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Recent Trends in Herbal Drugs: A Concise Review

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[1]Pulla Udaya Chandrika*, [2]Avanapu Srinivasa Rao, [3]Yella Sirisha, [4]S.RamaChandra

1. *Assistant Professor, Department of pharmacognosy, Bhaskar Pharmacy College, Hyderabad*
2. *Professor, Department of pharmacology, Bhaskar Pharmacy College, Hyderabad*
3. *Assistant Professor, Department of pharmaceutics, Bhaskar Pharmacy College, Hyderabad*
4. *Associate Professor, Department of pharmacology, Bhaskar Pharmacy College, Hyderabad, India.*

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ABSTRACT

In recent years, more people throughout the world are turning to use medicinal plant products in the healthcare system. The worldwide need for alternative medicine has resulted in the growth of natural product markets and interest in traditional systems of medicine. Herbal drug technology is used for converting botanicals materials into medicines, where standardization and quality control with proper integration of modern scientific techniques and traditional knowledge are important. This article provides a general idea of herbal medicines and intended to explain the therapeutic effectiveness of various herbal medicines, adverse drug reactions, drug interactions, standardization and stability testing of herbal medicines, pharmacovigilance and regulatory status of herbal medicines.

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INTRODUCTION

Herbal drugs referred as plants materials or herbalism, involves the use of whole plants or parts of plants, to treat injuries or illnesses[1]. Herbal drugs are the use of therapeutic herbs to prevent and treat diseases and ailments or to support health and healing[2]. These are drugs or preparations made from a plant or plants and used for any of such purposes. Herbal drugs are the oldest form of health care known to mankind[3]. There are many herbal products offered that assert to treat the symptoms of a broad range of problems, from depression to cold and flu. World Health Organization[4] (WHO) has distinct herbal drugs as complete, labeled medicinal products that have vigorous ingredients, aerial or secretive parts of the plant or other plant material or combinations. World Health Organization has set precise guidelines for the evaluation of the safety, efficacy, and quality of herbal medicines. WHO estimates that 80% of the world populations currently use herbal drugs for major healthcare. Exceptionally, in some countries herbal drugs may also enclose by tradition, natural organic or inorganic active constituents which are not of plant source. The herbal drug is a chief constituent in traditional medicine and a common constituent in ayurvedic, homoeopathic, naturopathic and other medicine systems[5]. Herbs are usually considered as safe since they belong to natural sources[6]. The use of herbal drugs due to toxicity and side effects of allopathic medicines has led to rapid increase in the number of herbal drug manufacturers. For the past few decades, herbal drugs have been more and more consumed by the people with no prescription. Seeds, leaves, stems, bark, roots, flowers, and extracts of all of these have been used in herbal drugs over the millennia of their use. Herbal products have reached extensive adequacy as beneficial agents like antimicrobial, antidiabetic, antifertility, antiageing, antiarthritic, sedative, antidepressant, antianxiety, antispasmodic, analgesic, anti-inflammatory, anti-HIV, vasodilatory, hepatoprotective, treatment of cirrhosis, asthma, acne, impotence, menopause, migraine, gall stones, chronic fatigue, Alzheimer's disease, and memory enhancing activities[7]. Herbal drugs have been recognized for approximately 4000 years. These drugs have survived real world testing and thousands of years of human testing. Some drugs have been discontinued due to their toxicity, while others have been modified or combined with additional herbs to counterbalance side effects.

ADVANTAGES OF HERBAL DRUGS

- Low/Minimum cost
- Potency and efficiency
- Enhanced tolerance
- More protection
- Fewer side-effects
- Complete accessibility
- Recyclable

DISADVANTAGES OF HERBAL DRUGS

- Not able to cure rapid sickness and accidents
- Risk with self-dosing
- Complexity in standardizations

USAGE AND PREPARATION OF HERBAL DRUGS

The use of herbal drugs in the correct way provides effectual and safe treatment for many ailments. The efficiency of the herbal drugs is typically subjective to the patient[8]. The strength of the herbal drugs varies based on the genetic distinction, growing conditions, timing and method of harvesting, revelation of the herbs to air, light and dampness, and type of conservation of the herbs. Some of the plants that make up herbal drugs are cultured and processed in the country and others are imported from around the world. Raw materials for herbal drugs may be derived from carefully cultivated plants or collected in the wild[9]. Herbal drugs are accessible in several forms and often require preparation before their use. They can be normally purchased in mass form as dried plants, plant parts or insecurely packed for herbal teas and decoctions. Decoctions are made by boiling the herb in water, then straining out of the plant material. More intense forms of herbal drugs are available in the form of hydroalcoholic tinctures and fluid extracts. Methods of preparation may differ because of the nature of the plants active chemical constituents[10].

Table.1:

Pharmacological actions of herbal drugs	**Examples**
anti-inflammatory activity	*Achillea millefolium, Artemisia vulgaris, Bauhinia tarapotensis, Curcuma longa,*
antidiabetic activity	*Acacia nilotica, Aconitum ferox, Adhatoda vasika, Adiantum capillus,Agrimonia eupatoria, Allium sativum, Aloe barbadensis, Apium graveolens, Embilica officinalis, Eucalyptus globules, Ginseng panax, Gymnema sylvestris, Nigella sativa, Panex quinquefolius, Polygala senega, Plantago ovata, Punica granatum, Salvia officinalis, Scoparia dulcis, Tecoma stans,Zea mays* [12-15].
analgesic activity	*Bougainvilla spectabilis, Chelidonium majus, Ficus glomerata, Dalbergia lanceolaria, Glaucium grandiflorum, Glaucium paucilobum, Nepeta italic*[16]
anticancer activity	*Acalypha fruticosa, Alangium lamarki, Catharanthus roseus, Celastrus paniculatus, Embelia ribes, Ficus glomerata, Ficus racemosa, Ocimum basilicum, Plumbago zeylanica, Terminalia chebula, Tylophora indica, Wrightia tinctoria.*[17-19]
antiageing activity	*Allium sativum, Arnicamontana, Cucumis sativum, Curcuma longa, Ficus bengalenis, Lycium barbarum, Ocimum sanctum, Panax ginseng, Prunus amygdalus, Santalum album, Rosa damascene* and *Withania somnifera*[20, 21].
antifertility activity	*Podophyllum peltatum, Punica granatum, Raphanus sativus, Rehmannia glutinosa, Semecarpus anacardium, Sesbania sesban, Stemona japonica, Thuja occidentalis, Taxus baccata* and *Verbena officinalis*[22].

HERBAL- DRUG INTERACTIONS[23]:

Herbs are often administered in combination with therapeutic drugs, raising the potential for herb-drug interactions. Cases have been published reporting enhanced anticoagulation and bleeding when patients on long-term warfarin therapy also took *Salvia miltiorrhiza* (danshen). *Allium sativum* (garlic) decreased the area under the plasma concentration-time curve (AUC) and maximum plasma concentration of saquinavir, but not ritonavir and paracetamol (acetaminophen), in volunteers. *A. sativum* increased the clotting time and international normalised ratio of warfarin and caused hypoglycemia when taken with chlorpropamide. *Ginkgo biloba* (ginkgo) caused bleeding when combined with warfarin or aspirin (acetylsalicylic acid), raised blood pressure when combined with a thiazide diuretic and even caused coma when combined with trazodone in patients. *Panax* ginseng (ginseng) reduced the blood concentrations of alcohol (ethanol) and warfarin, and induced mania when used concomitantly with phenelzine, but ginseng increased the efficacy of influenza vaccination. *Scutellaria baicalensis* (huangqin) ameliorated irinotecan-induced gastrointestinal toxicity in cancer patients.*Piper methysticum* (kava) increased the 'off' periods in patients with parkinsonism taking levodopa and induced a semicomatose state when given concomitantly with alprazolam. Kava enhanced the hypnotic effect of alcohol in mice, but this was not observed in humans. *Silybum marianum* (milk thistle) decreased the trough concentrations of indinavir in humans. Piperine from black (*Piper nigrum Linn*) and long (*P. longum Linn*) peppers increased the AUC of phenytoin, propranolol and theophylline in healthy volunteers and plasma concentrations of rifamipicin (rifampin) in patients with pulmonary tuberculosis. Interactions between herbal medicines and prescribed drugs can occur and may lead to serious clinical consequences. There are other theoretical interactions indicated by preclinical data. Both pharmacokinetic and/or pharmacodynamic mechanisms have been considered to play a role in these interactions, although the underlying mechanisms for the altered drug effects and/or concentrations by concomitant herbal medicines are yet to be determined. The clinical importance of herb-drug interactions depends on many factors associated with the particular herb, drug, and patient. Herbs should be appropriately labeled to alert consumers to potential interactions when concomitantly used with drugs, and to recommend a consultation with their general practitioners.

STANDARDIZATION OF HERBAL DRUGS

Standardized herbal products of consistent quality and containing well-defined constituents are required for reliable clinical trials and to provide consistent beneficial therapeutic effects. Pharmacological properties of an herbal formulation depend on phytochemical constituents present therein. Development of authentic analytical methods which can reliably profile the phytochemical composition, including quantitative analyses of marker/bioactive compounds and other major constituents, is a major challenge to scientists. Without consistent quality of a phytochemical mixture, a consistent pharmacological effect is not expected. The resurgence of interest and the growing market of herbal medicinal products necessitate strong commitment by the stakeholders to safeguard the consumer and the industry. Standardization is the first step for the establishment of a consistent biological activity, a consistent chemical profile, or simply a quality assurance program for production and manufacturing. Therefore, the EU has defined three categories of herbal products:

- Those containing constituents (single compounds or families of compounds) with known and experienced therapeutic activity that are deemed solely responsible for clinical efficacy.
- Those containing chemically defined constituents possessing relevant pharmacological properties which are likely to contribute to the clinical efficacy.
- Those in which no constituents have been identified as being responsible for the therapeutic activity.

Standardization, as defined in the text for guidance on the quality of herbal medicinal products, means adjusting the herbal drug preparation to a defined content of a constituent or group of substances with known therapeutic activity. The European Medicines Agency (EMEA) makes the distinction between constituents with a known therapeutic activity which can be used to standardize a biological effect and marker compounds which allow standardization on a set amount of the chosen compound. The EMEA defines marker compounds as chemically defined constituents of a herbal drug which are of interest for control purposes, independent of whether they have any therapeutic activity or not. Examples of markers are the valerenic acids in *Valeriana officinalis* L., ginkgolides and flavonoids in *Ginkgo biloba* L. and hypericin and hyperforin in *Hypericum perfoliatum.*[24,25]

STABILITY TESTING OF HERBAL PRODUCTS

Stability testing is necessary to ensure the product is of acceptable quality throughout its entire storage period. An important part of quality control of herbal products is the evaluation of the chemical stability of a finished product during the storage period. Stability testing of herbal products is a challenging task because the entire herb or herbal product is regarded as the active substance, regardless of whether constituents with defined therapeutic activity are known. The objective of a stability testing is to provide evidence on how the quality of the herbal products varies with Stability testing examines the quality and potency of drug at suitable time intervals under the influence of environmental factors such as temperature, light, oxygen, moisture, other ingredient or excipient in the dosage form, particle size of drug, microbial contamination, trace metal contamination, leaching from the container.[26]

Products are normally required to have shelf lifes that are measured in years. Accelerated stability studies are designed to increase the rate of chemical degradation or physical change of a drug substance, therefore, tests must also be conducted under conditions, which accelerate any changes occurring at ambient temperature and humidity.

Table no.2: Types of stability and conditions required throughout the shelf-life

Chemical	Every active constituent retains its chemical integrity and potency within specified time
Physical	The original physical properties like appearance, palatability, uniformity, dissolution are retained
Microbiological	Sterility or resistance to microbial growth is retained
Therapeutic	Therapeutic effect remains unchanged
Toxicological	No significant increase in toxicity occurs

Table 3: Types of changes occur on storage

Chemical	Degradation of active constituents, interaction between constituents, loss of constituents by sorption of container
Physical	Viscosity, texture, colour, odour, pH, loss of volatile constituents, uptake of water, oxygen or carbon dioxide
Microbiological	Loss of antimicrobial preservative efficacy
Container	Leakage, corrosion, stress cracking

Table 4: Storage conditions and sampling times for stability testing

Conditions	**Sampling times**	**Parameters studied at each condition**
Long term testing $25^0 \pm 2^0$C/60%RH±5%RH	0,3,6,9,12,18,24,36,48,60 months	Organoleptic properties Assay pH Viscocity Particle size Weight loss
Accelerated testing $40^0 \pm 2^0$C/75%RH±5%RH	3,6 months	
Intermediate testing $30^0 \pm 2^0$C/60%RH±5%RH	3,6,9,12 months	

Table 5: Different stability test conditions

Test	**Test conditions**
Elevated temperature	4^0C/ambient humidity;25^0C/60%±5% relative humidity;$37^0 \pm 2^0$C/60%±5% relative humidity;45^0C$\pm 2^0$C/70%±5% relative humidity.
Elevated humidity	45^0C/70% relative humidity
Cycling tests	37^0C/80%RH. Alternating 24 hourly with 20^0C ambient humidity
Freeze –thaw tests	-30^0C/80%RH. Alternating 24 hourly with ambient temperature
Exposure to light	Continuous exposure in a light testing cabinet
Mechanical tests	In centrifuge or vibration apparatus
Stress testing	Severe condition of 50-60^0C above and 75% RH

Table 6: Suggestions for herbal product stability testing.

All finished products, bulk products in relation to dosage, packing type have to be tested	Only two batches of drug substance and 03 batches of drug product have to be tested
Test to be carried out continuously throughout the year	Only room temperature stability testing should be carried out without intermediate or long term testing
Studies have to be carried out for long term for mentioned shelf life	Assay of marker substance with ±10% from declared value should be allowed

With the help of modern analytical techniques like HPLC, HPTLC and by employing proper guidelines it is possible to establish sound stability data for herbal products and predict their shelf life which will help in global acceptability of herbal products.

PHARMACOVIGILANCE OF HERBAL DRUG

Pharmacovigilance is relating to detection, assessment, understanding and prevention of adverse effects particularly long term and short term effect of medicines. In other words, it is collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications. It is also the study of marketed drugs under practical conditions of clinical usages. Information on adverse drug reactions can be generated from spontaneous reports or normal clinical trials. Systematic pharmacovigilance is essential to building up reliable information on the safety of herbal medicines for the development of appropriate guidelines for safe effective use. It is to improve patient care and safety in relation to the use of medicines and all the medical and paramedical interventions, to improve public health and safety in relation to the use of medicines[26].

The WHO has welcomed the active participation of drug regulatory authorities and national pharmacovigilance centers, among others, in the development of these guidelines. This has provided a useful starting point for strengthening communication between these authorities, which will be needed to ensure progress toward the common goal—the safety of herbal medicines.[27] The guidelines, therefore, identify the particular challenges posed in monitoring the safety of herbal medicines effectively and propose approaches for overcoming them. Special

attention is also given to the reporting system for adverse reactions to herbal medicines, and to the analysis of the causes of the reported adverse reactions[28].

The safety monitoring of herbal medicines is compared and contrasted with that of other medicines currently undertaken in the context of the WHO International Drug Monitoring Program. Although there are regulatory and cultural differences in the preparation and use of different types of medicines, they are all equally important from a pharmacovigilance perspective. The inclusion of herbal medicines in pharmacovigilance systems is becoming increasingly important given the growing use of herbal products and herbal medicines globally. Herbal medicines are frequently used in conjunction with other medicines, and it is essential to understand the consequences of such combined use and monitor whether any adverse effects are arising. This can be achieved most readily within the existing pharmacovigilance systems. To handle herbal medicines and, in particular, to analyze the causes of adverse events, the national pharmacovigilance centers (or equivalent institutions) will need to acquire specific technical expertise. This will include trained personnel in the relevant technical areas and facilities to analyze the products concerned, for which there is often insufficient information and lack of access to reliable information support. Many countries currently lack this expertise and, in particular, access to suitable analytic laboratories. The Member States have therefore recommended the establishment of regional laboratories specializing in the analysis of herbal products. The WHO encourages the Member States to explore the feasibility of this proposal.

REGULATORY STATUS [29]

Phytotherapeutic agents are standardized herbal preparations consisting of complex mixtures of one or more plants which contain as active ingredients plant parts or plant material in the crude or processed state. A marked growth in the worldwide phytotherapeutic market has occurred over the last 15 years. For the European and USA markets alone, this will reach about $7 billion and $5 billion per annum, respectively, in 1999, and has thus attracted the interest of most large pharmaceutical companies. Insufficient data exist for most plants to guarantee their quality, efficacy, and safety. The idea that herbal drugs are safe and free from side effects is false. Plants contain hundreds of constituents and some of them are very toxic, such as the most cytotoxic anti-cancer plant-derived drugs, digitalis and the pyrrolizidine alkaloids, etc. However, the

adverse effects of phytotherapeutic agents are less frequent compared with synthetic drugs, but well-controlled clinical trials have now confirmed that such effects really exist. Several regulatory models for herbal medicines are currently available including prescription drugs, over-the-counter substances, traditional medicines and dietary supplements. Harmonization and improvement in the processes of regulation are needed, and the general tendency is to perpetuate the German Commission E experience, which combines scientific studies and traditional knowledge (monographs). Finally, the trend in the domestication, production, and biotechnological studies and genetic improvement of medicinal plants, instead of the use of plants harvested in the wild, will offer great advantages since it will be possible to obtain uniform and high-quality raw materials which are fundamental to the efficacy and safety of herbal drugs.

CONCLUSION

Medicinal herbs as a potential source of therapeutics aids have attained a significant role in health care system all over the world for human beings not only in the diseased condition but also as a potential material for maintaining proper health. It is clear that the herbal industry can make great strides in the world. With the increased use of herbal products, the future worldwide labeling practice should adequately address quality aspects. Standardization of methods and quality control data on safety and efficacy are required for an understanding of the use of herbal drugs. A major factor impeding the development of the medicinal plant based industries in developing countries has been the lack of information on the social and economic benefits that could be derived from the industrial utilization of medicinal plants. Further research is required to exploit the compounds responsible for the observed biological activity.

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