International Journal of Pharmacy and Pharmaceutical Sciences, Vol. 1, Issue 1, July-Sep. 2009

Review Article

PLANTS IN TRADITIONAL MEDICINAL SYSTEM - FUTURE SOURCE OF NEW DRUGS

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ABSTRACT

The approach to new drugs through natural products has proved to be the single most successful strategy for the discovery of new drugs, but in recent years its use has been deemphasized by many pharmaceutical companies in favor of approaches based on combinatorial chemistry and genomics, among others. Again with rapid industrialization of the planet and the loss of ethnic culture and customs, some of the information on ethnomedicine will no doubt disappear. An abundance of ethnomedical information on plant uses can be found in scientific literature but has not yet been compiled into a usable form. Collection of ethnomedical information especially in the developing countries remains primarily an academic endeavour of little interest to most industrial groups. This article reviews some of the past successes of the natural products approach and also explores some of the reasons why it has fallen out of favor among major pharmaceutical companies and the challenges in drug discovery from Natural Products especially Higher Plants. In this review we consider the past, present, and future value of employing information from plants used in traditional medical practices (ethnomedicine) for the discovery of new bioactive compounds.

Keyword: Ethnomedicine, HTS, Bioprospecting, Prefractionation, Combinational chemistry

INTRODUCTION

Ayurveda is the most ancient health care system and is practiced widely in India, Srilanka and other countries[1]. Atharvveda (around 1200 BC), Charak Samhita and Sushrut Samhita (100 - 500 BC) are the main classics that given detailed descriptions of over 700 herbs [2]. In the western world documentation of use of Natural substances for medicinal purposes can be found as far back as 78 A.D., when Dioscorides wrote "De Materia Medica", describing thousands of medicinal plants[3]. This treatise included descriptions of many medicinal plants that remain important in modern

medicine, not because they continue to be used as crude drug preparations, but because they serve as the source of important pure chemicals that have become mainstays of modern therapy. The term "materia medica" which means "Medical Materials"[3] is no longer utilized routinely in Western medicine, the fact remains that the physicians of today continue to use many substances and products derived from natural sources, usually for the same therapeutic benefit as the crude drug. These single chemical entities, i.e., drugs, form the basis for much of our ability to control disease.

In recent times, there have been increased waves of interest in the field of Research in Natural Products Chemistry. This level of interest can be attributed to several factors, including unmet therapeutic needs, the remarkable diversity of both chemical structure and biological activities of naturally occurring secondary metabolites, the utility of novel bioactive natural products as biochemical probes, the development of novel and sensitive techniques to detect biologically active natural products, improved techniques to isolate, purify, and structurally characterize these active constituents, and advances in solving the demand for supply of complex natural products [4]. The R & D thrust in the pharmaceutical sector is focused on development of new innovative/indigenous plant based drugs through investigation of leads from the traditional system of medicine[5]. The World Heath Organization has also recognized the importance of traditional medicine and has created strategies, guidelines and standards for botanical medicines. Proven agro-industrial technologies need to be applied to the cultivation and processing of medicinal plants and the manufacture of herbal medicines [6].

Over the past decade, there has been a resurgence of interest in the investigation of natural materials as a source of potential drug substance. This review is not intended to be an exhaustive review of natural product-derived pharmaceuticals, but rather is aimed at highlighting the invaluable role that natural products have played, and continue to play, in the drug discovery process and its future perspectives.

Background and issues

Natural products have played an important role throughout the world in treating and preventing human diseases. Natural product medicines have come from various source materials including terrestrial plants, terrestrial microorganisms, marine organisms, and terrestrial vertebrates and invertebrates [7] and its importance in modern medicine

has been discussed in different reviews and reports[7-12].

The value of natural products in this regard can be assessed from: (i) the rate of introduction of new chemical entities of wide structural diversity, including serving as templates for semisynthetic and total synthetic modification, (ii) the number of diseases treated or prevented by these substances, and (iii) their frequency of use in the treatment of disease.

The large proportion of natural products in drug discovery has stemmed from the diverse structures and the intricate carbon skeletons of natural products. Since secondary metabolites from natural sources have been elaborated within living systems, they are often perceived as showing more "drug-likeness and biological friendliness than totally synthetic molecules,"[9] making them good candidates for drug development[11,13]. Analysis of the sources of new and approved drugs during the period 1981 to 2002 reveals that natural products play a highly significant role in the drug discovery and development process [12]. Review of all approved agents during the time frame of more than 25 years from 01/1981 to 06/2006 for all diseases worldwide and from 1950 (earliest so far identified) to 06/2006 for all approved antitumor drugs worldwide reveals the utility of natural products as sources of novel structures, but not necessarily the final drug entity, is still alive and well[14].

The development of high throughput screens based on molecular targets had led to a demand for the generation of large libraries of compounds to satisfy the enormous capacities of these screens and the shift away from large combinatorial libraries has continued, with the emphasis now being on small, focused (100 to ~ 3000) collections that contain much of the "structural aspects" of natural products[8]. Various names have been given to this process, including "Diversity Oriented Syntheses", preferably can be termed as "more natural product-like", in terms of their combinations of heteroatoms and significant numbers of chiral centers within a single molecule[15], or even "natural product mimics" if they happen to be direct competitive inhibitors of the natural substrate. It should also be pointed out that Lipinski's fifth rule effectively states that the first four rules do not apply to natural products or to any molecule that is recognized by an active transport system when considering "druggable chemical entities" [14].

Although combinatorial chemistry in one or more of its manifestations has been used as a discovery source for

approximately 70% of the period 01/1981 to 06/2006, only one new chemical entity (NCE) reported in the public domain as resulting from this method of chemical discovery and approved for drug use anywhere. This is the antitumor compound known as sorafenib from Bayer, approved by the FDA in 2005[14]. Proudfoot also reported that 8 out of 29 small molecule drugs launched in 2000 were derived from Natural Products or hormones and concluded that HTS did not have a significant impact on the derivation of these drugs [16]. Despite competition from other drug discovery methods, Natural Products are still providing their fair share of new clinical candidates and drugs and there is rapidly evolving recognition that a significant number of natural product drugs/leads are actually produced by microbes and/or microbial interactions with the "host from where it was isolated", and therefore this area of natural product research should be expanded significantly [14].

Importance of plants as a source of new drugs

The development of traditional medicinal systems incorporating plants as means of therapy can be traced back to the Middle Paleolithic age some 60,000 years ago as found from fossil studies[17]. In recent times, developed countries are turning to the use of traditional medicinal systems that involve the use of herbal drugs and remedies[18] and according to the World Health Organization (WHO), almost 65% of the world's population has incorporated the value of plants as a methodology of medicinal agents into their primary modality of health care[19].

It is often noted that 25% of all drugs prescribed today come from plants[20, 21]. This estimate suggests that plant-derived drugs make up a significant segment of natural product– based pharmaceuticals. Out of many families of secondary metabolites, or compounds on which the growth of a plant is not dependent, nitrogen-containing alkaloids have contributed the largest number of drugs to the modern pharmacopoeia, ranging in effects from anticholinergics (atropine) to analgesics (opium alkaloids) and from antiparasitics (quinine) to anticholinesterases (galantamine) to antineoplastics (vinblastine/vincristine) [22]. Although not as plentiful as alkaloids in the modern pharmacopoeia, terpenoids (including steroids) have made an equally important contribution to human health. They range from Na^+/K^+ pump-inhibiting cardiac glycosides from *Digitalis* spp.[23], to antineoplastic paclitaxel[24] to antimalarial artemisinin[25], to anti-inflammatory triptolide[26, 27]. It is

important to note that, the activity of some natural products has yet to be certified by extensive testing or clinical trials; as multicomponent botanical therapeutics (MCBTs). This overrepresentation of natural product–derived drugs begs the question of whether plant secondary metabolites and related synthetic compounds perform better as drugs than randomly synthesized compounds. Despite the increasing use of medicinal plants and their importance in drug discovery, their future, seemingly, is being threatened by complacency concerning their conservation. Reserves of herbs and stocks of medicinal plants in developing countries are diminishing and in danger of extinction as a result of growing industrialization.

The goals of using plants as sources of therapeutic agents are,

a) to isolate bioactive compounds for direct use as drugs, e.g., digoxin, digitoxin, morphine, reserpine, taxol, vinblastine, vincristine; *b*) to produce bioactive compounds of novel or known structures as lead compounds for semisynthesis to produce patentable entities of higher activity and/or lower toxicity, e.g., metformin, nabilone, oxycodon (and other narcotic analgesics), taxotere, teniposide, verapamil, and amiodarone, which are based, respectively, on galegine, morphine, taxol, podophyllotoxin, khellin, and khellin; *c*) to use agents as pharmacologic tools, e.g., lysergic acid diethylamide, mescaline, yohimbine; and *d*) to use the whole plant or part of it as a herbal remedy, e.g., cranberry, echinacea, feverfew, garlic, ginkgo biloba, St. John's wort, saw palmetto.

The number of higher plant species (angiosperms and gymnosperms) on this planet is estimated at 250,000[28], with a lower level at 215,000[29, 30] and an upper level as high as 500,000[31, 32] and only about 6% have been screened for biologic activity, and a reported 15% have been evaluated phytochemically[33]. With high throughput screening methods becoming more advanced and available, these numbers will change, but the primary discriminator in evaluating one plant species versus another is the matter of approach to finding leads. There are some broad starting points to selecting and obtaining plant material of potential therapeutic interest. However, the goals of such an endeavor are straightforward. Plants have an advantage in this area based on their long-term use by humans (often hundreds or thousands of years). One might expect any bioactive compounds obtained from such plants to have low human toxicity. Obviously, some of these plants may be toxic within

a given endemic culture that has no reporting system to document these effects. It is unlikely, however, that acute toxic effects following the use of a plant in these cultures would not be noticed, and the plant would then be used cautiously or not at all. Chronic toxic effects would be less likely to signal that the plant should not be used. In addition, chemical diversity of secondary plant metabolites those results from plant evolution may be equal or superior to that found in synthetic combinatorial chemical libraries.

Approaches of drug discovery from higher plants

Shaman Pharmaceuticals in South San Francisco, California is supposed to be the first company in United States to investigate plants through ethnomedical approach[34] and SP-303, an oligomeric proanthocyanidin[35] found in the process, was shown to be clinically efficacious and is currently marketed as a dietary supplement for diarrhea. In addition, a major effort was directed toward discovery of novel antidiabetic agents, which resulted in the discovery of several patented compounds: cryptolepine[36-38], maprouneacin[39], 3β,30-dihydroxylupen-20(29)-en-2-one[40], harunganin, vismin[41], and quinines SP18904 and SP18905[42]. The most interesting discovery was nordihydroguaiaretic acid (ndga)[43] which, besides being active orally in db/db diabetic mice, also lowered cholesterol levels.

Some examples of drugs from plants that served as models for the next generation of drugs are exemplified as follows: Khellin [from *Ammi visnaga* (L.) Lamk] was used as a bronchodilator in the United States until it was shown to produce nausea and vomiting after prolonged use. In 1955 a group of chemists in England set about to synthesize khellin analogs as potential bronchodilators with fewer side effects. This eventually led to the discovery of chromolyn (used as sodium chromoglycate), which stabilized cell membranes in the lungs to prevent the allergeninduced release of the substance ultimately causing bronchoconstriction in allergic asthma patients[44]. Further studies led to the synthesis of amiodarone, an useful antiarrythmia agent[44]. Papaverine, useful as a smooth muscle relaxant, provided the basic structure for verapamil, a drug used to treat hypertension[44]. Galegine was isolated as an active antihyperglycemic agent from the plant *Galega officinalis* L. used ethnomedically for the treatment of diabetes. Galegine provided the template for the synthesis of metformin and opened up interest in

the synthesis of other biguanidine-type antidiabetic drugs[44].

It is always difficult to assess the value of any approach to the use of higher plants to develop new drugs. Artuso has outlined the entire process: formulating an appropriate strategy, obtaining biologic extracts, screening those extracts, isolating active compounds, conducting preclinical tests and chemical modification, submitting an Investigational New Drug Application, performing clinical trials, submitting a New Drug Application, and beginning commercial production. According to his estimation the entire process would take 10–20 years or more[45]. As it is improbable that one could collect all the 250,000 higher plant species to screen for one or more biologic activities, and because the number of bioassays that one could screen these species for is unlimited, the species most likely to produce useful activity should be selected judiciously. In addition, the biologic targets must represent the activities that correlate best with the rationale for plant selection. It would appear that selection of plants based on long-term human use (ethnomedical) in conjunction with appropriate biologic assays that correlate with the ethnomedical uses would be most appropriate.

A number of reviews relating to approaches for selecting plants as candidates for drug discovery programs have been published[46,47-60] and these approaches can be briefly outlined as follows,

- Random selection followed by chemical screening
- Random selection followed by one or more biologic assays
- Follow-up of biologic activity reports
- Follow-up of ethnomedical (traditional medicine) uses of plants
- Use of databases

Challenges and opportunities

In spite of the success of different 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 approach of herbal drug development is associated with several problems.

- The advent of routine HTS has been one of the most important changes to the drug discovery process[61-63]. Screening of one hundred thousand samples in a

routine assay can now be completed in just over a week using 384-well formatting, a data handling system, and limited robotics. This screening time can be decreased further using higher density formats and advanced robotics[61,64,65]. Therefore, the number of compounds or extracts that can be screened for each drug target is generally not the rate-limiting step.

- The decision when to screen Natural Product extracts compared to compound libraries is extremely important for the successful integration of Natural Product hits into a lead discovery program. This is because no matter how quickly the active compounds can be isolated and their structures identified, there will always be a lag time behind the evaluation of pure compounds whose structure and method of synthesis is known at the onset. In fact, screening of Natural Product extracts well before a synthetic library would be preferable, but in practice this rarely, if ever, happens.
- The screening of Natural Product extract libraries is generally more problematic than screening compound libraries [61-63, 66-71]. This is because Natural Product extracts contain complex mixtures of mostly uncharacterized compounds, some of which have undesirable properties. An added complication is that interfering compounds may be present in the extract in addition to compounds of interest, which may mask the biological effect. Compounds or families of compounds also may be present in an extract, which can interfere with the screen in a nonspecific manner[72].
- Traditionally, crude extracts have been used for screening, but the extra screening capacity available from HTS has enabled the possibility of economically screening prefractionated extracts. The prefractionation process can produce fractions that can range from relatively crude fractions to mixtures of only a few compounds. The advent of sophisticated separation and analytical instruments has enabled some companies to assemble large libraries of pure Natural Products, which can then be

screened in a manner analogous to pure compound libraries[73-82]. The advantage of these libraries is that no further purification is generally required, which enables active compounds to be evaluated on an equivalent basis to synthetic compound libraries. The disadvantages are that it is a time-consuming process and minor active components may be missed using an isolation strategy based solely on peak collection. There is also a significant cost involved in preparation and screening of the extra fractions generated by prefractionation.

- Dereplication is the process of identifying known compounds that are responsible for the activity of an extract before bioassay-guided isolation has started[69, 83-86]. The dereplication process, which has been an ongoing concern in Natural Product chemistry since the beginning of antibiotic research, is used to eliminate, group, and/ or prioritize extracts for further study and can save considerable research time. The dereplication procedure also can be extended to group like-extracts that contain the same or similar unidentified compounds that are responsible for the biological activity. This grouping of extracts with like dereplication profiles significantly reduces the possibility of different chemists independently isolating and identifying the same active component.
- The bioassay guided fractionation procedure used to identify bioactive natural products is often perceived as rate limiting and resource intensive. However, the rapid improvement of instrumentation and robotics used to revolutionize other aspects of drug discovery can also be used to improve the speed of the isolation and structure elucidation of Natural Products. The advent of new probe technology [87] and higher magnetic fields has led to a significant shortening in acquisition time for NMR data, and the structure elucidation of Natural Products can be achieved routinely on amounts less than 1 mg. [88]. Progress has also been

made in automated structure solving algorithms [89-91], but presently none can rival the structure elucidation skills of an experienced Natural Product chemist. However, these programs can be a valuable tool to search for alternative structures that fit the same NMR data.

- The biggest obstacle to Natural Product chemistry is the continuous supply of large amounts of Natural Product required for further biological evaluation. The identification of a sustainable source of the Natural Product needs to be addressed if a semisynthesis or total synthesis is not available. This is not so much trouble if there is a microbial source of the compound. A systematic approach called OSMAC (one strain-many compounds) to increase the yield and diversity of compounds produced by microorganisms was proposed by Zeeck and co-workers[92], while advances are being achieved rapidly in the area of microbial combinatorial biosynthesis[93].
- 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 [94].

- Innovative strategies to improve the process of plant collection are needed, especially with the legal and political issues surrounding benefit-sharing agreements[95,96].
- The design, determination and implementation of appropriate, clinically relevant, high-throughput bioassays are difficult processes for all drug discovery programmes[96, 97]. Although the design of high-throughput screening assays can be challenging[98], 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[94, 100].
- To get appropriate compound from screeing of Natural Products is to design a complementary orthogonal assay or assays to remove as many false positive hits as possible. Dereplication can then be used to remove nuisance compounds or group like-extracts. Some other new screening methods[64] include the novel microarray compound screening (microARCS) technology, which utilizes agarose matrixes to introduce a majority of the reagents throughout the assay[101], and on-line biochemical detection coupled to mass spectrometry, which already has been used for the screening of natural products extracts[102].
- 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 LCNMR 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[103,104,105]. One can also improve the natural

products compound development by creating natural products libraries that combine the features of natural products with combinatorial chemistry.

- 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.

Future perspectives

Despite several problems, one cannot discount the past importance of plants as sources of structurally novel drugs and it provides a great opportunity to the scientists in the field of Natural Product Chemistry, Pharmacognosy, Pharmacology, Ethnobotany and other related fields of life science to come together and work in the direction of getting new drugs fro Natural Sources, especially from Plants for betterment of mankind.

- The importance of natural products in the future of drug discovery is clear: novel biologically active natural products will continue to serve as lead compounds for drug development and is biochemical probes for the discovery of pharmacological and biochemical process.
- Combining the strengths of the knowledge base of traditional systems such as ayurveda with the dramatic power of combinatorial chemistry and HTS will help in the generation of structure–activity libraries.
- Traditional knowledge and experiential database can provide new functional leads to reduce time, money and toxicity – the three main hurdles in drug development. These records are particularly valuable, since effectively these medicines have been tested for thousands of years on people[106].
- Bioprospecting demands a number of requirements which should be co-coordinated, such as team of scientific experts along with expertise in a wide range of human endeavours, including international laws and legal understanding, social sciences, politics and anthropology.
- 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-targeted 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 Indigenous Intellectual Property and Indigenous Intellectual Property Rights as well as short- and long-term benefit sharing need to be taken into account[107, 108].
- 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.
- Innovation and creativity regarding the molecular scaffolds will be substantially enhanced with the discovery of relatively simple, small molecular weight bioactive natural products. Combinatorial approach with a nucleus that is already known to possess exciting biological activity will increase the likelihood of creating interesting drug candidate. Similarly, mixing of genetic information encoding for specific secondary metabolites may produce “unnatural” natural products with specific therapeutic activity [109].

CONCLUSION

Ethnomedicine may be defined broadly as the use of plants by humans as medicines where as Traditional medicine is a broad term used to define any non-Western medical practice. Ethnopharmacology is a highly

diversified approach to drug discovery involving the observation, description, and experimental investigation of indigenous drugs and their biologic activities. It is based on botany, chemistry, biochemistry, pharmacology, and many other disciplines (anthropology, archaeology, history, and linguistics) that contribute to the discovery of natural products with biologic activity. As evident from the above discussion, nature is the best combinatorial chemist and 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. 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. Key factors to remain competitive with the modern system of medicine includes continual improvements in the speed of dereplication, isolation, structure elucidation, and compound supply processes and prudent selection of drug targets for the screening of Natural Product libraries.

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