily human life since hundreds or thousands of years. Medicinal plant products have been exposed to a long selection process thus leading to their optimization with molecular targets resulting into very low toxicity and side effects [14]. Many structural features common to natural products like aromatic rings, chiral centers, complex ring (phenols and their oxygen-substituted derivatives), degree of saturation, and number of heteroatoms provide the base for generation of chemically diverse secondary metabolites. The chemical diversity of secondary plant metabolites those resulting from plant evolution is high in comparison with synthetic combinatorial chemical libraries. Due to the chemical diversity of the secondary metabolite in plants, the possibility of drug resistance is limited. Chemical diversity of the secondary metabolites overcomes the resistance problem as it exists in a combined form of more than one molecule in plant cell. However, UK- based Botanic Gardens Conservation International warns that many plants and organisms are being lost through the destruction of rainforests, coral reefs, and other natural habitats [15].

Chemical diversity of the secondary metabolites also helps in the identification of novel lead structures, templates and scaffolds, which is not possible in the finite world of synthetic combinatorial chemical libraries. Natural secondary metabolites have shown more drug-likeness and biological friendliness than synthetic molecules because they have been associated with living systems. First four rules of Lipinski's rule of five are not applicable for natural products as well as for molecule that is recognized by an active transport system. It is due to low-molecular mass compounds of the products from natural origin. In modern or allopathic medicine, a number of drugs have been derived from plants sources which are free from serious side effects and also cost-effective. The natural compounds show diverse structural variety, especially

Table 1 Some known lead compounds, its natural sources and therapeutic role

S. no.	Lead	Source organism	Type	Therapeutic role	References
1.	Ephedrine	Ephedra	Plant	Cold, allergic disorder	[16]
2.	Silymarin	*Silybum marianum*	Plant	Liver diseases, gallstones	[17]
3.	Cephalosporin	Acremonium	Fungus	Antibacterial	[18]
4.	Morphine	*Papaver somniferum*	Plant	Pain medications	[18]
5.	Vancomycin	*Amycolatopsis orientalis*	Bacteria	Bacterial infections	[18]
6.	Paclitaxel	*Taxus brevifolia*	Plant	Anticancer	[18]
7.	Myricocin	*Mycelia sterilia*	Fungus	Antibiotic, anticancer	[19]
8.	Halichondrin B	*Halichondria okadai*	Sponge	Anticancer	[18]
9.	Capsaicin	Chili peppers	Plant	Analgesic	[18]
10.	Dolastatin	*Dollabella auricularia*	Plant	Anticancer	[18]
11.	Ingenol mebutate	*Euphorbia peplus*	Plant	Actinic keratosis	[20]
12.	Artemisinin	*Artemisia annua*	Plant	Antimalarial	[18]
13.	Phlorizin	Apple	plant	diabetes mellitus	[21]
14.	Maytansine	*Maytenus serrata*	Plant	Antibiotic	[22]
15.	Teprotide	*Bothrops jararaca*	Snake	Anti-hypertensive	[18]
16.	Ziconotide	*Conus magus*	Snail	Analgesic	[18]
17.	Plitidepsin	*Aplidium albicans*	Tunicate	Anticancer	[23]
18.	Betulinic acid	*Betula pubescens*	Plant	antiretroviral	[18]
19.	Torreyanic acid	*Pestalotiopsis microspora*	Fungus	Anticancer	[24]
20.	Wedelolactone	*Wedelia calendulacea*	Plant	Anti-allergic	[24]
21.	Theasinensin	*Thea sinensis*	Plant	Anti-viral	[24]
22.	Momordicoside	*Momordica charantia*	Plant	Anti-diabetic	[25]
23.	Digoxin	*Digitalis purpurea*	Plant	Cardiac disease	[24]
24.	Quinidine	*Cinchona officinalis*	Plant	antiarrhythmic	[26]
25.	Withanolides	*Withania somnifera*	Plant	Anti-inflammatory	[27]

as new environmental niche is studied. The utility of these natural compounds can be further explored by studying the related synthetic pathway and engineering the proteins that produce them. There are many drugs used at present having plants are their sources of origin. Some of them are also listed below in Table 1.

Current Challenges

Medicinal plants are the important source of new lead compounds for drug discovery. Many challenges have been faced in the procurement of plant, the selection and implementation of bioassays for high-throughput screening. Plant-based medicines have much importance towards advancing modern medical system. A vast amount of ethnomedical information on plant uses is available in the literature but have not yet been compiled and represented in a systematic form. The literature and resources on ethnomedical information are generally scattered, which hinders the access of required information about medicinal plants. The literature on Indian medicinal plants is also present in Sanskrit, Hindi and other regional languages that are often not accessible to people belonging to other languages. The literature, monographs and books in English are also available. But sometimes problem arises with the right translation of technical Sanskrit and Indian words into English. Therefore, the original Sanskrit textbooks should be properly consulted in the process of application of information regarding Indian medicinal plants.

There have been many scientific reviews on Indian medicinal plants too. Many government and industrial institutes are conducting research on the Indian medicinal plants. But a systematic review of plant secondary metabolites and its therapeutic application is not available. Many international databases and websites do not include the work published in many journals. Hence, there is a global lack of awareness of work carried out on medicinal application by workers. Thus, it is important to extract, store and present traditional and modern medical information in a well-organized format for the purpose of data mining so that proper bioprospecting and bioscreening can be explored. Despite the increasing use of medicinal plants in drug discovery, their future is being threatened due to lack of efficient strategies for the conservation. In developing countries, biodiversity of herbs and medicinal plants are diminishing very fast and may be at the edge of extinction in future as a result of industrialization. Since safety is a major issue with the use of herbal drugs, therefore, regulatory authorities should adopt suitable strategy to ensure that all herbal medicines are safe [28]. The dynamic process of evolution could affect the identity and structure of natural compounds. The correct identification and evaluation of raw material has become a challenge.

Natural pharmaceuticals, nutraceuticals and cosmeceuticals are reservoir of chemical diversity. Examples of plant products and derivatives used by the medical industry include vincristine, paclitaxel, vinblastine, camptothecin, artemisinin, and podophyllotoxin. Globally, there should be efforts to check the quality of herbal drugs and traditional medicine. Safety elements of herbal medicines should not be ignored because a brand is associated with these products. Systematic pharmacovigilance on herbal medicines is essential for the development of appropriate guidelines for its safe and effective use [29]. Despite the beneficial roles of herbs, the herbs have also shown toxicity, severe adverse effects and fatalities. There is need of protocols and guidance for natural health product as well as for safety and toxicity testing of herbal products [30]. Globalization and economic liberalism has accelerated the interchange of knowledge between local and global level via internet, television news, blogs, international trade and print media.

Plants grown from seeds are most often highly heterozygous and show phenotypic variation, and may be discarded because of the poor quality. Some medicinal plants either do not produce seeds or have small seeds and they do not have potential to germinate in soils. Thus, the mass multiplication of diseases-free plant is a general problem. This limitation can be overcome by plant tissue culture techniques. Tissue culture technique can be utilized to develop genetically pure plants under in vitro culture. The screening of natural product extract is more complex than screening of compound libraries. The study of biological effects and screening of a compound from a herbal mixture is very problematic task; and natural product extracts are complex mixtures of mostly uncharacterized compounds. Some interfering compounds in complex mixture may mask the biological effect. Compounds or families of compounds may interfere with the screen in a nonspecific manner. Also there are many plants and their resources are becoming endangered. Some of those are listed below in Table 2. They need to be preserved and protected for the availability of medicinal plant resources.

Future Perspective

There will be more advances in sequencing technologies, which will generate huge amount of genomic data resulting in identification of more and more optimized drug targets in humans, pathogens and plants. Genomic development will allow the researchers to have deep insight into the molecular mechanism of the genes and their interaction involved in the biosynthesis of the medicinally significant

Table 2 Endangered plants and their therapeutic role

S. no.	Endangered plant	Endemic	Therapeutic role	References
1.	*Aconitum chasmanthum*	India and Pakistan	Analgesic, diuretic, irritant and sedative	[31]
2.	*Chlorophytum borivilianum*	Rajasthan, Maharashtra, Gujarat	Diabetes, arthritis, natal	[31]
3.	*Gymnocladus assamicus*	North east India	Dermatological disorders, anthelminthic	[31]
4.	*Lilium polypyllum*	Pakistan, Afghanistan, India	Expectorant, astringent, aphrodisiac, antipyretic	[31]
5.	*Tribulus rajasthanensis*	Rajasthan, Gujarat	Fever, sterility and skin	[31]
6.	*Valeriana leschenaultia*	Kerala, Tamil Nadu	Diseases of eye, blood, liver, hysteria	[31]
7.	*Commiphora wightii*	Western, India, Pakistan	Cholesterol synthesis	[31]
8.	*Saussurea costus*	Jammu-Kashmir,	Antiseptic and asthma	[31]
9.	*Gentiana kurroo*	Pakistan, Nepal and India	Cough, stomach ache, fever	[31]
10.	*Glycyrrhiza glabra*	Southern Europe and parts of Asia	Anti-inflammatory, anti-diabetic, antiviral, anti-ulcer, anti-oxidant	[32]
11.	*Gymnema sylvestre*	India, Africa, and Australia	Anti-diabetic	[33]
12.	*Saussurea lappa*	South Asia	Cough, piles, epilepsy, leprosy	[34]
13.	*Gynocardia odorata*	South Asia - India	Anti-inflammatory, Anti-helmentic, analgesic	[35]
14.	*Alpinia calcarata*	Sri Lanka, India, and Malaysia	Antibacterial, anthelmintic, anti-inflammatory, antioxidant, antidiabetic	[36]
15.	*Mucuna pruriens*	Africa and tropical Asia	Nervous disorders, arthritis, Parkinson's disease	[37]
16.	*Swertia chirayita*	Himalaya	Antimalarial, blood purifier	[35]
17.	*Picrorhiza kurroa*	Himalayas	Fever, dysentery, anemia, asthma	[35]
18.	*Tinospora cordifolia*	India, Myanmar and Sri Lanka	Jaundice, bone fracture	[35]
19.	*Ginkgo biloba*	China	Neuroprotective and anti-apoptotic	[38]
20.	*Oroxylum indicum*	India and South East	Antimicrobial	[39]

secondary plant metabolites [40]. The number of angiosperms and gymnosperms species on earth is estimated at 250,000, with a lower level at 215,000 and an upper level as high as 500,000 and biological activity of only about 6% plant species have been studied [14]. India is also very rich in its flora owing to its diverse climate, topology and environmental conditions. India has about 45,000 plant species. Medicinal role of many plant species have been studied and there are many more species still waiting for proper bioprospecting so that their medicinal properties can be assigned. Many compounds from terrestrial and marine organisms are used for cure of diseases and are used in natural form as well as core structure for further modification. Several plant species that are not found anywhere else in the world. Traditional bioscreening approaches for identifying active ingredients of medicinal plants are not enough to fulfill the need of current demand. Herbal medicines have great demand in the developing countries because they are inexpensive and less toxic. Therefore, there is urgent need to set up collaborative research where different computational, genomics, bioinformatics and chemoinformatics approaches will provide the platform for development of the essential tools to facilitate intentional, focused and safe natural products. It can be possible by developing comprehensive database resources by integrating genomic, molecular and structural information of bioactive compounds, and various computational biology tools.

Conclusion

The traditional system of medicine is basically based on non-systematic practices based on theories and experiences. Recent advances in science and technology have explored the metabolic and synthetic pathways. The genome projects of some medicinal plants have been completed and many projects are going on. These works give the opportunity for analysis of functional genomics studies on unique biosynthetic pathways of a secondary metabolite, genome annotation and data mining. This review explores, how medicinal plant legacy can be utilized in post-genomic era utilizing the bioinformatics, genomics and systems biology approaches. This approach can help in systematic analysis of traditional and modern medicinal data in order to validate medicinal plant based knowledge.

There are many medicinal plants which are at the edge of extinction due to human activities and other causes, there is need to protect and propagate these plant species using tissue culture techniques.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest to publish this manuscript.

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