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Natural Product and Health - A Review on All Aspects

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ABSTRACT

India is the largest producer of medicinal herb and is called as Botanical garden of the World. During the thousands of years of early human existence many natural material were identified for combating human ailments either by instinct or intuition or trial and error. India is one of the world's 12 leading biodiversity centers. It is endowed with more than 47,000 known species of plants. Out of these, about 20,000 plants have good medicinal value. According to the WHO survey 80% of the populations living in the developing countries rely almost exclusively on traditional medicine for their primary health care needs.The global market for herbal medicines currently stands at over $60 billion annually. Medicinal plants play a great role in food supplements for care as well as in personal care of the mankind alongside the therapeutically active substances, thus medicinal plant based industry is a promising sector and enormous economic growth potential. Nutraceuticals (Health Food) are in great demand in the developed world.

Keywords: Natural product, Drug discovery, Nutraceuticals, Standardization, Phytochemical.

1. INTRODUCTION

Indian sub-continent is a rich source of plant and animal wealth, which is due to its varied geographical and agro-climatic regions. India is the largest producer of medicinal herb and is called as Botanical garden of the World. Besides its varied biodiversity, it has a diverse cultural heritage too. Though at present Indian health care delivery consists of both traditional and modem systems of medicines, both organized traditional systems of medicine like Ayurveda, Siddha and Unani and unorganized systems like folk medicine have been flourishing well. Ayurveda and Siddha are of Indian origin and accounted for about 60% health care delivery in general and 75% of rural Indian population depends on these traditional systems. These two systems of medicine use plants, minerals, metals and animals as source of drugs, plants being the major source. It is estimated that about 1500 plant species in Ayurveda and 1200 plant species in Siddha have been used for drug preparation. In Indian folk medicine use, about 7500 plant species are recorded as medicinal plants. Though the Indian traditional systems of medicine are time-tested and practiced successfully from time immemorial, there is lack of standardization with regard to identity of crude drugs, methods of preparation and quality of finished products.

According to the WHO survey 80% of the populations living in the developing countries rely almost exclusively on traditional medicine for their primary health care needs. Researches on pharmacognosy, chemistry, pharmacology and clinical therapeutics have been carried out on Ayurvedic medicinal plants and many of the major pharmaceutical corporations have renewed their strategies in favor of natural products drug discovery. Numerous drugs have entered the international pharmacopoeia through the study of ethnopharmacology and traditional medicine.

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. The World Health Organization has recognized the importance of traditional medicine and has created strategies, guidelines and standards for botanical medicines.

During the thousands of years of early human existence many natural material were identified for combating human ailments either by instinct or intuition or trial and error. The earliest mention of the medicinal use of plants has been found in 'Rig Veda', which was written between 4000 and 1600 BC[1]. Indian traditional medicines are based on use of plant drugs[2]. Indian Materia Medica includes about 2,000 drugs of natural origins, out of these 400 are of mineral and animal origin while the rest are of vegetable origin.

The World Health Organization (WHO) has recognized the Unani System of Medicine (USM) as an alternative system to cater the health care needs of human population. Alternative medicine is being practiced worldwide. Unani is one of the most well known traditional medicine systems and draws on the ancient traditional systems of medicine of China, Egypt, India, Iraq, Persia and Syria. It is also called Arab medicine. Unani is still popular in many Arab and East Asian countries. In fact Unani medicine and herbal products are gradually more being used in many countries where modern medicine is easily available. India has accepted it as one of the alternative health care system and has given it official status[3].

India is endowed with more than 47,000 known species of plants[4] of these about 20,000 plants have good medicinal value. However, only about 7,500 are used for their medicinal uses by traditional communities .The Siddha system of medicines uses about 600, Ayurveda 700, Unani 700 and Modern medicines about 30. Effective western style medicine is neither accessible nor affordable for millions of people worldwide. Now here is this more true than in India, where in spite for the rapid and wide spread of western medical practices throughout the country during past 150 years, the majority of the people still continues to rely on traditional medicine for their health care needs.

There is a famous line; one man's aspirin is another man's peptic ulcer[5] also led people to look for alternative. Moreover, the synthetic drug and intermediary chemicals are expensive. The World Health Oarganization has emphasized the utilization of indigenous system of medicine based on the locally available raw material, i.e., medicinal plants. It has been estimated that up to 50% of the prescription presently dispensed in USA may contain one or more natural product drug[6].

2. TRADITIONAL MEDICINES IN INDIA

The Indian subcontinent is endowed with one of the richest expertise in traditional medicines. Traditional systems of medicine in India like Ayurveda, Unani and Siddha are also based on the use of herbal medicines[2]. In India, the earliest awakening of the application of medicinal plants is seen in Rig Veda which dates back to 4600-4500 BC and mentions 67 herbal drugs. Yajurveda contains 81 and Atharvaveda (2500 BC) includes 290 plant drugs in a separate part called Ayurveda which wholly devotes to medicines. The next landmark in the history of Indian medicine is the Samhitas or the collections of Charka and Sushruta at about 1000 BC. The Sushruta Samhita deals more with surgery and describes 395 medicinal plants, 57 drugs of animal origin and 64 minerals. Charaka Samhita is concerned mainly with medicines and describes 341 plants and plant products for use in medicines.

India is one of the world's 12 leading biodiversity centers. It is endowed with more than 47,000 known species of plants[2]. Out of these, about 20,000 plants have good medicinal value. However, only about 2,500 herbal drugs are used for their medicinal importance by traditional communities. The Siddha system of medicine uses about 600, Ayurveda 700, Amchi 600, Unani 700 and modern medicines about 30 plant drugs[7].

Since independence, Indian scientists of CSIR-recognized laboratories and some other R & D centers have been engaged in updating various technologies particularly agro and processing technologies with the result that the production of medicinal herbs and their derivatives like phytochemicals, essential oils and oleoresins became economically viable. In this regard, particular mention must be made of CIMAP in Lucknow, RRL Jammu, Jorhat, Bhubeneswar and Trivandrum, NCL in Pune and private enterprises like, CIPLA in Mumbai, Amsar in Indore, Chemiloids in Vijaywada and Mehta Pharmaceuticals in Amritsar.

In addition to India there are many other countries in Africa, Asia and Arab countries where many medicinal herbs of commercial value grow wild and in some cases these are cultivated[7].

3. PLANTS AS A SOURCE OF DRUGS

For thousands of years, 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[8]. The importance of natural products in this regard can be assessed using 3 criteria:

1. The rate of introduction of new chemical entities of wide structural diversity, including serving as templates for semi-synthetic and total synthetic modification.

2. The number of diseases treated or prevented by these substances, and

3. Their frequency of use in the treatment of disease.

An analysis of the origin of the drugs developed between 1981 and 2002 showed that natural products or natural product-derived drugs comprised 28% of all new chemical entities (NCEs) launched into the market[9]. In addition, 24% of these NCEs were synthetic or natural mimic compounds, based on the study of pharmacophores related to natural products[8].This combined percentage (52% of all NCEs) suggests that natural products are important sources for new drugs and are also good lead compounds suitable for further modification during drug development. 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[10], making them good candidates for further drug development[11].

4. NATURAL PRODUCT CHEMISTRY IN DRUG DISCOVERY

Natural products have been the source of most of the active ingredients of medicines. This is widely accepted to be true when applied to drug discovery in 'olden times' before the advent of high-throughput screening and the post-genomic era: more than 80% of drug substances were natural products or inspired by a natural compound[12]. It is, however, arguably still true: comparisons of the information presented on sources of new drugs from 1981 to 2010 indicate that almost half of the drugs approved since 1994 are based on natural products[13,14,15].

Natural products may serve as lead compounds for new drugs.

- They give us information on possible biomechanisms and thus on the molecular origin and the basis of diseases.
- Their isolation has provoked novel analytical techniques and spectroscopic instrumentation.
- Natural products are a permanent challenge with respect to total synthesis and stimulate the development of new reagents and reactions

Plant medicine is a broad category of medicament, which includes drugs used in traditional system of medicine, folklore and ethnomedical products, as well as drugs discovered from plants having no documented therapeutic use. The objective of phytochemical, pharmacognostical and pharmacological investigations of the selected plants are to:

- Find a new drug.
- Discover lead molecules (essentially novel chemical moiety), which can be modified through chemical means into new drugs.
- Provide a rationale for clinical use of traditional drugs even if activity is not of an order high enough to warrant development of the active moiety as a new drug.

Although interest in natural products as a source of new biologically active compounds decreased in the last few decades as synthetic chemistry programmes expanded, natural products continued to form a significant proportion of drugs in current use and of those under investigation. It has been estimated that 56% of the lead compounds for medicines in the British National Formulary are natural products or are derived from natural products (amoxycilin, cefaclor, ceftriaxone and lovastatin) and two others (captopril and analapril) resulted from leads provided by a natural product[16]. In 1991, 42 new agents were introduced to medical practice. Of these, 16 were natural products or were derived from natural sources. Similarly, there were 43 new chemical entities introduced in 1992 and 18 were natural products or their derivatives[17].

Given the vast repertoire of chemical structures provided by natural sources, screening of libraries of natural products seemed to be good. There are estimated to be at least 2,50,000 species of higher plants and around 30 million species in total, most of these have not be tested for biological activity. However, the worldwide fund for Nature estimates that at least 50,000 species are being lost annually through destruction of tropical forests and more efforts to maintain biodiversity are clearly necessary.

5. PRACTICAL ASPECTS OF DRUG DISCOVERY EFFORTS FROM PLANT SOURCES

The plant samples should be taxonomically identified as far as possible prior to starting the phytochemical investigation. The following scheme represents a summary of the stages involved in the development of a pure natural product drug candidate from a plant source[18].

- Collect and taxonomically identify plant material and deposit voucher samples in local and major herbaria.
- Extract the dried, milled plant acquisition with solvent and prepare non-polar and polar extracts for initial biological testing.
- Evaluate such plant extracts against a panel of biological test methods.
- Confirm initial biological activity on larger quantities of recollected plant material.

- Perform literature surveillance on the plant species selected for isolation studies to aid in the dereliction of known active compounds.
- Conduct activity-guided fractionation on the extract showing activity, by monitoring each chromatographic fraction with a bioassay chosen from the panel available to the investigation.
- Determine structure of pure active isolate(s) using spectroscopic techniques and chemical methods.
- Test each active compound in vitro and in vivo biological test methods available, in order to determine potency and selectivity.
- Perform molecular modeling studies and prepare derivatives of the active compounds of interest.
- When total synthesis is not in practical, carry out large scale re-isolation of interesting isolated active compounds for toxicological, pharmacological and formulation studies.
- Clinical trials (phase I-III).

Table 1.1: Drugs based on natural products at different stages of development
Source: Pharmaprojects database (March 2008)

Development stage	Plant	Bacterial	Fungal	Animal	Semi-synthetic	Total*
Preclinical	46	12	7	7	27	99
Phase I	14	5	0	3	8	30
Phase II	41	4	0	10	11	66
Phase III	5	4	0	4	13	26
Pre-registration	2	0	0	0	2	4
Total	108	25	7	24	61	225

* This does not include reformulations of existing products (66 such products were listed).

6. NEW APPROACHES TO THE VALUE OF NATURAL PRODUCTS

With advances in fractionation techniques to isolate and purify natural products (e.g. counter-current chromatography[19] and in analytical techniques to determine structures[20], screening of natural product mixtures is now more compatible with the expected timescale of high-throughput screening campaigns point out that pure bioactive compounds can be isolated from fermentation broths in less than 2 weeks and that the structures of more than 90% of new compounds can be elucidated within 2 weeks. With advances in NMR techniques, complex structures can be solved with much less than 1 mg of compound. Quinn *et al* recently demonstrated that it is possible to prepare a screening library of highly diverse compounds from plants with the compounds being pre-selected from an analysis of the Dictionary of Natural Products to be drug-like in their physicochemical properties[21]. It will be interesting to see if such a collection proves to be enriched in bioactive molecules. Several alternative approaches are also being explored in efforts to increase the speed and efficiency with which natural products can be applied to drug discovery.

Table 1.2: Therapeutic categories of natural product-derived drugs at different stages of development

Source: Pharmaprojects database (March 2008).

Therapeutic area	Preclinial	Phase I	Phase II	Phase III	Pre-registration	Total
Cancer	34	15	26	9	2	86
Anti-infective	25	4	7	2	2	40
Neuropharmacological	6	3	9	4	0	22
Cardiovascular/gastrointestinal	9	0	5	6	0	20
Inflammation	6	2	9	1	0	18
Metabolic	7	3	6	1	0	17
Skin	7	1	2	0	0	10
Hormonal	3	0	2	1	0	6
Immunosuppressant	2	2	0	2	0	6
Total	99	30	66	26	4	225

7. FUTURE SCENARIO OF NATURAL DRUGS

There is a growing interest in herbal drugs, and as an example of this, the consumption of medicinal plants has doubled in the last ten years in Western Europe. Use of medicinal plants is expected to raise globally, due to increasing trend towards self-medication, reduction in costs of subsidized health care, various international and national organizations improving the status of

herbal medicine industry and renewed interest of companies in isolating useful compounds from the plants.

It implies increasing pressure on wild plant resources and, therefore, the need for serious conservation efforts including development of cultivation techniques has never been greater. Serious over-exploitation of many medicinal plants such as *Rauwolfia, Dioscorea, Swertiachirata, Valeriana, Orchis* and *Harpagophytum procumbens* has already occurred[22].

Fortunately, the traditional medicine programme has many linkages with other programme in the WHO, with other international agencies and organization and with numerous government and university departments of almost equal importance are ready access to technical expertise at home and abroad, the ability to keep in touch with developments in other counties, and the opportunity to exchange ideas and experience. This traditional role of international organization and universities is one that has considerable potential for expansion, so far as medicinal plants are concerned.

There are some aspects of particular relevance for the rational utilization of medicinal plants and other natural products. Significant progress over the next few years will depend on the imagination and determination, which can be brought to bear on the subject[23].

Despite of so much potential and scope of future development of plant drugs, a mere two per cent of the flora provided by nature is being used beneficially. The major pitfalls in plant drug research include a lack of standardization, confusion in nomenclature, controversial botanical identification, danger of extinction of some plants due to extensive exploitation, lack of proper dosage formulation, and bitter experiences of searching for a single active principle[24]. Modern instrumentation and biological assay methods provide the possibility of developing suitable quality control criteria for herbal drugs.

Table1.3: Global market for herbal supplements in 1999[36]

Region	Herbal supplements (billion US$)
World	> 15
Europe	7.0
North America	3.0
Japan	2.4
Rest of Asia	2.7

Table 1.4: Numbers and plants used medicinally worldwide[37]

Country	Plant species	Medicinal plant species	%
China	26,092	4941	18.9
India	15000	3000	20.0
Indonesia	22500	1000	4.4
Malaysia	15500	1200	7.7
Nepal	6973	700	10.0
Pakistan	4950	300	6.1
Philippines	8931	850	9.5
Sri Lanka	3314	550	16.6
Thailand	11625	1800	15.5
USA	21641	2564	11.8
Vietnam	10500	1800	17.1
Average	13366	1700	12.5
World	422000	52885	

The structural determination of novel plant constituents can be performed with minimal delay by using a combination of sophisticated spectroscopic and X-ray crystallographic techniques. High-throughout automated bioassays are widely available, so that a detailed biological profile can be obtained easily on just a few milligrams of a natural product. Thus, there is every indication that the direct utility and promise of plants for the improvement of human health will continue well into the 21st century[25].

8. 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 product 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. 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. Lead optimization (involving medicinal and combinatorial chemistry), lead development (including pharmacology, toxicology,

pharmacokinetics, ADME and drug delivery), and clinical trials all take considerable time[26].

The objective of the research approach is the targeted 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). As drug discovery from plants has traditionally been time-consuming, faster and better methodologies for plant collection, bioassay screening, compound isolation and its development must be employed. The design, determination and implementation of appropriate, clinically relevant, high-throughput bioassays are difficult processes for all drug discovery programmes[27,28]. Although the design of high-throughput screening assays can be challenging, once a screening assay is in place, compound and extract libraries can be tested for biological activity[29].

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. 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. One can also improve the natural products compound development by creating natural products libraries that combine the features of natural products with combinatorial chemistry[26].

9. INDIAN HERBAL TRADE IN WORLD SCENARIO

The utilization of herbal drugs is on the flow and the market is growing step by step[30]. The annual turnover of the Indian herbal medicinal industry is about Rs. 2,300 crore as against the pharmaceutical industry's turnover of Rs. 14,500 crores with a growth rate of 15 percent[31]. The export of medicinal plants and herbs from India has been quite substantial in the last few years. India is the second largest producer of castor seeds in the world, producing about 1,25,000 tonnes per annum. The major pharmaceuticals exported from India in the recent years are isabgol, opium alkaloids, senna derivatives, vinca extract, cinchona alkaloids, ipecac root alkaloids, solasodine, Diosgenine/16DPA, Menthol, gudmar herb, Mehdi leaves, papian, rauwolfia guar gum, Jasmine oil, agar wood oil, sandal wood oil, etc[32]. The turnover of herbal medicines in India as over-the-counter products, ethical and classical formulations and home remedies of traditional systems of medicine is about $ one billion and export of herbal crude extract is about $ 80 million[30]. The herbal drug market in India is about $1 billion.

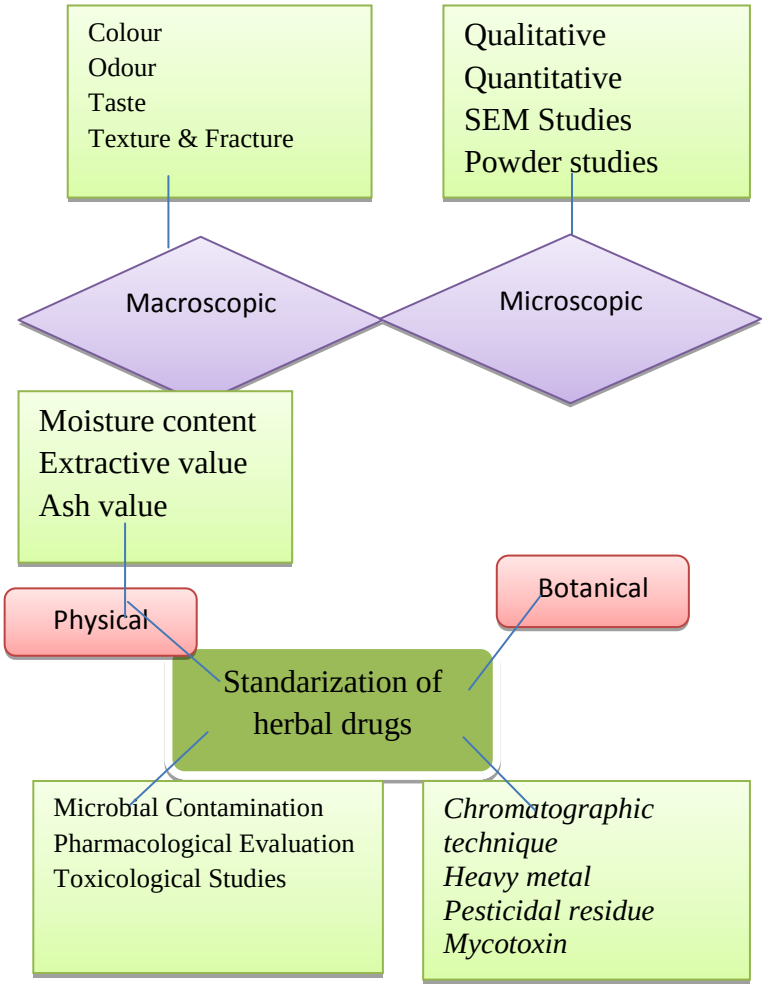

Figure 1: A schematic representation of herbal drug standardization

10. WORLDWIDE HERBAL TRADE

The global market for herbal medicines currently stands at over $60 billion annually. The sale of herbal medicines is expected to get higher at 6.4% an average annual growth rate[33]. Due to the contribution of numerous significant factors, the market of herbal medicines has grown at an expressive rate worldwide. Some of them are: preference of consumers for natural therapies; concern regarding undesirable side effects of modern medicines and the belief that herbal drugs are free from side effects, since millions of people all over the world have been using herbal medicines for thousands of years; great interest in alternative medicines; preference of populations for preventive medicine due to increasing population age; the belief that herbal medicines might be of

effective benefit in the treatment of certain diseases where conventional therapies and medicines have proven to be inadequate; tendency towards self-medication; improvement in quality, proof of efficacy and safety of herbal medicines and high cost of synthetic medicines[34]. According to World Health Organization, herbal medicines are lucrative globally and they represent a market value of about US$ 43 billion a year. According to an estimate in 1991, the herbal medicine market in the European countries was about $ 6 billion, with Germany accounting for $ 3 billion, France $ 1.6 billion and Italy $ 0.6 billion while in other countries was 0.8 billion. In 1996, the herbal medicine market in the European countries was about $ 10 billion, in USA about $ 4 million, in India about $ 1.0 billion and in other countries was $ 5.0 billion[35]. In 1997, the European market alone reached about $ 7.0 billion. The German market corresponds to about 50% of the European market, about $ 3.5 billion. This market is followed by France, $ 1.8 billion; Italy, $ 700 million; the United Kingdom, $ 400 million; Spain, $300 million; the Netherlands, about $ 100 million[34].

11. DEVELOPMENT IN HERBAL MEDICINE INDUSTRY WITH REFERENCE TO TRADE

There is a great demand for herbal medicine in the developed as well as developing countries like India, because of their wide biological activities, higher safety of margin than the synthetic drugs and lesser costs[38]. Medicinal plants play a great role in food supplements for care as well as in personal care of the mankind alongside the therapeutically active substances, thus medicinal plant based industry is a promising sector and enormous economic growth potential. Nutraceuticals (Health Food) are in great demand in the developed world particularly USA and Japan. Nutraceutical market in USA alone is about $ 80-250 billion, with a similar market size in Europe and Japanese sales worth $ 1.5 billion[32]. Such huge markets have arisen because of the Dietary Supplement Health Education Act passed by USA in 1994, which permits unprecedented claims to be made about food or the dietary supplement's ability about health benefits including prevention and treatment of diseases. This act has motivated pharma to include not only compounds isolated from fauna and flora but also herbal medicines as Nutraceuticals, which is unfortunate. The Indian herbal pharma companies also see this as a good opportunity and are marketing such products[30]. However, the importance of medicinal plants in the national economy and their potential for the rapid growth of herbal products, perfumery and allied industry in India has been emphasized from time to time[32]. New trends are emerging in the standardization of herbal raw materials whereby it is carried out to reflect the total content of phytoconstituents like polyphenols, which can be correlated with biological activity. The major traditional sector pharmas, namely Himalaya, Zandu, Dabur, Hamdard, Maharishi, etc, are Standardizing their herbal Formulations by Chromatography techniques like TLC/ HPTLC finger printing, etc[39].

12. REGULATORY ASPECT OF HERBAL DRUGS

European and North American industries and institutions patented plant based drugs of India. It is a gross violation of Intellectual Property Rights (IPR). Neem wax and neem oil from *Azadirachta indica* as fungicides and insecticides by Monsanto and turmeric rhizome (*Curcuma longa*) as wound healer by the University of Mississippi were patented. The plant drugs used in Indian medicinal systems are also claimed to be originated in other countries. *Evolvulus alsinoids* L. (Convolvulaceae), commonly known as shankhpushpi or sankhaholi, is a popular nervine tonic used in Ayurvedic and Unani systems of medicine. Recently, this plant is reported to be an American herb[40]. Therefore, it is important to publish any information related to Indian herbal drugs without any delay in a documentary form.

The legal process of regulation and legislation of herbal medicines changes from country to country. WHO has published guidelines in order to define basic criteria for evaluating the quality, Safety & efficacy of herbal drugs aimed at existing national regulatory authorities, scientific organizations and manufacturer in the particular area. Furthermore the WHO has prepared pharmacopoeia monograph on herbal medicines and basis for guidelines for the assessment of herbal drugs.

Some of the guidelines that the WHO developed and issued are:

- Guidelines for the assessment of herbal medicines.
- Research guidelines for evaluating the safety and efficacy of herbal medicines
- Guidelines for clinical research in herbal medicines

The purpose of this guideline is to provide the proper use and development of traditional medicine the specific objective for this guideline is to

- Harmonize the use of certain accepted and important terms in traditional medicine.
- Summarize key issues developing methodologies for research and evaluation of traditional medicines.
- Provide appropriate evaluation methods to facilitate the development of regulation and registration in traditional medicine.

These guideline covers a wide range of issues and are intended to meet the different situation that exist in various countries and region of the world – these guidelines serves as a

reference sources for researchers, healthcare professional, manufactures and health authorities. Apart from these guidelines several regulatory models for herbal medicines currently exists.

13. GCP AND CLINICAL STUDIES OF HERBAL DRUGS

Phytomedicines consist of many chemical constituents with complex pharmacological effects on the body. Therapeutic efficacy and clinical trials are two most important criteria for the development of herbal drugs. In persuing good clinical research in herbal medicine the problems usually encountered with are as follows: -

- Herbal medicine in the west can boast few teaching hospitals or research institutions or support from public researches institutions or support from public resources as well industrial development has been limited.
- The indication often claimed for phytomedicines include many without robust outcome measures.
- Herbs are complex medicine occupying and unusual position in being medicine with many of the characteristics of foods.
- The application of herbs and their effect not always the same as usually understood for conventional medicines.
- Lack of standardization and quality control of herbal drug used in clinical trials.
- Difficulties in establishing appropriate placebo because of the taste and aromas. .
- Wide variation in duration of treatment using herbal medicines.
- Presence of toxic or adverse effects of herbal drugs.

Keeping the above mention problems in mind the role of evaluation of the efficacy and safety of herbal medicines and existence of controlled clinical trials comes into play. Survey of specialized literature research allows that few well-controlled double blind trials have been carried out with herbal medicines. Recent Meta analysis of reviews published in important medical journals such as the Annals of internal medicines, the Journal of the American Medical Association (JAMA) the British Medical Journal and the British Journal of chemical pharmacology confirms this assumption. However a large no. of clinical trials has been performed with some herbal drugs including the extract of *Ginkgo biloba* used for the treatment of CNS and cardiovascular disorders and *Hypericum perforatum*. It is important to mention that these clinical trials have faced the some criticism and difficulties related to randomization, variation in efficacy and sample size.

Other herbal drugs which are widely used in different clinical trials have been carried out are ginseng used as tonic, *Allium sativum* used to lower LDL cholesterol and same cardiovascular disturbances and *Silybum marianum* used for their dysfunction including cirrhosis.

14. QUALITY CONTROL

The major hindrance in the amalgamation of herbal medicine into modern medical practices is the lack of scientific and clinical data and better understanding of efficacy and safety of herbal products. To ensure the quality and safety of herbal products, standardization is of vital importance[41,42].

Efficacy testing of the traditional and new herbal products in experimental screening method is important to establish the active component and appropriate extract of the plant. However, there should be adequate bioactivity data to validate the substandard source materials or finished products which yield less therapeutically effective drugs. Hence, the quality control of herbal drugs has to be dealt from cultivation of the plant to the finished products. The WHO guidelines are to regulate the agriculture methods such as use of insecticides, cultivation, harvest, post harvest transport and storage practices[43].

The research on traditional medicinal plants has focused on providing scientific evidence for the presence of active principles in assessment of toxicities. There are many herbal drugs and their products from India and China that are exported to western countries and their constituents are not declared on their labels. Some of the Indian herbal products contain toxic metals like lead and mercury and pesticides. Therefore, there is limited scope of Indian drugs in worldwide trade. Many Indian scientists are engaged in developing technical finger printing chromatograms of herbal drugs. It is useful for single plant drugs, but in polyherbal formulation, one particular drug having specified potent constituents may be easily substituted by a similar drug. Recently all sorts of small and large chemical constituents including warfare agent, explosives, computer CD surface, currency note, flower petals and herbal formulations can be determined by Desorption Electrospray Ionization (DESI) mass spectroscopy without sample preparation in few minutes at ambient temperature and pressure. In an herbal drug the active component vary in different environmental conditions. Red sandal from Cuddpah, Chittoor and Nellore regions of Andhra Pradesh, Eucalyptus oil from Nilgiri hills, Mentha oil from western Uttar Pradesh and Calicut ginger from Kerala have important place in the trade. All WHO parameters are required in quality control of such drugs and chromatographic techniques will not be much useful.

The majority of herbal medicines are safe when taken at recommended doses, but some may cause adverse effects, including drug interactions in patients concurrently taking other drugs. *Hypericum perforatum*, used to treat depression, interacts with digoxin, HIV inhibitors, theophylline and warfarin. Some plant

drugs affect cytochrome P450 iso-enzyme by which drugs are metabolized or phosphoglycoprotein transport systems that affect drug distribution and excretion. Simultaneous prescription of some herbal medicines with other drugs may lower either blood plasma level of the drugs or result in toxic concentration in blood. A slimming preparation manufactured in Belgium contained *Aristolochia fangchi*. Several women developed severe kidney damage. The toxic constituents are substituted nitro-phenanthrene carboxylic acids which are nephrotoxic, carcinogenic and mutagenic causing kidney failure and cancer[44]. Kava products prepared from the roots of Piper methysticumare used to relax the mind allay pain and induce sleep. But these products cause hepato-toxicity and kidney problems. Collaboration between phytochemists and toxicologists may establish the toxic principles of herbal drugs. There are many toxic plants growing in India e.g., *Nicotiana tobacum*, *Cannabis sativa* (Indian hemp), grass pollens and mould spore causing asthma, skeletal abnormalities, teratogenic and carcinogenic effects and neurological diseases and there is a need to start a programme for general awareness in public. Numerous scientific medical and pharmaceutical books have been published to provide the general public and healthcare professionals with benefits and risks of herbal drugs. There is a need for up-to- date monographs. For preparing such monographs, it is essential to have knowledge of Phytochemistry for defining the chemical profile of medicinal plants and an understanding of analytical tests for identification of the herbs and for the quantitative assessment of any known active ingredient.

Identification of active principle(s), wherever it is known, or a biologically active marker compound requires their standardization using appropriate techniques such as TLC, HPTLC, HPLC and GLC. For example, HPTLC of Asian ginseng, American ginseng, Notoginseng (Sanchi) and some of their preparations have been reported by Xie and Yan. In order to rationalize the use of natural products in different forms more particularly the extracts in therapy as is being used nowadays, a need-based and novel concept of biomarkers is getting momentum. A bio-marker on the other hand is a group or chemical compound which is in addition to being unique for that plant material also correlative with biological efficacy.

15. STANDARDIZATION

Plant materials and herbal remedies derived from them represent substantial portion of global market and in this respect internationally recognized guidelines for their quality control are necessary. WHO has recognized the need to ensure quality control of medicinal plants products by using modern techniques and by applying suitable standards. Several Pharmacopoeia including Indian Pharmacopoeia, British Pharmacopoeia, Pharmacopoeia of republic of China, Japanese Pharmacopoeia, United state Pharmacopoeia do cover monograph and quality control test for few of medicinal plants used in the respective countries but basically these pharmacopoeia are designed to cater to chemical based medicine and pharmaceutical necessities by giving their standards, test methods. For pharmaceutical purpose the quality of medicinal plant materials must be as high as that of other medicinal preparations. However, it is impossible to assay for specific chemical entity when the bioactive ingredient is not known. Further problem posed by those preparations, which contain heterogeneous mixtures. Directive on the analytical control of vegetable drug must take account of the fact that material to be examined has complex and inconsistent composition. Therefore, the analytical limits cannot be as precise as for the pure chemical compound. Vegetable drugs are inevitably inconsistent because of their composition and hence the standardization may be influenced by several factors such as age and origins, harvesting period, method of drying and so on. To eliminate some of the causes of inconsistency, one should use cultivated rather than wild plant which are often heterogeneous in respect of the factors and consequently in their content of active principles. Some problems facing standardization of crude drugs include the confusion existing over the identity of source material, the impossibility to assay for a specific chemical entity when the bioactive ingredient is not known and the problem posed by those preparations which contain heterogeneous mixtures. The purpose of standardization of medicinal plant products is obviously to ensure therapeutic efficacy and to check any adulteration or non-deliberate mixing in commercial batches[41,45].

HPTLC: Standardized manufacturing procedures and suitable analytical tools are required to establish the necessary frame work for quality controls in herbals. Among those tools high performance thin layer chromatography (HPTLC) is the most widely used to establish reference fingerprints of herbs, against which raw material can be evaluated and finished product can be assayed.

The analysis of herbals and herbal preparation is challenging for several reasons:

- As analytes, herbs are extremely complex. Even herbal preparations such as extracts contain numerous compounds in concentrations that can over several orders of magnitude.
- In many instances, chemical composition of the herb is not completely known. For several of the Ayurvedic and Chinese herbs, there are no established methods of analysis available.
- The requirements for a finger print analysis can be completely different from those for a quantitative determination of marker or key compounds, although the herbal preparation is the same in both instances.

- Constituents of herbals that belong to very different classes of chemical compounds can often create difficulties in detection. With this in mind HPTLC can offer many advantages[46].

    - There is almost no limitation to the composition of mobile phase.
    - To maximize selectivity of the separation, an enormous choice of stationary phase and mobile phase combination is available.
    - Multiple samples (up to 72) can be analyzed on one plate. This results in low analysis costs per sample.
    - Automation sample application takes 0.5 to 2 min per sample depending on size, application mode and number of replicates.
    - Equilibration time of 15 min is sufficient and drying times normally do not exceed 10 minutes.
    - Each step of chromatographic process can be monitored easily and effects of changes made to the procedures are visible.
    - The planar chromatogram can offer two dimensional information based on migration distance and colour of the substance zone. At the same time all samples on the plate can be compared with each other.

16. PHYTOCHEMICAL ANALYSIS

The subject of Phytochemistry, or plant chemistry, has developed in recent years as a discipline, somewhere in between natural product organic chemistry and plant biochemistry and is closely related to both. It is concerned with the enormous variety of organic substances that are elaborated and accumulated by plants and deals with the chemical structures of these substances, their biosynthesis, turnover and metabolism, their natural distribution and their biological function.

In all these operations, methods are needed for separation, purification and identification of the many different constituents present in plants. Thus, advances in our understanding of Phytochemistry are directly related to the successful exploitation of known techniques, and the continuing development of new techniques to solve outstanding problems as they appear. One of the challenges of Phytochemistry is to carry out all the above operations on a small material.

In identifying a plant constituent, once it has been isolated and purified, it is necessary first to determine the class of compound and then to find out which particular substance it is within that class. Its homogeneity must be checked beforehand i.e. It should travel as a single spot in several TLC. The class of compound is usually clear from its response to colour tests, its solubility and R_f properties and its UV spectral characteristics.

Complete identification within the class depends on measuring other properties and then comparing these data with those in the literature. These properties include melting point (for solid), boiling point (for liquids), optical rotation (for optically active compounds), and R_f (under standard condition). However, usually informative data on a plant substance are its spectral characteristics. These include U.V, IR, NMR, Mass spectral instruments. A known plant compound can usually be identified on the above basis. Direct comparison with authentic material should be carried out as final confirmation. If authentic material is not available careful comparison with literature data may suffice for its identification. If a new compound is present, all the above data should be sufficient to characterize it.

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