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REVIEW ARTICLE

Future Prospects and Aspects of Herbal Drug Discovery in Herbal Medicines

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ABSTRACT:

Herbal drugs constitute a major share of all the officially recognised systems of health in India *viz*. Ayurveda, Yoga, Unani, Siddha, Homeopathy and Naturopathy, except Allopathy. More than 70% of India's 1.1 billion population still use these non-allopathic systems of medicine. There has been an increase demand for the pharmaceutical products of Ayurveda in all over the world because of fact that the allopathic drugs have a side effect. In the present context the Ayurvedic system of medicine is widely accepted and practiced by peoples no only in India but also in the developed countries- such as Europe, USA, Japan, China, Canada etc. Plant based therapy are marked due to its low cost, easy availability based on generation to generation knowledge. The aim of the present review was to understand the knowledge of herbal medicines in respect to its development, herbal wealth, demand in market, aspects of herbal drug discovery, prospects in herbal medicines, promotion and Ethnopharmacological approach to herbal drugs.

1. INTRODUCTION:

Man's existence on this earth has been made possible only because of the vital role played by plant kingdom. Nature always stands as golden mark to amplify the outstanding phenomenon of symbiosis. Medicinal plants existing even before human being made their appearance on the earth[1].

Traditional medicine using herbal drugs exists in every part of the world. The major areas are Chinese, Indian and European traditions. The philosophies of these traditional medicines have some resemblance to each other but differ widely from modern Western medicine. In view of the progress of Western medicine not only new synthetic drugs but also herbal drugs have to fulfill the international requirements on quality, safety and efficacy. Herbal drugs have the advantage of being available for patients in the geographical area of the special traditional medicine. The development procedure of herbal drugs for world-wide use has to be different from that of synthetic drugs[2].

Practically every country develops its own medical system, which includes the ancient civilization of China, Egypt and India. Thus, the Indian Medical System-Ayurveda came into existence. The raw materials for Ayurvedic medicines were mostly obtained from plant sources in the form of crude drugs such as dried herbal powders or their extracts or mixture of products[3]. Also, Siddha, Unani and Tibb are traditional health care systems have been flourishing for many centuries. Apart from these systems there has been a rich heritage of ethnobotanical usage of herbs by various colorful tribal communities in the country[4].

Vast ethnobotanical knowledge exists in India from ancient time. Our work over four decades, both in the field and literary studies, has resulted in a dictionary of

Indian folk-medicine and ethnobotany that includes 2532 plants. India has about 45,000 plant species; medicinal properties have been assigned to several thousand. About 2000 figure frequently in the literature; indigenous systems commonly employ 500. Despite early (4500-1500 BC) origins and a long history of usage, in the last two centuries Ayurveda has received little official support and hence less attention from good medical practitioners and researchers. Much work is now being done on the botany, pharmacognosy, chemistry, pharmacology and biotechnology of herbal drugs. The value of ethnomedicine has been realized; work is being done on psychoactive plants, household remedies and plants sold by street drug vendors. Statistical methods are being used to assess the credibility of claims. Some recent work in drug development relates to species of *Commiphora* (used as a hypolipidaemic agent), *Picrorhiza* (which is hepatoprotective), Bacopa (used as a brain tonic), *Curcuma* (anti-inflammatory) and *Asclepias* (cardiotonic). A scrutiny of folk claims found 203 plants for evaluation. Less well known ethnomedicines have been identified that are used to treat intestinal, joint, liver and skin diseases[5]. Routine random efforts are not likely to increase the desired success rate of discovery, while experience indicates that a modified collection policy offers the best chances for the discovery and development of agents for the treatment of AIDS (acquired immune deficiency syndrome) and cancer[6].

Searching for new biologically active compounds from natural sources starts, obviously, in the field. Plant, microbial or animal materials to be sought and investigated may be selected through a number of approaches. No matter what selection criterion (a) is (are) used, the first step in obtaining the organism concerned is to undertake field collecting work to search for and to collect the organism. Good knowledge on the ecogeographic distribution and precision in the taxonomic identification of the organism(s) sought are crucial if the field work involves the search for a pre-determined organism or set of organisms. Such knowledge and precision during field work are of secondary importance, however, if the search and collection are based on biodiversity or ethnomedical uses, since accurate taxonomic identification may be made at a later date, in a Museum or Herbarium environment[7].

If we do well for a moment on our hoary past, Rigveda, one of our oldest repositories of human knowledge written between 4,500-1,500 B.C. mentions the use of 67 plants for the therapeutic purposes and Yajurveda enlists 81 plants whereas Atharvaveda written somewhere 1,200 B.C. describes 290 plants.

India unquestionably occupies the top position in the use of herbal drugs. It is one of the foremost countries exporting plant drugs or their derivatives and excels in home consumption too. According to Indian mythology, when the illness and diseases got rampant on the earth, the sages learnt the science of healing from Lord Indra and recorded them in scriptures[8].

It has been estimated that about 75,000 species of higher plants exist on the earth. A reasonable estimate of about 10% has been used in traditional medicine. However, perhaps only about 1% of these are acknowledged through scientific studies to have therapeutic value when used in extract form by human[9].

Traditional healers and pharmacists in developing countries are in important source of information about plant sources of new drugs. Only a fraction of the earth's natural pharmacopoeia has been analyzed with modern techniques. The threat of imminent extinction of many plant species, especially in tropical areas, makes it urgent that scientists learn as much as possible before old remedies are forgotten or their raw materials are destroyed. This process requires the observation and recording of medical techniques, identification of plant materials and experimental investigation of the ingredients and their effects. Ethnopharmacology can also be an important element of a developing nation's medical and economic system. Third World governments are being encouraged to seek a synthesis between modern and traditional medicine. Although developing countries are providing many of the raw materials needed in drug manufacturing, the final products are often returned as high-priced medicines. As more plants are needed for large-scale production, over harvesting has led to stock depletion. Chemists have so far been unable to reproduce the complex structure of many plant compounds. Further coordinated research into folk traditions, plant species, growing conditions and local medical needs is urged. Care must be taken, however, to preserve the main advantages of traditional medical care: low cost and easy access[10].

Many higher plants produce economically important organic compounds such as oils, resins, tannins, natural rubber, gums, waxes, dyes, flavors and fragrances, pharmaceuticals and pesticides. However, most species of higher plants have never been described, much less surveyed for chemical or biologically active constituents and new sources of commercially valuable materials remain to be discovered. Advances in biotechnology, particularly methods for culturing plant cells and tissues, should provide new means for the commercial processing of even rare plants and the chemicals they produce. These new technologies will extend and enhance the usefulness of plants as renewable resources

of valuable chemicals. In the future, biologically active plant-derived chemicals can be expected to play an increasingly significant role in the commercial development of new products for regulating plant growth and for insect and weed control[11].

Natural products have served as a major source of drugs for centuries and about half of the pharmaceuticals in use today are derived from natural products. Interest in natural products research is strong and can be attributed to several factors, including unmet therapeutic needs, the remarkable diversity of both chemical structures and biological activities of naturally occurring secondary metabolites, the utility of bioactive natural products as biochemical and molecular 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. Opportunities for multidisciplinary research that joins the forces of natural products chemistry, molecular and cellular biology, synthetic and analytical chemistry, biochemistry and pharmacology to exploit the vast diversity of chemical structures and biological activities of natural products[12]. Special attention is paid to the present role of natural products in therapy: as biologically active compounds as such, as starting materials for (semi)synthetic drugs and, last but not least, as source of inspiration or as models for the synthesis of new drugs with better therapeutic, chemical or physical properties than the original compounds[13].

2. HERBAL WEALTH OF INDIA:[14]

Now-a-days natural products are an integral part of human health care system, because there is popular concern over toxicity and resistance of modern drugs. India is one of the 12 leading biodiversity centers with presence of over 45,000 different plant species, 15000-18000 flowering plants, 23,000 fungi, 16,000 lichens, 18,000 bryophytes and 13 million marine organisms. From this flora, 15,000 to 20,000 have good medicinal value. Among those only about 7,000 plants are used in Ayurveda, 600 in Siddha, 700 in Unani and 30 in modern medicines.

3. HERBAL DRUG MARKET:[14]

The global herbal products market is worth of US $32 billion and is growing at a rate of about 9-15%. The average turnover of Indian herbal medicine industry is about 2,300 crore rupees. However, to achieve the goal of major exporter of herbal remedies, several steps need to be taken.

- Systematic study of world market demand and short listing of medicinal herbs with good potential.
- Systematic cultivation of medicinal herbs on a large scale.
- Encouragement for agro-based photochemical and pharmaceutical industries to manufacture value added herbal products.
- Strict legislation to control quality and purity.
- Upgradation of cultivation and collection process.
- Documentation of research work and standardization for quality.

4. STEPS NECESSARY FOR PROMOTING HERBAL DRUGS:[15]

Phytochemistry or natural product chemistry research is the backbone of herbal industry. For promoting use of herbals in modern medicine, phytochemistry should be envisaged for:

- Isolation, purification and characterization of new phytoconstituents.
- Use of newly isolated phytoconstituents as “lead” compound for the synthetic design of analogues with either improved therapeutic activity or reduced toxicity.
- Conservation of lead phytoconstituents into medicinally important drugs.

5. ETHNOPHARMACOLOGICAL APPROACH TO HERBAL DRUGS[16]

The term ethno-pharmacology refers the interdisciplinary scientific observation, description and experimental investigation of indigenous drugs and biological activities. There are 9 drugs of known structure that are still extracted from higher plants and used globally in allopathic medicine. About 74% of these were discovered by chemists who were attempting to identify the chemical substances in the plants that were responsible for their medical uses by humans. These 9 plant-derived drugs are produced commercially from less than 90 species of higher plants. Since there are at least 250,000 species of higher plants on earth, it is logical to presume that many more useful drugs will be found in the plant kingdom if the search for these entities is carried out in a logical and systematic manner. The first and most important stage in a drug development programme, using plants as the starting material, should be the collection and analysis of information on the use(s) of the plant(s) by various indigenous cultures. Ethnobotany, ethnomedicine, folk medicine and traditional medicine can provide information that is useful as a 'pre-screen' to select plants for experimental pharmacological studies. Examples are given to illustrate how data from ethnomedicine can be analyzed with the aim of selecting a reasonable number of plants to be tested in bioassay systems that are believed to predict the action of these drugs in humans. The ultimate goal of ethnopharmacology should be to identify drugs to

alleviate human illness via a thorough analysis of plants alleged to be useful in human cultures throughout the world.

6. PRACTICAL ASPECTS OF HERBAL DRUG DISCOVERY:[15]

The following scheme represents a summary of the stages involved in the development of pure drug from a plant source.

- Collection and identification of the plant and deposition of voucher sample in herbaria.
- Literature survey on the plant species selected for studies.
- Extraction with solvent and preparation of non-polar and polar extracts for initial biological testing.
- Evaluation of plant extract against a panel of biological test methods, as exemplified by receptor binding, enzyme inhibition and /or cytotoxicity assays.
- Activity guided fractionation on the extract showing activity, by monitoring each chromatographic fraction with bioassay chosen from the panel available to the investigation.
- Structure elucidation of pure active isolate(s) using spectroscopic techniques and chemical methods, if necessary.
- Test each active compound (whether of novel or known chemical structure) in all *in vitro* and *in vivo* biological test methods available, in order to determine potency and selectivity of the drug.
- Molecular modeling studies and preparation of derivatives of active compound.
- Large-scale isolation of interesting active compounds for toxicological, pharmacological and for mutation studies, when total synthesis is not practical.
- Clinical trials (Phase I – III).

7. CURRENT STATUS OF HERBAL DRUGS:

The executive board of WHO (World Health Organization) recently passed a resolution calling on countries

1) To promote the role of traditional practitioners in the health care systems of developing countries and,
2) To allocate more financial support for the development of traditional medical systems.

The board also urged the medical profession not to undervalue the traditional medical system. WHO recognizes that modern medical care is unavailable to the majority of the world's poor residents and that traditional birth attendants deliver 2/3 of the world's babies. To fulfill the primary health needs of all the world's inhabitants it will be necessary to utilize both the Western and the traditional medical system. In some countries, such as Sri Lanka, India and China the traditional health system is legally recognized. WHO also advocates utilizing those medicinal plants and remedies used by traditional practitioners to effectively treat their patients. Example of some of these plants are *Ammi visnage*, a Mediterranean plant, used to treat angina pectoris, *Cymbopogan proximus*, an Egyptian plant, used to remove urinary tract stones, the root of *Combretum*, used in Ghana to treat guinea-worm, *bitter leaf*, a Nigerian plant which kills mouth bacteria and *Desmodium adcendens*, *Thonningia sanguinea*and *Deinbollia pinnata* used in various combinations to treat bronchial asthma[17].

An early objective of the World Health Organization's (WHO) traditional medicine program was to promote a realistic approach to the subject. The realism with which countries around the world, both developed and developing, examine their own traditional practices suggests that progress is being made towards this goal. The current challenge is to pursue action along 3 lines: evaluation, integration and training. In traditional medicine it is necessary to separate myth from reality so that valid practices and remedies can be distinguished from those that are patently ineffective and/or unsafe. Thus, WHO will continue to promote the development, teaching and application of analytical methods that can be used to evaluate the safety and efficacy of various elements of traditional medicine. Traditional practitioners also require training. They need to be provided with additional skills. It is essential to make practitioners of traditional medicine allies rather than competitors. The training of traditional birth attendants in aseptic delivery techniques and simple antenatal and postpartum care provides a good example of the possibilities that exist for collaboration between the traditional and modern health care sectors. In the past 2 years WHO has carried out numerous activities in the field of traditional medicine. For example, among the activities coordinated by WHO headquarters was the continuing search for indigenous plants for fertility regulation in men and women. In 1983, WHO collaboration centers for traditional medicine continued to strengthen national efforts in research and development. A prerequisite for the success of primary health care is the availability and use of suitable drugs. It is reasonable for decision makers to identify locally available plants or plant extracts that could usefully be added to the national list of drugs or that could even replace some pharmaceutical preparations that need to be purchased and imported. NAPRALERT (for national products alert) is a computerized database derived primarily from scientific information gathered from the world literature on the chemistry, pharmacology and ethnopharmacology of natural plant products. It can

provide both a general profile on a designated plant and a profile on the biological effects of a chemical constituent thereof. A valuable feature of the NAPRALERT database is its ability to generate information on plants from a given geographical area[18].
Plant-derived drugs have an important place in both traditional and modern medicine. For this reason a special effort to maintain the great diversity of plant species would undoubtedly help to alleviate human suffering in the long term. Proven agro industrial technologies should be applied to the cultivation and processing of medicinal plants and the manufacture of herbal medicines. About 80% of the world's people depend largely on traditional plant-derived drugs for their primary health care (PHC). Medicinal plants serve as sources of direct therapeutic agents and raw materials for the manufacture of more complex compounds, as models for new synthetic products and as taxonomic markers. Some essential plant-derived drugs are atropine, codeine, morphine, digitoxin/digoxin and quinine/artemisinin. Use of indigenous medicinal plants reduces developing countries' reliance on drug imports. The Napralert database at the University of Illinois establishes ethnomedical uses for about 9200 of 33,000 species of monocotyledons, dicotyledons, gymnosperms, lichens, pteridophytes and bryophytes. Even though many people use medicinal plants, pharmaceutical firms in industrialized nations do not want to explore plants as sources of new drugs. Scientists in China, Germany and Japan are doing so, however. Screening, chemical analysis, clinical trials and regulatory measures are needed to ensure safety of herbal medicines. WHO has hosted interregional workshops to address methodologies for the selection and use of traditional medicines in national PHC programs. WHO, the International Union for the Conservation of Nature and Natural Resources and the World Wide Fund for Nature developed guidelines for conservation of medicinal plants. Their 2-pronged strategy includes prevention of the disappearance of forests and associated species and the establishment of botanical gardens. WHO's Traditional Medicine Programme hopes that people will apply known and effective agro industrial technologies to the cultivation and processing of medicinal plants and the production of herbal medicines and the creation of large-scale networks for the distribution of seeds and plants[19].

Alternative medicine use and expenditures in the United States is increased substantially between 1990 and 1997, attributable primarily to an increase in the proportion of the population seeking alternative therapies, rather than increased visits per patient[20].

Natural products research continues to provide a tremendous variety of lead structures which are used as templates for the development of new drugs by the pharmaceutical industry. Advances in bioassay technology and in chemical methodology have combined to make natural products a cost effective source for new leads. While microbial products have been the mainstay of industrial natural products discovery, in recent years phytochemistry has again become a field of active interest. Drug discovery programs based on microbial products and phytochemical are discussed and contrasted[21].

Glaxo PLC has had a significant involvement with Natural Product Source Materials for all of its commercial history and, most recently, has pursued this interest by use of such materials as templates for new lead discovery. Through the expertise and facilities in its Natural Products Discovery Department, Glaxo extracts relatively small quantities of plant material (typically 200-250 g dry weight) and cultures microorganisms from environmental samples (typically 10-50 g). Extracts and fermentation broths are screened in order to detect bioactive principles (BPs). If the potency, selectivity and specificity of the BP are acceptable, isolation, purification and structural elucidation follows. It is most unlikely, that the BP itself will become a drug; it is much more likely to initiate a medicinal chemistry synthesis program in order to try to produce a molecule that has both the essential biological and desirable chemical properties to become a drug development candidate[22].

Plants have been used as medicine for millennia. Out of estimated 2,50,000 to 3,50,000 plant species identified so far, about 35,000 are used worldwide for medicinal purposes. It has been confirmed by WHO that herbal medicines serve the health needs of about 80 percent of the world's population; especially for millions of people in the vast rural areas of developing countries. Meanwhile, consumers in developed countries are becoming disillusioned with modern healthcare and are seeking alternatives. The recent resurgence of plant remedies results from several factors: 1) the effectiveness of plant medicines; 2) the side effect of most modern drugs; and 3) the development of science and technology. It has been estimated that in the mid-1990s over 200 companies and research organizations worldwide are screening plant and animal compounds for medicinal properties. Actually, several important drugs used in modern medicine have come from medicinal plant studies, e.g., taxol/paclitaxel, vinblastine, vincristine, topotecan, irinotecan, etoposide, teniposide, etc. As for drugs derived from orchids, some novel discoveries, both in phytochemical and pharmacological properties, were reported by some

universities. However, studies on plants are very limited. Only about a third of the million or so species of higher plants have been identified and named by scientists. Of those named, only a tiny fraction has been studied. Nowadays the linking of the indigenous knowledge of medicinal plants to modern research activities provides a new approach, which makes the rate of discovery of drugs much more effective than with random collection[23].

8. FUTURE PROSPECTS IN HERBAL MEDICINES:

At the moment, scientific research on medicinal plants is being carried out most intensely in research institutes, universities and pharmaceutical laboratories as well as in the clinics of many developed countries. This research is oriented mainly in two directions. Firstly, the active ingredients of plants that have long been known for their healing properties are investigated. The second sphere of basic research is directed towards the discovery of new kinds of medicinal plants and new drugs from the more remote regions of the world, which have not been explored so far.

Drugs of each and every traditional medicine, like Ayurveda, Unani and Siddha need to be tested and validated scientifically. Council for Scientific and Industrial Research (CSIR), New Delhi, is already involved in this field and validated about 350 formulations for different activities. This is a welcome trend since it attempts to marry traditional practice with modern knowledge for the betterment of health[24].

WHO has emphasized the need to ensure the quality control of herbs and herbal formulations by using modern techniques. Several countries have herbal pharmacopoeias and lay down monographs to maintain their quality. Ayurvedic Pharmacopoeia of India recommends basic quality parameters for 80 common herbal drugs[25].

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