Challenges and opportunities in drug discovery from plants

Sanjay M. Jachak* and Arvind Saklani

Department of Natural Products, National Institute of Pharmaceutical Education and Research, Sector-67, SAS Nagar, Punjab 160 062, India

Drug discovery from plants involves a multidisciplinary approach combining botanical, ethnobotanical, phytochemical and biological techniques. Plants continue to provide us new chemical entitities (lead molecules) for the development of drugs against various pharmacological targets, including cancer, HIV/AIDS, malaria, Alzheimer's disease and pain. Several natural-product drugs of plant origin are in clinical use, including paclitaxel, camptothecin-derived analogues, arteether, galanthamine, tiotropium to name a few, and some are undergoing Phase II and Phase III clinical trials. Although plant-based drug discovery programmes continue to provide an important source of new drug leads, numerous challenges are encountered, including procurement and authentication of plant materials, implementation of high-throughput screening bioassays and scale-up of bioactive lead compounds. At the same time, there are opportunities for India as it is rich in genetic resources and traditional knowledge, which are key components for bioprospecting and value-addition.

Keywords: Bioprospecting, drug discovery, ethnobotany, ethnopharmacology, medicinal plants.

PLANTS have been the basis of many traditional medicine systems throughout the world for thousands of years and continue to provide mankind with new remedies. Plant-based medicines initially dispensed in the form of crude drugs such as tinctures, teas, poultices, powders, and other herbal formulations[1], now serve as the basis of novel drug discovery. The process of drug discovery is multi- and inter-disciplinary. Apart from the core disciplines related to pharmaceutical research, classical sciences like taxonomy and the newer discipline ethnobotany have now become an integral part of drug discovery from plants. The plant-based indigenous knowledge was passed down from generation to generation in various parts of the world throughout its history and has significantly contributed to the development of different traditional systems of medicine. The use of plants as medicines has involved the isolation of active compounds, beginning with the isolation of morphine from opium in the early 19th century[2] and subsequently led to the isolation of early drugs such as cocaine, codeine, digitoxin and quinine, of which some are still in use[3,4]. Isolation and characterization of pharmacologically active compounds from medicinal plants continue today. More recently, drug discovery techniques have been applied to the standardization of herbal medicines, to elucidate analytical marker compounds.

It is estimated that around 250,000 flowering plant species are reported to occur globally. Approximately half (125,000) of these are found in the tropical forests. They continue to provide natural product chemists with invaluable compounds for development of new drugs. The potential for finding new compounds is enormous as till date only about 1% of tropical species have been studied for their pharmaceutical potential. The success of drug discovery from plants resulted principally in the development of anti-cancer and anti-bacterial agents. The success of anti-cancer drug development can be illustrated from the efforts of the National Cancer Institute (NCI), USA. In this effort, field explorations are largely guided by the so-called biodiversity or 'random' collection approach, with ethnobotanical or ethnopharmacological information playing a minimal or no role. NCI launched its effort in 1955, and for the period 1960–82, about 114,000 extracts from an estimated 35,000 plant samples (representing 12,000–13,000 species) collected mostly from temperate regions of the world had been screened against a number of tumour systems[5]. A wide variety of compound classes were isolated and characterized. Clinically significant cancer chemotherapeutic agents that emerged from this programme included paclitaxel (*Taxus brevifolia* Nutt. and other *Taxus* sp., Taxaceae), hycamptamine (topotecan), CPT-11 and 9-aminocamptothecin. The latter three compounds are semi-synthetic derivatives of camptothecin (*Camptotheca acuminata* Decne., Nyssaceae)[6]. The programme was extended from 1986 to 2004, with an emphasis on global plant collections and screening against tumour cell cultures.

Drug discovery from plants has evolved to include numerous interdisciplinary fields and various methods of analysis. The process typically begins with a botanist, ethnobotanist, ethnopharmacologist, or plant ecologist who collects and identifies the plants of interest. Collection may involve species with known biological activity for which active compound(s) have not been isolated or may involve taxa collected randomly for a large screening programme. It is necessary to respect the intellectual property rights of a given country where plants of interest are collected[7]. Phyto-

*For correspondence. (e-mail: sanjayjachak@niper.ac.in)

chemists (natural product chemists) prepare extracts from the plant materials, subject these extracts to biological screening in pharmacologically relevant assays, and commence the process of isolation and characterization of the active compound(s) through bioassay-directed fractionations. Molecular biology has become essential to medicinal plant drug discovery through the determination and implementation of appropriate screening assays directed towards physiologically relevant molecular targets.

Importance of medicinal plants in drug discovery

Numerous methods have been utilized to acquire compounds for drug discovery, including isolation from plants and other natural sources, synthetic chemistry, combinatorial chemistry and molecular modelling[8,9]. Despite the recent interest in molecular modelling, combinatorial chemistry and other synthetic chemistry techniques by pharmaceutical companies and funding organizations, natural products and particularly medicinal plants, remain an important source of new drugs, new drug leads and new chemical entities (NCEs). According to Newman *et al.*[10], 61% of the 877 small-molecule NCEs introduced as drugs worldwide during 1981–2002 was inspired by natural products. These include: natural products (6%), natural products derivatives (27%), synthetic compounds with natural products-derived pharmacophore (5%) and synthetic compounds designed from natural products (natural products mimic, 23%)[4,10]. Ten examples of successful drugs derived from plants (Figure 1) are briefly described here.

Arteether (**1**) is a potent anti-malarial drug and is derived from artemisinin, a sesquiterpene lactone isolated from *Artemisia annua* L. (Asteraceae), a plant used in traditional Chinese medicine[11,12]. Galanthamine (**2**) is a natural product discovered through an ethnobotanical lead and first isolated from *Galanthus woronowii* Losinsk. (Amaryllidaceae) in Russia. Galanthamine is approved for the treatment of Alzheimer's disease, slowing the process of neurological degeneration by inhibiting acetylcholine esterase as well as binding to and modulating the nicotinic acetylcholine receptor[13,14]. Tiotropium (**3**) has been released recently in the US for treatment of chronic obstructive pulmonary disease[15,16]. Tiotropium is an inhaled anticholinergic bronchodilator, based on ipratropium, a derivative of atropine, isolated from *Atropa belladonna* L. (Solanaceae) and other members of the Solanaceae family[17]. Morphine-6-glucuronide (**4**) is a metabolite of morphine from *Papaver somniferum* L. (Papaveraceae), reported as an alternative pain medication with fewer side effects than morphine[18]. Exatecan (**5**) is an analogue of camptothecin isolated from *Camptotheca acuminata* Decne. (Nyssaceae) and being developed as an anticancer agent[4,19]. Vinflunine (**6**) is a modification of vinblastine from *Catharanthus roseus* G. Don (Apocynaceae) for use as an anticancer agent with improved efficacy[20]. Compounds (**4–6**) all are in phase III clinical trials[21]. Thus, from these three examples, it is evident that modifications of existing natural products can lead to NCEs and possible drug leads, from medicinal plants. (+)-Calanolide A (**7**) is a dipyranocoumarin compound isolated from *Calophyllum lanigerum* var. *austrocoriaceum* (Whitmore) P.F. Stevens (Clusiaceae), a Malaysian rainforest tree[22,23]. (+)-Calanolide A is an anti-HIV drug with specific mechanism of action as a non-nucleoside reverse transcriptase inhibitor of type-1 HIV and is effective against AZT-resistant strains of HIV. It is currently undergoing phase II clinical trials[23,24]. Recently, (+)-calanolide A has been reported as an anti-tubercular agent. (+)-Calanolide A was consistently active (MIC 8–16 μg/ml) against drug-susceptible strains of *Mycobacterium tuberculosis*. Efficacy evaluations in macrophages revealed that (+)-calanolide A significantly inhibited intracellular replication of *M. tuberculosis* H37Rv at concentrations below the MIC observed *in vitro*. Preliminary mechanistic studies indicated that (+)-calanolide A rapidly inhibits RNA and DNA synthesis followed by inhibition of protein synthesis. (+)-Calanolide A and related pyranocoumarins represent the first class of compounds identified to possess antimycobacterial and antiretroviral activities and thus, a new pharmacophore for anti-TB activity[25].

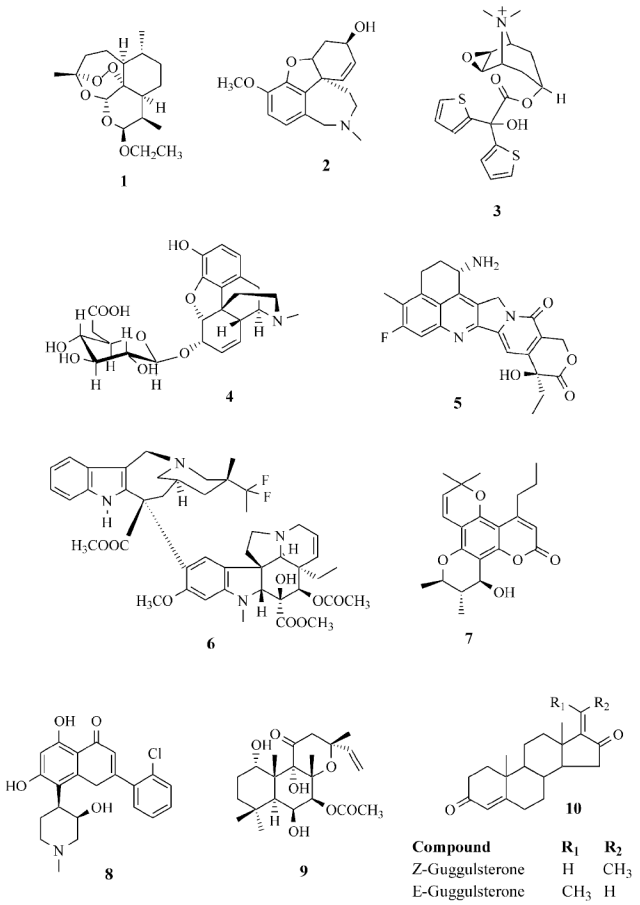

Figure 1. Chemical structures of plant-derived drugs.

The current emphasis of new drug discovery processes from plants is the development of products with new pharmacological modes of actions, apart from the known advantage of structural novelty. From India, three drugs qualify, i.e. flavopiridol (**8**), forskolin (**9**) and guggulsterone (**10**), on account of their modes of action. Flavopiridol is totally synthetic, but the basis of its novel flavonoid structure is a natural product, rohitukine. The latter isolated as the constituent responsible for anti-inflammatory and immunomodulatory activity from *Dysoxylum binectariferum* Hook. f. (Meliaceae), which is phylogenetically related to the Ayurvedic plant, *Dysoxylum malabaricum* Bedd., is used for rheumatoid arthritis. Flavopiridol was one of the over 100 analogues synthesized during structure–activity studies, and was found to possess tyrosine kinase activity and potent growth inhibitory activity against a series of breast and lung carcinoma cell lines[26]. It also showed broad-spectrum *in vivo* activity against human tumour xenografts in mice, which led to its selection for preclinical and clinical studies by the NCI in collaboration with Hoechst. It is currently in 18 phase I and phase II clinical trials, either alone or in combination with other anticancer agents, against a broad range of tumours, including leukaemias, lymphomas and solid tumours[27]. Forskolin, a labdane diterpenoid isolated from the Indian herb, *Coleus forskohlii* Briq., is a unique, potent, adenylate cyclase activator. In view of the cyclic AMP-dependent effects produced by forskolin, it was considered for development as an agent for the treatment of congestive cardiomyopathy, glaucoma and asthma. Later, several analogues were synthesized and structure–activity relationships developed. The semi-synthetic derivatives were approved for clinical use, mainly in the treatment of glaucoma[28]. The gum resin of *Commiphora mukul* (Stocks) Engl., commonly referred to as the Guggul tree, has been used in traditional Ayurvedic medicine for nearly 3000 years. It was reported to be effective in the treatment of several conditions, including obesity and disorders of lipid metabolism. An organic extract of this gum resin, referred to as gugulipid, has been approved for use in India since 1987 for the treatment of hyperlipidaemia. Studies of patients receiving this therapy and experiments with rodent models have demonstrated that gugulipid effectively lowers serum low-density lipoprotein and triglyceride levels[29]. Guggulsterone [4,17(20)-pregnadiene-3,16-dione], the active component of gugulipid, is largely responsible for antihyperlipidemic effects of this extract. The hepatic conversion of cholesterol to bile acids is an important mechanism for the elimination of excess dietary cholesterol. Bile acid biosynthesis and transport are regulated by the farnesoid X receptor (FXR), a member of the nuclear hormone receptor gene superfamily. Thus, therapeutic strategies that target FXR represent a promising new approach for the treatment of hypercholesterolaemia. It has been reported that guggulsterone is a highly efficacious antagonist of the FXR. Guggulsterone treatment decreases hepatic cholesterol in wild-type mice fed with a high-cholesterol diet, but is not effective in FXR-null mice. Thus, it was proposed that inhibition of FXR activation is the basis for the cholesterol-lowering activity of guggulsterone[30].

Challenges in drug discovery from medicinal plants

In spite of the success of drug discovery programmes from plants in the past 2–3 decades, future endeavours face many challenges. Natural products scientists and pharmaceutical industries will need to continuously improve the quality and quantity of compounds that enter the drug development phase to keep pace with other drug discovery efforts. The process of drug discovery has been estimated to take an average period of 10 years and cost more than 800 million dollars[31]. Much of this time and money is spent on the numerous leads that are discarded during the drug discovery process. It is estimated that only one in 5000 lead compounds will successfully advance through clinical trials and be approved for use. In the drug discovery process, lead identification is the first step (Figure 2). Lead optimization (involving medicinal and combinatorial chemistry), lead development (including pharmacology, toxicology, pharmacokinetics, ADME and drug delivery), and clinical trials all take considerable time.

Different approaches to drug discovery from plants can be enumerated as: random selection followed by chemical screening, random selection followed by one or more biological assays, follow-up of biological activity reports, follow-up of ethnomedical (traditional medicine) use of plants, use of appropriate plant parts as such in powdered form or preparation of enriched/standardized extracts (herbal product development), use of a plant product, biologically potent but beset with other issues, as a lead for

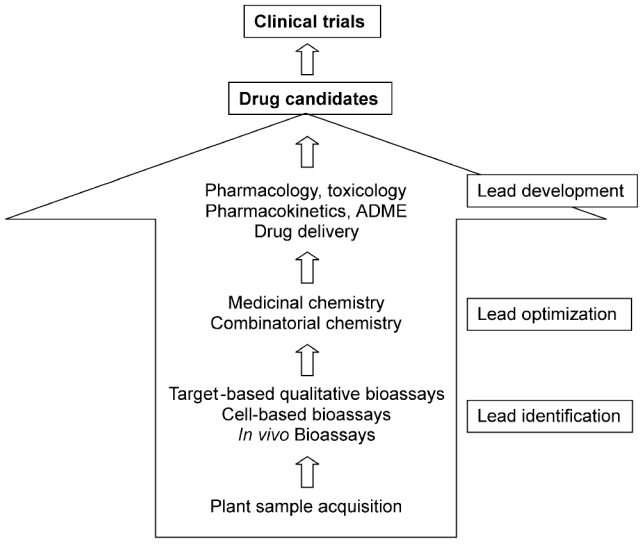

Figure 2. Drug discovery process from plants.

further chemistry, and single new compounds as drugs. The objective of the latter approach is the targetted isolation of new bioactive plant products, i.e. lead substances with novel structures and novel mechanisms of action. This approach has provided a few classical examples, but the problem most often encountered here is not enough availability. The problem of availability can be overcome by semi-synthesis/synthesis or using tissue-culture techniques (by genetically modifying the biosynthetic pathway of the compound of interest).

The approach of herbal drug development is associated with several problems. Crude herbs/plants (various plant parts and exudates) are mostly formulated as tablet and capsule, and to some extent as oral liquid preparations. These dosage forms are not successful due to problems encountered in absorption, therapeutic efficacy and poor compliance. Tablet or capsule dosage form requires powdering of crude herbs and particle size affects the process of blending, compression and filling. In addition, homogeneity is difficult to achieve due to the handling of large bulk quantities, high moisture content and inherent nature of raw materials (crude drug). Crude extracts are difficult to formulate in solid dosage forms due to their hygroscopic nature, poor solubility and stickiness.

As drug discovery from plants has traditionally been time-consuming, faster and better methodologies for plant collection, bioassay screening, compound isolation and compound development must be employed[32]. Innovative strategies to improve the process of plant collection are needed, especially with the legal and political issues surrounding benefit-sharing agreements[33,34]. The design, determination and implementation of appropriate, clinically relevant, high-throughput bioassays are difficult processes for all drug discovery programmes[35,36]. Although the design of high-throughput screening assays can be challenging[37], once a screening assay is in place, compound and extract libraries can be tested for biological activity. The common problem faced during screening of extracts is solubility and the screening of extract libraries is many times problematic, but new techniques including pre-fractionation of extracts can alleviate some of these issues[4,32]. Challenges in bioassay screening remain an important issue in the future of drug discovery from medicinal plants. The speed of active compound isolation can be increased using hyphenated techniques like LC-NMR and LC-MS. Development of drugs from lead compounds isolated from plants, faces unique challenges. Natural products, in general, are typically isolated in small quantities that are insufficient for lead optimization, lead development and clinical trials. Thus, there is a need to develop collaborations with synthetic and medicinal chemists to explore the possibilities of its semi-synthesis or total synthesis[9,38,39]. One can also improve the natural products compound development by creating natural products libraries that combine the features of natural products with combinatorial chemistry.

After considering all these issues, we would like to discuss the Indian scenario with respect to challenges in drug discovery from plants.

Indian scenario

India represented by rich culture, traditions and natural biodiversity, offers a unique opportunity for drug discovery researchers. This knowledge-based country is well recognized for its heritage of the world's most ancient traditional system of medicine, Ayurveda. Even, Dioscorides (who influenced Hippocrates) is thought to have taken many of his ideas from India[40]. We in India have two (Eastern Himalaya and the Western Ghats) of the 18 hotspots of plant biodiversity in the world. Interestingly, we are seventh among the 16 megadiverse countries, where 70% of the world's species occurs collectively. We are rich in our own flora, i.e. endemic plant species (5725 angiosperms, 10 gymnosperms, 193 pteridophytes, 678 bryophytes, 260 liverworts, 466 lichens, 3500 fungi and 1924 algae)[41]. Unfortunately, due to various reasons including inaccessibility of some tough terrains, only 65% flora of the country have been surveyed so far.

With the dwindling population of taxonomists and rare introduction of youngsters in this field, it might take another 20–30 years with the current pace to survey the complete flora of the country. Now the question before us is, could we assess the pharmaceutical potential of all the floristic components that we know? The answer is no. Realizing that we have approximately 17,500 species of higher plants, 64 gymnosperms, 1200 pteridophytes, 2850 bryophytes, 2021 lichens, 15,500 fungi and 6500 algae at our disposal, surprisingly, hardly a few institutions like Central Drug Research Institute, Lucknow with its concerted efforts could test a few plants and have published results on 3488 species of plants for limited indications in almost 28 years[42] between 1968 and 1996. This resulted into some promising leads that were later developed as drugs, viz. bacoside, the memory enhancer from *Bacopa monnieri* (L.) Penn.; picroliv, the hepatoprotective from *Picrorhiza kurroa* Benth., curcumin, the anti-inflammatory from *Curcuma domestica* Valeton, consap, the contraceptive cream from *Sapindus mukorossi* Gaertn., etc. Other CSIR laboratories and some private pharmaceutical companies have also made some efforts in this direction. However, assessing the pharmaceutical potential of our whole flora even for the important disease indications may take several decades. The reason could be the availability of source plant material, expertise to authenticate the taxa, developing enough suitable *in vitro* screens for all indications, reproducibility of results and so on. Whatever the case may be, can we afford to wait any longer to evaluate our flora for its medicinal efficacy?

The procedure for access to biological resources now is somewhat tedious. According to 'The Biological Diver-

sity Rules, 2003' of the Govt of India (notified on 24 March 2004), any person who is not a citizen of India (foreigner, non-resident Indian) or any foreign corporate, seeking approval of the Authority (National Biodiversity Authority – NBA) for access to biological resources and associated knowledge for research or for commercial utilization shall make an application in Form I as given in schedule. Every application shall be accompanied by a fee of Rs 10,000. The Authority on being satisfied with the merit of the application, may grant the approval as far as possible within a period of six months of receipt of the same. One has to specify each time the quantity to be collected of exact species, quantum of monetary and other incidental benefits and also guarantee to deposit a reference sample of the biological material sought to be accessed with the repositories identified and submitting to the Authority a regular status report of research and other developments[43]. However, according to the Biodiversity Act 2002, a citizen of India need not seek permission of NBA for the access of biodiversity, but one has to inform the respective State biodiversity boards for collection of plant material. As the process of plant-based drug discovery involves continuous collection of plant material from different places at various point of time, it is rather impractical to wait for obtaining permission each time. At the same time, the authorities cannot also give blanket permission for any collector. We have to find a way out. A lot of field experience and wide floristic knowledge is required if one wants to go for the random collection programme required for preliminary screening. Once found active, target plant collection in bulk quantity may be a problem due to its threatened status in some cases, or biomass and scattered distribution in others. Authentication of plant material is an important and most crucial factor in plant-based drug discovery. This needs to be supported by a set of suitable voucher specimens of the target species authenticated by a botanist and then deposited with a recognized herbarium. In the absence of vouchers, it is next to impossible to remember the location/phytogeographical conditions and time/season of collection of the exact plant material for repeat studies. Reproducibility of the results depends on various other factors too. Proper collection procedures need to be laid and documented. Collection practices should ensure long-term survival of wild populations and their associated habitats. Management plans for collection should provide a framework for setting sustainable harvest levels and describe appropriate collection practices that are suitable for each medicinal plant species and plant part used[44]. This should also include good field documentation, use of global positioning system to pinpoint site locations, mapping of sites and availability of good supporting databases. In case of tree or shrub species where root or bark is being used or found active, phytochemical and biological evaluation of leaves, twigs, stems, flowers and fruits must be done in order to ensure sustainable utilization of the plant. Potential herbs have an added advantage over others, as the bulk quantity and quality of target material can easily be assured through cultivation using Good Agricultural Practices (GAP) and Good Collection Practices (GCP).

Another important issue here is the pharmaceutical evaluation of rare or endangered species. According to the Govt of India notification (Notification No. 2(RE-98)/1997–2002), 29 taxa have been banned and the export of plants, plant portions and their derivatives and extracts obtained from the wild is prohibited[45]. These species, including other Red-listed threatened species, following the current IUCN norms, cannot be collected from the wild and in turn remain dead for science as far as their pharmaceutical potential is concerned. Interestingly, many of these species do find mention in our traditional Indian systems/tribal systems of medicine.

After collection, the drying procedures that vary for different plant materials, may alter the chemical properties of the material. The commonly employed drying procedures are sun- and/or shade-drying. Right kind of packaging procedures adopted in order to avoid fungal infection also need to be carefully worked out before transportation of material to the laboratory. Processing of plant materials mainly includes pulverization and then preparation of extracts. Various extracts such as hexane, chloroform, ethyl acetate, *n*-butanol and ethanol or 70% ethanol are generally prepared for chemoprofilings as well as for biological screening.

Opportunities

Bioprospecting demands a number of requirements which should be co-coordinated, such as team of scientific experts (from all the relevant interdisciplinary fields) along with expertise in a wide range of human endeavours, including international laws and legal understanding, social sciences, politics and anthropology. In the Indian context, Ayurveda and other traditional systems of medicine, rich genetic resources and associated ethnomedical knowledge are key components for sustainable bioprospecting and value-addition processes. For drug-targetted bioprospecting an industrial partner is needed, which will be instrumental in converting the discovery into a commercial product. Important in any bioprospecting is the drafting and signing of an agreement or Memorandum of Understanding that should cover issues on access to the genetic resources (biodiversity), on intellectual property related to discovery, on the sharing of benefits as part of the process (short term), and in the event of discovery and commercialization of a product (long term), as well as on the conservation of the biological resources for the future generations. When ethnobotanical or ethnopharmacological approach is utilized, additional specific requirements that relate to prior informed consent, recognition of Indige-

nous Intellectual Property and Indigenous Intellectual Property Rights as well as short- and long-term benefit sharing need to be taken into account[46,47].

In order to screen thousands of plant species at one go for as many bioassays as possible, we must have a collection of a large number of extracts. Globally, there is a need to build natural products extract libraries. The extract libraries offer various advantages, such as reduction in cost and time for repeat collection of plants and availability of properly encoded and preserved extracts in large numbers for biological screening in terms of high-throughput screenings and obtaining hits within a short period. In India, though some institutions have small plant extract libraries, they are not in public domain. The only information is available from Nicholas Piramal India Ltd. (NPIL), one of the major pharma players in India. NPIL has built up a plant extract library having 6000 extracts prepared from around 2300 plant species collected from all over India[48]. Such libraries could serve as a powerful tool and source of extracts to be screened for biological activities using high-throughput assays.

Glimpse of Indian initiatives on plant prospecting

Various government agencies like Department of Biotechnology (DBT), Council of Scientific and Industrial Research (CSIR) and Department of Ayurveda, Unani, Siddha and Homeopathy (AYUSH), Ministry of Health and Family Welfare have initiated efforts on bioprospecting. DBT initiated the network programme on 'Bioprospecting of biological wealth using biotechnological tools' during the 9th plan involving 13 institutions. The objectives of the DBT programme were characterization of biodiversity in different agro-ecological regions, bioresources mapping, inventorization and monitoring of biological diversity, characterization and conservation of Himalayan endangered species, including medicinal and aromatic plants, and bioprospecting of molecules and genes for product development. The leads obtained from the first phase of bioprospecting have been taken up for detailed investigation, with a focus on product and process development and commercialization.

CSIR has initiated a coordinated programme on drug discovery with a network of 19 CSIR laboratories and other R&D institutions working in the field of traditional medicines as well as universities. The programme was initiated in 1996, and aims at discovering new bioactive molecules from plants, fungi, microbes, insects, etc. using new technologies. The Planning Commission sponsored the New Millennium Indian Technology Leadership Initiative (NMITLI), one of the most innovative bioprospecting programmes. NMITLI started a major herbal drug development programme for developing effective herbal remedies for diabetes, arthritis and hepatic disorders, which has shown highly encouraging results within a short period of time.

The Ministry of Health and Family Welfare, Govt of India initiated two important task-force programmes relating to creation of Traditional Knowledge Digital Library and designing a Traditional Knowledge Resource Classification (TKRC). The TKRC has information on 5000 subgroups and the structure of TKRC is compatible with the International Patent Classification. TKRC will help enhance the quality of patent examinations by facilitating the patent examiners to access pertinent information on traditional knowledge in an appropriately classified form[49].

Conclusion

As evident from the above discussion, nature is the best combinatorial chemist and possibly has answers to all diseases of mankind. Till now, natural products compounds discovered from medicinal plants (and their analogues thereof) have provided numerous clinically useful drugs. In spite of the various challenges encountered in the medicinal plant-based drug discovery, natural products isolated from plants will still remain an essential component in the search for new medicines. The fact that only about one-tenth of the flowering species occurring globally are investigated for their pharmaceutical potential, can be the obvious advantage to begin with plant/medicinal plant-based drug discovery programmes. The diverse genetic resources and associated rich traditional knowledge available in India form the strong basis for bioprospecting. Proper utilization of these resources and tools in bioprospecting will certainly help in discovering novel lead molecules from plants by employing modern drug discovery techniques and the coordinated efforts of various disciplines.

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