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Bioprospecting of Phytodiversity for New Therapeutic Products:Trends, Potential and Challenges

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Abstract

Plants have remained the major source of medicines, nutrition and other health-care products since antiquity. In modern age, it is widely realized that scientific exploration of vast phytodiversity may provide many more effective therapeutic products for tackling challenging health problems. Researchers and pharmaceutical industries are gearing to discover hitherto unknown medicinal plants to develop new scientifically tested recipes for more effective treatment of specific illness for which no satisfactory cure is available to date. During the past few decades, prospecting of medicinal plant diversity has become the focal activity of several R&D and industrial sector across the world with the realization that it is likely to result in new lead discovery thus providing an extensive economic opportunity for pharmaceutical industries. Traditional knowledge yet confined among indigenous peoples has a crucial role in prospecting of phytodiversity. However, the future resource potential of phytodiversity and opportunities for bioprospecting industries will depend on many factors, ranging from the conservation status to the trends in a variety of markets. Therefore a well-regulated approach to phytodiversity prospecting is vital to achieve the joint goals of ecosystem conservation and social and economic development through partnerships and benefit-sharing. The paper discusses about potential, scope and challenges of phytodiversity prospecting.

Keywords: Phytodiversity; Indigenous knowledge; Bioprospecting; Therapeutic products; Industrial Trends; Benefit Sharing

Introduction

Probing biodiversity for new organic products of socioeconomic significance is termed as bioprospecting. Biodiversity encompass all organisms and species, their genetic distinction as well as their complex assemblages of communities and ecosystem diversity present on the earth. The concept, knowledge and mass awareness about the biological diversity is one of the most talked subjects of 21st century. Obviously, human survival is directly linked to its ambient diversity of nature. In contradiction to the fact that the biological resources of the world have been in use to the humanity since ages and thoroughly explored by ancient society, our knowledge of biodiversity is still very limited. Plant diversity as a global resource also remained poorly understood, inadequately documented and often wasted, but still possesses immense potential for further development of useful natural products [1].

With the burgeoning human population, the life support system of earth including plant resources are becoming increasingly threatened as the rate of global change accelerates [2]. It is now widely realized that scientific exploration of vast phytodiversity likely to yield many more useful products for an unexpectedly wide variety of human needs and pursuits. Flowering plants provide a wide variety of foods, drugs, cosmetics, fibers, and building materials. However, these constitute only a minor part of the total number of species on the Earth and vast resources remain are yet unexplored [3]. The importance of biodiversity exploration for new products was acknowledged during the meeting of International Society of Chemical Ecology in Goteborg, Sweden, in the Goteborg Resolution 1990 [4].

In fact plants and plant products are attributed to array of pharmacological efficacies in other to other biological activities. Now-a-days, in contrast to the synthetics which are considered as hazardous and unsafe to environment and human health, plant derived products represent safety and environment-affability. This has necessitated prospecting of botanical resources for exploring safe and effective remedies for human ailments. Bioprospecting of plants for therapeutic products

involves the use of a wide variety of species by industries [5]. Pharmaceutical companies use indigenous knowledge as a precursor to screening.

Indigenous peoples across the world possess a vast store of knowledge about the properties of many native plants. So far, the resource values of a plant species are measured either in term of the plant itself that provides the product or the derived products that serves as a model for a modification, imitation or otherwise. Discovery is often achieved by considering where the desired product might have evolved naturally. Habitats or a group of species are then identified and explored. Further, combinatorial chemistry and rational drug design are modern approaches for drug discovery. While these have been developed independently of natural products, current thought is that natural products are likely to provide the best lead-molecules in the future [6].

Prospecting Phytodiversity

Many drugs of modern medicine have had their origin in traditional medicine. Last few decades have witnessed a renewed interest in herbal medicines globally. In recent years, the increasing demand for herbal medicines is being fueled by a growing consumer interest in natural products [7,8]. Based on the knowledge that many important drugs, such as aspirin were derived from natural products [9], the industries have at various times invested heavily in the exploration of wild plants in search of commercially profitable pharmaceuticals [10,11]. Some common examples include the discovery of anti-malarial drug quinine from *Cinchona* sp. alkaloid Diosgenin from *Dioscorea deltoidea* used as source for the partial synthesis of cortisone and steroid hormones, hypertensive alkaloid Reserpine from *Rauvolfia serpentina* and the analgesic alkaloid aspirin from *Filipendula ulmaria*, anti-asthmatic alkaloid ephedrine from *Ephedra sinica* and anti-cancer alkaloid Podophyllotoxin from *Podophyllum hexandrum*, to mention a few [12]. In addition, a number of new, small molecules, no synthetic chemical entities developed for cancer research are derived from natural products. In ant hypersensitive drug research, 65% of drugs currently synthesized can be traced to natural structures [13]. This emphasizes the important role of many natural products as blueprints rather than the actual end points. Today, a significant number of plant derived pure chemical substances are used in the modern pharmacopoeias throughout the world (Table 1).

Table 1: Important plant-derived drugs used in modern medicine

S.No.	Plant Drugs	Therapeutic Value	Source Plants	Family
1.	Ajmalicin	Antihypertensive, Tranquilizer	*Rauvolfia serpentina*	Apocynaceae
2.	Ajmalin	Antihypertensive, Heart arrhythmia, Tranquilizer	*Rauvolfia serpentina*	Apocynaceae
3.	Aspirin	Analgesic, Anti-inflammatory	*Filipendula ulmaria*	Apocynaceae
4.	Artemisia	Antimalarial	*Artemisia annua*	Asteraceae
5.	Atropine	Ophthalmologic	*Atropa belladonna*	Solanaceae
6.	Benzene	Oral disinfectant	*Styrax tonkinensis*	Styracaceae
7.	Caffeine	Stimulant	*Camellia sinensis*	Thecae
8.	Camphor	Rheumatic pain	*Cinnamomum camphora*	Lauraceous
9.	Cascara	Purgative	*Rhamnus purshiana*	Rhamnaceae
10.	Cocaine	Ophthalmologic, Anaesthetic	*Erythroxylum coca*	Erythroxylaceae
11.	Codeine	Analgesic, Antitussive	*Papaver somniferum*	Papaveraceae
12.	Colchicines	Gout	*Colchicum autumnale*	Liliaceous
13.	Demecolcine	Leukemia	*Colchicum autumnale*	Liliaceous
14.	Deserpidine	Hypertension	*Rauvolfia canescens* *Rauvolfia serpentina*	Apocynaceae
15.	Dicoumarol	Thrombosis	*Mililotus officinal*	Fabaceae
16.	Digitoxin	Atrial fibrillation	*Digitalis purpurea*	Scrophulariaceae
17.	Digoxin	Atrial fibrillation	*Digitalis purpurea*	Scrophulariaceae
18.	Digoxin	Cardiotonic	*Digitalis lanata*	Scrophulariaceae
19.	Diosgenin	Induces sterilization	*Dioscorea deltoidea*	Dioscoreaceae
20.	Emetine	Antiamoebic	*Psychotria ipecacuanha*	Rubiaceae
21.	Emetine	Amoebic dysentery	*Cephaelis ipecachuanha*	Rubiaceae
22.	Ephedrine	Bronchodilator	*Ephedra sinica*	Ephedraceae
23.	Eugenol	Toothache	*Syzygium aromaticum*	Myrtaceae
24.	Gallotanins	Hemorrhoid suppository	*Hamamelis virginiana*	Hamamelidaceae
25.	Gossypol	Male contraceptive	*Gossypium herbaceous*	Malvaceae

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26.	Hyoscyamine	Ant cholinergic	*Atropa belladonna* *Datura stramonium* *Hyoscyamus muticus* *Hyoscyamus niger*	Solanaceae
27.	Ipecac	Emetic	*Cephaelis ipecacuanha*	Rubiaceae
28.	Ipratropium	Bronchodilator	*Hyoscyamus niger*	Solanaceae
29.	Khellin	Vascodilator	*Ammi visnaga*	Apiaceae
30.	L-DOPA	Antiparkinsonian	*Mucuna pruriens*	Papilionaceae
31.	Marsilin	Sedative, anticonvulsant	*Marsilea minuta*	Marsileaceae
32.	Morphine	Analgesic	*Papaver somniferum*	Papaveraceae
33.	Noscapine	Antitussive	*Papaver somniferum*	Papaveraceae
34.	Papain	Attenuates mucus	*Carica papaya*	Caricaceae
35.	Papaverine	Antispasmodic	*Papaver somniferum*	Papaveraceae
36.	Physotigmine	Glaucoma	*Physostigma venenosum*	Fabaceae
37.	Picrotixon	Barbiturate antidote	*Anamirta cocculus*	Menispermaceae
38.	Pilocarpine	Glaucoma	*Pilocarpus jaborandi*	Rutaceae
39.	Podophyllotoxin	Vermifuge, Cancer	*Podophyllum hexandrum* *Podophyllum peltatum*	Berberidaceae
40.	Proscillaridin	Cardiac malfunction	*Drimia maritime*	Liliaceous
41.	Protoveratrine	Hypertension	*Veratrum album*	Liliaceous
42.	Pseudoephedrine	CNS stimulant, Rhinitis	*Ephedra sinica*	Ephedraceae
43.	Psoralen	Vitiligo	*Psoralea corylifolia*	Fabaceae
44.	Quinidine	Cardiac arrhythmia	*Cinchona pubescens*	Rubiaceae
45.	Quinine	Malaria prophylaxis	*Cinchona pubescens*	Rubiaceae
46.	Rescinnamine Reserpine	Hypertension	*Rauvolfia canescens* *Rauvolfia serpentina*	Apocynaceae
47.	Rutine	Decreases capillary fragility	*Ruta graveolens*	Rutaceae
48.	Sennoside-A& B	Laxative	*Cassia angustifolia*	Caesalpiniaceous
49.	Scopolamine	Motion sickness	*Datura stramonium*	Solanaceae
50.	Stigmasterol	Steroidal precursor	*Physostigma venenosum*	Fabaceae
51.	Strophanthin	Congestive heart failure	*Strophanthus gratus*	Apocynaceae
52.	Taxol	Ovarian & Breast cancer	*Taxus brevifolia* *Taxus wallichiana*	Taxaceae
53.	Teniposide	Bladder neoplasms	*Podophyllum hexandrum* *Podophyllum peltatum*	Berberidaceae
54.	THC	Antiemetic	*Cannabis sativa*	Cannabinaceae
55.	Theobromine	Diuretic, myocardial stimulant, vasodilator	*Camellia sinensis*	Thecae
56.	Theophylline	Cardiac stimulant vasodilator, smooth muscle relaxant	*Camellia sinensis*	Thecae
57.	Theophylline	Diuretic, asthma	*Camellia sinensis*	Thecae
58.	Toxiferine	Surgery, relaxant	*Strychnos guianensis*	Loganiaceous
59.	Tubocurarine	Muscle relaxant	*Chondrodendron tomentosum*	Menispermaceae
60.	Vinblastine	Hodgkin's disease	*Catharanthus roseus*	Apocynaceae
61.	Vincristine	Pediatric leukemia	*Catharanthus roseus*	Apocynaceae
62.	Xanthotoxin	Vitiligo	*Ammi majus*	Apiaceae

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The conventional process of drug discovery has several distinct and increasingly expensive stages like procurement of authentic plant material; extraction of the active compounds; primary screening against a range of human disease organisms; isolation and chemical characterization of the active compounds; secondary screening assaying the compounds on experimental animals; structural chemistry and synthesis; pre-clinical development with a view to human trials; and clinical development, marketing and distribution. Furthermore, owing to low hit rates from natural product exploration and consequent high risks of natural product investment coupled with advances in high throughput instrumentation, some big pharmaceutical companies primarily invest in rational drug design and combinatorial chemistry [14,15] rather than natural products. On the other hand, natural product bioprospecting remained as the main activity of a variety of active small companies that sell their products to the larger ones that can afford the massive costs of drug development. Some contemporary researchers believe that natural product research is more likely to result in new lead discovery and that the great advantage of combinatorial chemistry is its capacity to take advantage of such leads [6,7].

Role of Traditional Knowledge

Plants have been the only source of medicine to the indigenous people across the world's civilizations, who possess very rich repository of traditional/folk knowledge about the therapeutic uses of medicinal plants available in their vicinity. Ethno botanical studies list a large number of plant species used medicinally [16-18]. Historically, much corporate drug discovery depended on indigenous knowledge delivered to modern science through ethno botany [19]. The ethno botanical approach to drug discovery is more likely to succeed where people have lived in the same area over many generations and so have had more time to discover suitable medicines.

A number of plant-derived medicines used in the western world were originally discovered by studying indigenous medicine [20]. For example, the analgesic and antipyretic drug Aspirin was first isolated from *Filipendula ulmaria* because it had long been used in European folk medicine to treat pain and fevers. Drugs for heart ailments named Digitoxin and dioxin were derived from *Digitalis purpurea*, leaves of which were first used in European folk cure to treat congestive heart failure. Quinine obtained from the bark of Cinchona tree has been the single most effective cure for malaria. More recently, the drugs Vincristine and Vinblastine were discovered in the rosy periwinkle (*Catharanthus roseus*) from Madagascar. Vincristine is given to children with leukemia and Vinblastine has cured many people with Hodgkin's disease. Two important drugs have been derived from Mayapple (*Podophyllum peltatum*) used by Native Americans to treat warts; Teniposide to treat bladder cancer and Podophyllotoxin, from which a powerful anti-tumor agent has been synthesized [21,22]. Over 50% of modern prescription medicines were originally discovered in plants, and plants continue to be the source of significant therapeutic compounds [23,24]. Alarming levels of antibiotic resistance in many human pathogens has led to increased herbal bioprospecting, a vital source of lead drug discovery [25,26]. Personal care and cosmetics industries use wild harvested or cultivated products in a wide variety of products, including cosmetics, hygiene, hair care, baby care, nail care, oral hygiene, deodorants, skin care, and fragrance products.

The World Health Organization estimates that some 3.5 billion people in the developing world depend mainly on plants for their primary health care. The development of botanical medicines for local peoples is therefore an important contemporary area of research [27]. Many countries, such as Thailand, India, Sri Lanka, Mexico, and China, have integrated traditional medicine into their national health care systems. Ethno botanical bioprospecting has therefore contributed both to the enhancement of local medicine and to the search for modern drugs.

Resource Distribution and Valuation

Long history of use of phytodiversity by humanity together with the more recent history of bioprospecting shows that important commercial species have been found in all parts of the world. Indeed, it appears impossible to predict in which ecosystems and therefore in which countries future products will be found. At this point it is reasonable to say that bioprospecting will be more profitable in species-rich areas of the world, particularly the sub-tropical and tropical forest areas [28]. However, many biological resources have been derived from non-tropical areas, including some critical medicines such as aspirin and the drugs derived from the plant genera *Digitalis, Podophyllum*, and the Pacific Yew tree *Taxus brevifolia*, all of which are from temperate zones.

Recent pharmaceutical bioprospecting has been largely focused on species-rich ecosystems, especially tropical rain forests. Certainly, if the goal is to screen as many species as possible in the most cost-effective way, the use of species-rich ecosystems such as rain forests appears logical [29]. However, according to evolutionary theory herbivore, especially by insects is far more intense in the tropics than in the temperate zones. Therefore, plant chemical defenses against herbivore are likely to be both stronger and more diverse in ecosystems such as tropical rain forests and this may make some pharmaceutical bioprospecting more profitable in tropical than in temperate forests [30].

Many areas of modern bioprospecting are even more target-orientated where the desired product is most likely to have evolved. Certain kinds of biological resources emerge as being more frequent in species-rich ecosystems and the current expectation is still that novel drugs are more likely to come from the tropics [31]. Bioprospecting activities are valuable in several other ways, not least providing education and training, employment, and local and regional sources of revenues based on the harvesting, processing, manufacturing, distribution, and retailing of products [32]. The wide variety of products, especially

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drugs that have been derived from ecosystems, may suggest that there are likely to be many more awaiting discoveries and therefore floral diversity is a vast source of future economic development.

Recent Industrial Trends

Most novel products are researched, developed and produced in industrial countries, and there is a geographical mismatch between centers of biodiversity, which tend to be in the tropics, and centers of research and development, which are largely concentrated in the temperate zones [33]. In recent years, several laboratories and some small companies, located in different parts of the world, have applied natural history knowledge and ecological and evolutionary criteria and theory to increase lead discovery. While much pharmaceutical bioprospecting is still controlled by companies in industrial countries, there is a significant pharmaceutical industrial base emerging in developing ones as well [34]. The pace of discovery of pharmacologically useful constituents has been shown to be higher today from marine and microbial sources than from the historically important plant kingdom, including tropical forests.

Benefit Sharing

The issues including development of the drug, the fate of the indigenous intellectual property, benefit sharing and the creation of partnerships within diverse bioprospecting industries has been complex. The Convention on Biological Diversity (CBD) calls for fair and equitable sharing of benefits arising out of the utilization of genetic resources, including appropriate access to genetic resources. The application of the CBD has supported the intellectual rights of indigenous peoples. Since many legal issues were largely clarified in the CBD, the protection of the rights of indigenous communities and source countries has often created tensions, with the investment sector concerned with altered levels of returns and profitability [35].

The chain of events leading to sales frequently involves multiple stages that include generating the appropriate knowledge, harvesting, processing, manufacturing, and distribution. Accordingly, the economics of each stage vary greatly, and assigning and protecting intellectual property is often an underlying factor. The types of benefits are varied that may include benefits to society such as increased production, better health and cleaner environments; benefits to the local suppliers such as employment, training, and capacity-building, and benefits to local, regional, national, or international corporations in the form of profits [36]. Most current partnerships also emphasize the benefits of biodiversity conservation.

Although bioprospecting research and development tends are concentrated in industrial countries, the benefits to human well-being are often global [37]. The principles for the treatment of intellectual property are well established and include protection of inventions using patents or other legal mechanisms; clear designation of the rights and responsibilities of all partners; sharing of benefits with the appropriate source-country parties; disclosure and consent of indigenous or other local stewards; information flow that balances proprietary, collaborative, and public needs; and respect for and compliance with relevant national and international laws, conventions, and other standards [38]. There is potential conflict between the routine scientific documentation of traditional medicines and the protection of indigenous intellectual property.

However, some organizations are considering whether indigenous knowledge in the public domain might be protected in some way. The CBD provides guidance on these issues and calls for a fair and equitable sharing of benefits with indigenous peoples when their ethno botanical knowledge is used in drug research and development. At the global scale, the CBD provides guidelines with respect to terms for prior informed consent and mutually agreed terms; the roles, responsibilities, and participation of stakeholders; aspects relating to *in-situ* and *ex-situ* conservation and sustainable use; mechanisms for benefit-sharing, such as through technology transfer and joint research and development; and the means to ensure the respect, preservation, and maintenance of knowledge, innovations, and practices of indigenous and local communities embodying traditional lifestyles relevant to the conservation and sustainable use of biological diversity, taking into account the work by the World Intellectual Property Organization.

Conclusion

Phototherapy is rapidly gaining importance throughout the world and use of medicinal plants/products in modern medicine systems are gaining worldwide acceptance. These drugs are preferred over the synthetic drugs due to their natural affinity that allows total assimilation of a wide range of essential elements, developed by the growth organs of plants that are indispensable to human life. New commercial organizations gearing to discover hitherto unknown medicinal plants adding to the information to elaborate new scientifically tested recipes for the more effective treatment of specific illness. In spite of the development of a number of modern drugs, there is still genuine need to develop new therapeutic agents especially for the diseases like viral infections, liver diseases, diabetes, cancer and AIDS for which no satisfactory cure is available to date.

Plant products represent the most important source of unique chemical substances for evaluation with new assaying strategies for potential plant-based pharmaceutical applications. Rapidly diminishing biological diversity of the earth is also fostering a renewal of interest in natural products research. The loss of biodiversity, in turn, the loss of the chemical diversity and globalization of the world's economy are the important stimulus in this context. Plant derived natural products hold great promise for discovery and development of high value chemicals e.g. new generation of drugs, nutraceuticals and other healthcare products. Careful consideration of the entire R&D process and issues like conservation, bioprospecting, benefit-sharing, etc

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would be required to realize this great promise effectively.

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