Herbal formulations as pharmacotherapeutic agents

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Herbal medicines are popular as remedies for diseases by vast majority of world’s population. Polyherbal preparations are products from medicinal plants. These are considered as safe since they are natural products. Herbal formulations which have reached widespread acceptability as therapeutic agents in India include nootropics, antidiabetics, hepatoprotective agents and lipid lowering agents. Pharmacological effects of many plants have been studied in various laboratories in India. However, there are many limitations regarding safety and efficacy of these preparations. Knowledge about active principles of herbal preparations are not well defined, information on toxicity and adverse effects of these formulations are lacking. Information regarding pharmacokinetics and bioavailability is not available. Packet inserts providing details regarding safety, and warning are not required for sale of these which are available as over the counter preparations. The risk of untested and unregulated remedies should be known to the lay public. Selection of plant material based on quality, standardisation of methods of preparation, enforcement of regulation regarding appropriate labels, are measures which will improve the quality and acceptability of herbal preparations as therapeutic agents. Documentation of research publications in journals and availability of information on website, are other measures to assist research in this field.

Herbal medicines have been used since the dawn of civilisation to maintain health and to treat diseases. The World Health Organisation estimates that about three quarters of the world’s population currently use herbs and other forms of traditional medicines to treat their diseases. Even as we commence the new century with its exciting prospect of gene therapy, herbal medicine remains one of the common forms of therapy available to much of world’s population. Ayurveda, Siddha and Unani systems of medicine are widely used in India. Pharmacoepidemiological survey carried out by Karandikar et al. in adults over 60 years of age revealed that about 47% of the elderly population uses herbal drugs¹. China is another country where traditional medicines are widely used. Faith in these traditional systems of medicine is related to cultural practices and beliefs. Several publications are available on medicinal plants of India. Authors like Chopra and Nadkarni have published reviews on medicinal plants. Indian Council of Medical Research (ICMR) has published several reviews on the same subject and formed a scientific advisory group for traditional medicine. In spite of the widespread interest, knowledge regarding the scientific basis of the use of herbal medicines is not known to large majority of physicians and users of these preparations.

Herbal industry driven use of plants and phytomedicine increased dramatically in the last two decades in USA. A National Centre for Complementary and Alternative Medicine (NCCAM) has been established in USA. In 1994, Congress in USA enacted the Dietary Supplement Health and Education Act (DSHEA) which specifically empowered the public to make informal choices about herbal products they use, based on accessible balanced scientifically valid information. DSHEA also classified herbal products as “Dietary supplements”, thereby denying the herbal industry the right to make “drug” claims (i.e. intended to treat or prevent disease). As dietary supplements herbal medications are included with vitamins, minerals, amino acids and “other products intended to supplement the diet”. Provisions of DSHEA gave authority over manufacturing procedures for the FDA. However as long as no drug claim is made for a herbal product, the FDA cannot demand new safety or efficacy data prior to marketing. The labels of many herbal formulations have suggestive comments such as “promote health, improve memory and concentration”. These labels help to promote sales.

Study on information available from labels on herbal preparations in India

A survey of herbal formulations available at chemists’ shops was undertaken by us to gather information available on the labels. This was undertaken with the view to observe the extent of information available regarding these preparations from labels in our country. Information available on labels is probably the only information available to the consumer about the marketed herbal formulations in India. This study included 50 herbal formulations. Most of these are mixtures of herbs. The number of components in these
mixtures range from 3 to 21. The composition of formulation and license details are given on the label in all the 50 preparations, while packet insert and information on drug safety are available only in 8/50 (16%) of these preparations. Date of expiry is indicated in 32 (64%) of the formulations while indication for use is available in 43/50 (86%). The details of formulations are presented in Table 1.

The indications for the use of preparations vary widely in relation to specific effects. Few examples are listed below:

Medimix skin care capsule — For total skin protection and beauty.
Manix herbal capsules — For oligospermia, increases libido.
Contraindication and drug interactions are mentioned in the label.
Geri forte tablets — Anti stress adaptogenic comprehensive tonic for men and women.
Pilex tablets — For haemorrhoids.

Overview of the pharmacological studies on important herbal products and formulations marketed in India

Focus on plant research has been going on for many years in India. Large number of plants have been tested for their pharmacological effects. These have been presented in various reviews. A brief overview of commonly used polyherbal formulations and plants products are only included in this section. Herbal preparations which have achieved wide spread acceptability as therapeutic agents include nootropic, antihypertensives, hepatoprotective agents, anti-inflammatory agents, antidiabetics and lipid lowering agents. Some of these have undergone detailed experimental and clinical studies which are highlighted below.

Hepatoprotective agents
Liv.52, a polyherbal formulation improved ethanol metabolism in a rat model of chronic alcohol administration. It also prevented lipid peroxidation in CCl4 induced liver damage as seen by significant decrease in malondialdehyde content. Liv 100 an improvised herbal formulation of Liv.52, has been reported to reduce the peroxidazion effect to hydrogen peroxide in rat liver homogenate. Jigrine, an unani polypharmaceutical herbal formulation containing 14 medicinal plants was evaluated in 3 models of hepatic damage induced by either alcohol, carbontetrachloride or paracetamol in rats. Jigrine significantly reduced liver enzymes and improved histopathological findings. Thyagarajan et al. have studied the effects of P. amarus on hepatitis B virus.

Centrally acting drugs
Mentat, a polyherbal formulation, has been shown to augment acquisition and retention of learning in experimental studies. Trasina a herbal formulation is known to exert nootropic effects. Ginkgolic acid conjugates isolated from leaves of Indian Ginkgo biloba Linn is known to have anxiolytic activity. Jigrine, an unani polypharmaceutical herbal formulation containing medicinal plants was evaluated in 3 models of hepatic damage induced by either alcohol, carbontetrachloride or paracetamol in rats. Jigrine significantly reduced liver enzymes and improved histopathological findings. Withania somnifera is another plant which has been extensively for neuropharmacological effects.

Herbal formulations for cardiovascular disorders
Abana, a polyherbal formulation is marketed as an antihypertensive agent. This preparation has been tested in hypertensive animals. Bark extract of Terminalia arjuna has been tested in clinical trials in patients with refractory congestive cardiac failure and was reported to show improvement in symptoms and signs of heart failure. Rutin, a flavonoid from the plant Sophora japonica, is reported to have beneficial effects in ischaemic heart diseases. Guggu lipid (an active principle of Commiphora mukul) is an agent that has been widely investigated for its hypolipidaemic activity. Preparations containing garlic and onion are known to have anti atherogenic effect. The active ingredient is s-allyl cysteine sulphoxide which has antiatherogenic effect.

Antidiabetic agents
Numerous plants and natural products have been studied for antidiabetic activity in different laboratories. Phyllanthus amarus was found to have hypoglycemic effects in non-insulin dependend diabetes mellitus. Detailed studies have been undertaken on Pterocarpus marsupium for its effect in experimentally

| Table 1 — Analysis of data obtained from survey of 50 herbal formulations |
|-----------------|-----------------|-----------------|
| System of preparation | Nature of formulations | No of constituents |
| Ayurveda | Tablets | 11 |
| Siddha | Capsules | 14 |
| Unani | Syrup | 17 |
| Herbal medicine | Lotion | 2 |
| | Cream | 3 |
| | Powder | 2 |
| | Lehyam | 1 |
induced diabetes in animals as well as in patients. D-400, a polyherbal formulation has been studied for its effects on alloxan induced diabetes in rabbits. The list of agents which have been tested for hypoglycaemic activity includes wide variety plants, Ayurvedic and Unani preparations. Polyherbal formulations like Ease and Jigrine and Ayurvedic drugs like Sandhika are known to have antiarthritic effects. Plant products have been studied for various therapeutic effects such as anti and pro-fertility actions, cytoprotective effects, pro- and antikinetic effects in gastrointestinal system, ulcerative colitis, antimicrobial, antiviral and antifungal actions, anthelmintic and antiprotozoal actions. Many researchers have focused their attention also on anticancer plants, immunomodulatory plants and antimutagenic actions.

Miscellaneous

Anti-inflammatory activity has been studied in various models of inflammation in experimental animals. The plants which are reported to have anti-inflammatory property include Ocimum sanctum, Pongamia pinnata, Gmelina asiatica, Nelumbo nucifera, and Gymnema sylvestre. Polyherbal formulations like Ease and Jigrine and Ayurvedic drugs like Sandhika are known to have antiarthritic effects. Plant products have been studied for various therapeutic effects such as anti and profertility actions, cytoprotective effects, pro- and antikinetic effects in gastrointestinal system, ulcerative colitis, antimicrobial, antiviral and antifungal actions, anthelmintic and antiprotozoal actions. Many researchers have focused their attention also on anticancer plants, immunomodulatory plants and antimutagenic actions.

Extensive review of all the herbal formulations and plant products available in this country is beyond the scope of this review. It is clear that interest in herbal drugs has been a thrust area of scientific and academic activity in this country for many years. Reviews of medicinal plants used by tribals, like Siddis of Uttara Kannada merit special attention. Some of the marketed preparations have been based on the knowledge of their use by tribals eg. “Jeevani” from the Kinnar tribes of Kerala.

Concept of safety and efficacy

Herbal formulations are popular among rural and urban community in India. Part of the reason for the popularity and acceptability is because of the belief that all natural products are safe. In the literature, therapeutic efficacy or toxicity is sometimes attributed to a herb without describing the brand or its content of bioactive or quantitatively significant components. Pharmaceutical products used as medicines are usually single chemical entities with specific actions at receptors, enzymes and other cellular sites. These drugs or preparations are marketed after rigorous clinical trials to support rational pharmacotherapy. The most important question regarding any drug to be used is how safe it is for clinical use. Unfortunately this aspect is not addressed or transparent to the consumer who wants to use the herbal formulation.

The herbal formulations which are sold as “over the counter” preparations have a different protocol regarding preparation, acquiring license and marketing. The active principles of herbal preparations are often not well defined. Regulations regarding safety and efficacy are not known to scientists or consumers. The herbal medicine market is poorly regulated. Assurance of safety, quality and efficacy of medicinal plants and herbal products is a key issue which needs to be addressed. Both the general consumer and health care professional need up-to-date authoritative information on the safety and efficacy of phytomedicines. It is possible to regulate many of these issues by law. Conducting toxicity studies for herbal preparations is an essential step which will strengthen the acceptance of herbal medicines by scientific community. Documentation of adverse effects, warning regarding use in pregnancy and lactation and drug interactions are details which are usually incorporated in packet insert of medicines. Licensing authorities can take steps to enforce and implement some of these aspects. Some differences in the use regarding external applications and those intended for systemic administration have to be considered. For example, many Ayurvedic preparations for arthritis are intended for external use only. The toxicity testing for such preparations can be limited as compared to those which are intended for oral administration.

Pharmacologists should remind consumers and health care providers that the same principles that govern the effect of prescription drugs used also influence the action of herbal preparations. Knowledge of absorption, distribution, metabolism and excretion are all important in determining duration and magnitude of effect. For most herbal preparations this information is presently unknown or incomplete. Conducting bioavailability studies on herbal formulations will provide information about absorption and therapeutic drug levels of the active ingredients.

Steps to improve status of herbal preparations as chemotherapeutic agents

Development of drugs from medicinal plants requires integrated approach and financial support. In India, the Central Drug Research Institute at Lucknow, studied a large number of plants over a period of three decades. This did not result in development of many pure drugs although many leads were discovered. The isolation of pure phytochemicals from medicinal plants is very demanding and expensive. Ayurvedic (or other indigenous systems) formulations can be used as drugs with modern standards of safety and efficacy. It is cost effective and more relevant to Indian conditions.

Toxicity studies should be conducted on all polyherbal drugs intended for therapeutic use and the
results need to be documented. Acute and short term toxicity study and toxicological evaluations using experimental animals should be done in all preparations marketed for medicinal use. In future, co-ordinated multidimensional research involving phytochemical and specific pharmacological activities should be undertaken. With advances in cellular biology, a shift towards changes in cytosolic enzyme activities, DNA patterns and genetic effects can be studied instead of concentrating on the gross effects produced by the plant drug. Co-operation between industry and academia will go a long way in achieving these goals. British pharmacological society and pharmaceutical industry in Britain have tried to establish a joint academic industry group to provide funds for research. This is a good example to be followed in India.

Quality control of the plant raw materials is one important aspect in improving the use of traditional medicines. Authenticity of proper samples for preparation is important. The samples need to be confirmed from proper centres where facilities for identification is available. National Institute of Science Communication (NISCOM) at Delhi has such a facility. The major problem in quality control is the batch to batch variations in the quality of medicinal plants. Therapeutic value of medicinal plants could differ depending on soil conditions, nutritional status, climatic conditions, seasonal variations etc. Ecotype pharmacological evaluation is very essential when the drug is used in a crude form. The relative proportions of phytochemicals present in medicinal plants can vary in different ecotypes. The pharmacological activities of certain compounds can be influenced by their interaction with other compounds. Toxicity of certain chemicals can be reduced or increased by the presence of certain other chemicals. Therefore pharmacological evaluation of each ecotype is essential to determine even if the variations in major chemical constituents are known. The most appropriate ecotype of a medicinal plant should be used for drug development.

There is also a need for documentation of research and publication of results in peer reviewed journals. Most of the information on pharmacological studies of plants are incomplete since they are published as abstracts presented at conferences. Few journals like Ethnopharmacology and Natural Remedies are publications focusing on plant products. Availability of information on websites is another way of disseminating information. Development of one centre under ICMR, CSIR or DST as the advanced centre for information on herbal drugs may help scientists working in different areas. The advanced ICMR research centre at Seth GS Medical College under the guidance of Prof. Dahanukar has contributed considerably to the study of herbal medicines. Standardisation of tests and the methods of preparation is another area which requires attention. Standardisation of formulations using modern technology will add precision to quality control as well as minimize false claims and adulterations. The risk of untested and unregulated remedies should be known to the lay public. Even if the herbal formulation is in use in traditional system of medicine, there are possibilities of risk and adverse effects. Therefore documentation of adverse effects of herbal medicines merits attention. WHO has taken steps in this direction by establishing a centre for reporting of adverse reactions to herbal medicines, at the Uppsala Monitoring Centre, Sweden.

In conclusion, it is clear that herbal industry can make great strides in India, with the co-operation between drug regulatory authorities, scientists and industry. Standardisation of methods, quality control, data on safety and efficacy are need for proper understanding of the use of herbal medicines.

References