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QUALITY CONTROL, STANDARDIZATION & DEVELOPMENT OF SCIENTIFICALLY VALIDATED HERBAL FORMULATIONS/DRUGS

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ABSTRACT

The vast store house of indigenous, tribal, folklore and traditional systems of medicine, a valuable heritage of most countries of Asia, still needs to be explored adequately. Although, herbal medicines are widely used by the population, yet its potential, wider use for primary health care, its use also in the modern systems of medicine and discoveries of new medicines from these plants have been largely unrealized. The pharmaceutical houses are showing interest in supporting research towards the discovery of new medicines from plants. Further, research directed at a few of the chronic diseases against which more drugs are needed, could lead to the discovery of new drugs. It is important also to take steps to ensure that unethical and unjustified exploitation of medicinal plants is prevented. The need for proper standardization has also been recognized by practitioners of traditional systems of medicine. The paper provides rationale and perspective of quality control and standardization of herbal drugs.

In the last few decades there has been worldwide revival on the use of herbal drugs/phytochemical for the diverse purpose including medicinal, nutritional and as cosmetic. The revival of interest in natural drugs and the herbal products started in the last decade mainly because of the widespread belief that 'green' medicine is healthier than synthetic products. This has led to the rapid spurt of demand for health products like herbal tea, ginseng and such products of traditional medicine during the 1980s. The health promotion and disease prevention strategy in treatment is widely prevalent in oriental systems, especially the Indian ('Ayurveda', 'Siddha', 'Unani and 'Amchi') and the Chinese systems of medicine are finding increasing popularity and acceptance in the world over. Because of this sweeping 'greenwave' a large number of herbal drugs and the plant derived herbal products are sold in the health food shops all over the developed countries.

The global herbal medicine is about US$ 90 billion which is growing at the rate of 10-15% annually and is expected to cross 5 trillion US$ by 2030. The Indian share of the herbal World market is less than 2%, India set the

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target to export of herbal drugs/products worth of Rs. 10,000 corers by 2010 (Agarwal, 2005). These targets can be achieved by providing scientifically validated, safe and standardized herbal products in domestic and international markets. Further, by rediscovery of the connection between plants and health for launching a new generation of botanical therapeutics that include plant-derived pharmaceuticals, multicomponent botanical drugs, dietary supplements, functional foods and plant-produced recombinant proteins, many of these products will soon complement conventional pharmaceuticals in the treatment, prevention and diagnosis of diseases, while at the same time adding value to agriculture.

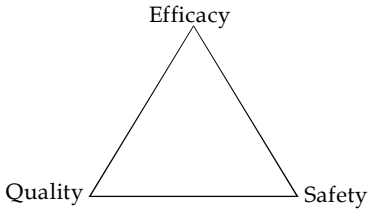
Need for Standardization of Medicinal Plants

New technologies are constantly being developed to isolate and identify the components responsible for the activity of these plants. But these technologies should consider and possibly use the fact that the biological activity of plant extracts often results from additive or synergistic effects of its components. Another possibility is the qualitative and quantitative variations in the content of bioactive phytochemicals, which are currently considered major detriments in its use as a medicine. Different stresses, locations, climates, microenvironments and physical and chemical stimuli, often called elicitors, qualitatively and quantitatively alter the content of bioactive secondary metabolites. Enzymatic pathways leading to the synthesis of these phytochemicals are highly inducible (Ebel and Costa, 1994). This is particularly true for phytochemicals that are well documented for their pharmacological activity, such as alkaloids (Facchini, 1994), phenylpropanoids (Dixon and Palva, 1995) and terpenoids (Trapp and Croteau, 2001) whose levels often increase by two to three orders of magnitude following stress or elicitation (Darvill and Albershelm, 1984). Thus, elicitation-induced, reproducible increases in bioactive molecules, which might otherwise be undetected in screens, should significantly improve reliability and efficiency of plant extracts in drug discovery while at the same time preserving wild species and their habitats. Standardization, optimization and full control of growing conditions should guarantee a cost-effective and quality-controlled production of many plant-derived compounds. This kind of standardization and quality control of the plant based drugs will improve safety of these drugs and promote its usage.

Most of the herbal drugs produced currently in the developing countries generally lack proper quality specification and standards and therefore, have no consistency in quality in batch to batch products. Most of these drugs do not have well defined and characterized composition. The three pillars of ideal herbal drug and their rational use are quality, safety and efficacy

(Fig. 1). The traditional medicines used to be an individual based treatment regime wherein the traditional physicians used hand picked plant materials to prepare drugs/formulations to treat their patients.

Figure 1
Herbal drugs



A well-experienced traditional physician in the past used to have specific knowledge and special ability to collect the right plants having the therapeutically useful agents from certain specific habitats. These experienced medicinal plant collectors had intimate knowledge of plant species and could identify therapeutically effective plant from a population of a species. With such unique expertise they were able to maintain certain level of standards in the therapeutic quality of the herbal drugs. There had been a decline or almost extinction of such experienced plant collectore by the turn of 20th century itself due to a variety of reasons. One of the reasons was the transformation of traditional medicine from the individualized system to a commercial manufacturing system. This transformation resulted in great deterioration in the whole procedure and process of traditional medicine. Indeed, quality of the drugs became the greatest casualty in this transformation.

Over 80 per cent of the raw material required for traditional medicines/ herbal medicines used to be collected from wild resources. With the increase in demand of medicinal plants for the commercial herbal medicine sector led to the indiscriminate and unscientific collection without any consideration for the quality of the material collected. Lack of societal support and encouragement the orally transmitted expertise in collecting the quality plant material suffered great setback and even loss of such knowledge system during the course of last 100 years. It has caused extensive erosion and corrosion in the traditional wisdom, knowledge and practice of particularly medicinal plant collection.

It is now well known that the therapeutic activity of a medicinal plant is due to the presence of certain biologically active chemical constituents, which are either primary or secondary metabolites. The expression of many of these compounds particularly those of the secondary metabolite category

are controlled and conditioned by a variety factors such as its genetic predisposition, habitat of the plant agro climatic conditions, season and also the stage of growth and development of the plant etc. The Traditional Indian System of Medicines like Ayurveda, Siddha, Unani and Amchi etc. provided specific instructions for collection by indicating location/edaphic conditions, habitat, seasonal and even the stage of the plant growth and developmental stage. Scientific investigations now provide ample evidence to the fact that there is a flux of change in the presence of very many of these chemical constituents, particularly those of the secondary metabolites, in such varied conditions described above. Therefore, it is extremely important to establish the reference samples and to determine the quality parameters of the medicinal plants by undertaking extensive and intensive study of the traditional treatise of the classical medicines or traditional practices, combined with the modern scientific knowledge and methods and using the latest analytical and computational tools like HPLC, GC, HPTLC, etc.

Some essential steps to ensure quality include compliance with GMP, preparation of standard formulations, preparation of SOP's, strict adherence to standard protocols etc. The essential steps to be followed are summarized in Table 1.

Table 1
Essential Steps for Production of Standardized Quality Herbal Products

Ist Step	Taxonomically identified authenticated crude drugs (devoid of foreign matter, mycotoxin, aflatoxin, heavy metals and pesticides).
IInd Step	Standard Formula.
IIIrd Step	GMP compliance equipments and infrastructure.
IVth Step	Standard operating protocol for manufacturing the formulations (Grinding, sieving, mixing, extraction, boiling etc.).
Vth Step	Final product and its quality parameter.
VIth Step	Good storage condition, good packaging, labeling, date of manufacturing, list of ingredients and dose.

In the whole process of herbal drug/product production the proper taxonomically identified safe raw material is primary requirement. To get constant supply of right raw material whether procured from wild or cultivated and their storage one has to follow. Good Agriculture Practices (GAP), Good Collection Practices (GCP), Good Ethical Practices (GEP), Good Procurement Practices (GPP), Good Safety Practices (GSP) *[Pesticide, heavy metal, microbial load as per WHO guidelines]* and Good Storage Practices (GSP).

The Complexity of Herbal Products

Herbal products may contain a single herb or combinations of several different herbs believed to have complementary and/ or synergistic effects.

Some herbal products, including many traditional medicine formulations, also include animal products and minerals (Rotblatt and Ziment, 2002). Herbal products are sold as either raw plants or extracts of portions of the plant. Extraction involves boiling or percolating the herb in water, alcohol, or other solvents to release biologically active constituents of the plant. These liquid extracts may then be heated or dried to create more concentrated liquids, pastes, or powders. Both the raw herb and the extract contain complicated mixtures of organic chemicals, which may include fatty acids, sterols, alkaloids, flavonoids, glycosides, saponins, tannins, and terpenes (Rotblatt and Ziment, 2002). It is often difficult to determine which component, if any, of the herb has biological activity in humans. In addition, the processing of herbs, such as heating or boiling, may alter the pharmacological activity of the organic constituents. Similarly, a host of environmental factors, including soil, altitude, seasonal variation in temperature, atmospheric humidity, length of daylight, rainfall pattern, shade, dew, and frost conditions, may affect the levels of components in any given batch of an herb. Other factors, including infections, insects, planting density, competition with other plant species, seeding time, and genetic factors, play an important role in producing uniform herbal products (Wijesekera, 1991).

Adulteration/substitution in Herbal Drugs in Indian Drug Market

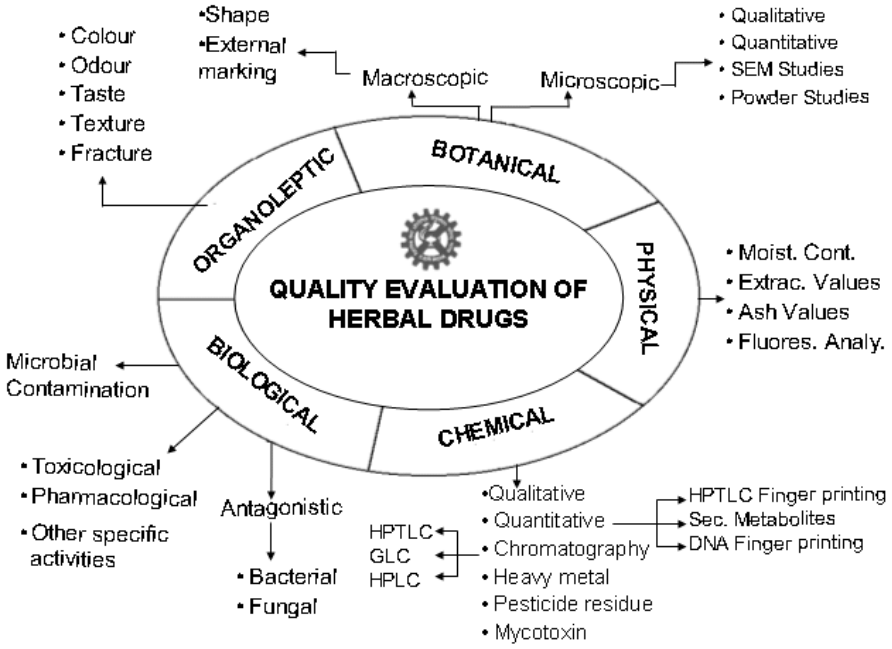
Indian herbal drug industries generally face the problem of adulteration & substitution. It is observed that in herbal markets of the country, sometimes not only the various species of particular genus but entirely different taxa are being sold under the same vernacular name. For example in the name of 'Talispatra' an important Ayurvedic drug, different leaves of *Taxus wallichiana*, *Abies spectabilis* and *Rhododendran anthopogan* are being sold in Dehradun, Kolkatta & Amritsar market respectively (Rawat et al., 1996). Similarly, on the name of drug 'Pittapapra' different plants viz. *Fumaria parviflora*, *Peristrophe bicalyculata* and *Oldenlandia corymbosa* and *Rungia* are being sold in various crude drug markets.

Drug Evaluation

To identify the adulterant/substitutes it is essential to develop pharmacognostical parameters for their identification and quality control. This involved botanical, physico-chemical studeies and qualitative and quantitative estimation of secondary metabolites. (Fig. 2).

Realizing the problem of adulteration and substitution in herbal drugs the pharmacognosy & Ethnopharmacology Division of National Botanical Research Institute, Lucknow is engaged for the last 2 decades in developing

Figure 2
Quality and standardization of herbal drugs/ formulations



parameters for quality control of crude drug and standardization of polyherbal formulations. Under the programme over 150 crude single herbal drugs and about 20 polyherbal formulations have been standardized. Some of the important raw drugs evaluated are 'Amraharidra', 'Ativisha', 'Bach', 'Bhuimala', 'Chiriata', 'Daruharidra', 'Kali Musli', 'Kalmegh', 'Pitpapra', 'Safed musli', 'Salam panja', 'Satawar', 'Resha khatmi', 'Talispatra', 'Vidarikand', etc. The pharmacognostical parameters developed for the drug 'Khatmi' seed (*Althaea officinalis*) which can be used for its identification. The studies involved microscopical studies of the seeds and development of HPTLC profiles.

Conclusion

Realizing the importance of quality raw material and prevalence of spurious raw material in herbal drug market, there is an urgent need for developing pharmacognostical parameter for the identification of substitutes of adulterants. The Govt. of India (Deptt. of Ayush, New Delhi), CSIR, ICMR & other agencies are working in this direction. The Dept. of Ayush has already published three volumes of Ayurvedic Siddha & Unani herbal pharmacopoeia wherein detailed botanical, chemical & physicochemical

standards of different crude drugs used in Ayurveda, Siddha & Unani has been described. (Anonymous, 1999, 2001, 2002, 2004).

Similarly, Indian Council of Medical Research (ICMR) New Delhi has initiated a programme on evolving standards for medicinal plants and under this programme the council has published two volume of "Quality Standards of Indian Medicinal Plants". (Anonymous, 2002, 2003).

To meet out the great demand of the botanicals for producing standardized and quality herbal drugs/products and to promote the export of Auyrvedic medicine it is essential to maintain the quality of herbs used for the preparation of these products. Therefore, identify of plant species, time of harvest, drying, storage are some of the important factors for producing quality herbal medicine having batch to batch consistency and desirable therapeutic effects.

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