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Research Paper

Need & Scope of Standardization of herbal medicines - A review

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ABSTRACT:
There is increasing awareness and general acceptability of the use of herbal drugs in today's medical practice. The starting materials for about one-half of the medicines we use today come from natural sources. This rise in the use of herbal product has also given rise to various forms of abuse and adulteration of the products leading to consumers and manufacturers disappointment and in some instances fatal consequences. Herbal drug technology is used for converting botanical materials into medicines, where standardization and quality control with proper integration of modern scientific techniques and traditional knowledge is important. For global harmonization WHO specific guidelines for the assessment of the safety, efficacy and quality of herbal medicines are of utmost importance. Standardization of drug means confirmation of its identity, quality and purity throughout all phases of its cycle.
This review seeks to need & scope of standardization processes of herbal medicine for good quality assurance.
KEY WORDS: *WHO, Herbal medicine, Standardization, Quality Control.*

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I. INTRODUCTION:

Standardization of herbal medicines is the process of prescribing a set of standards or inherent characteristics, constant parameters, definitive qualitative and quantitative values that carry an assurance of quality, efficacy, safety and reproducibility. It is the process of developing and agreeing upon technical standards. Specific standards are worked out by experimentation and observations, which would lead to the process of prescribing a set of characteristics exhibited by the particular medicines. Hence standardization is a tool in the quality control process [1].

Methods of standardization should take into consideration all aspects that contribute to the quality of the herbal drugs, namely correct identity of the sample, organoleptic evaluation, pharmacognostic evaluation, volatile matter, quantitative evaluation (ash values, extractive values), phytochemical evaluation, test for the presence of xenobiotics, microbial load testing, toxicity testing, and biological activity. Of these, the phytochemical profile is of special significance since it has a direct bearing on the activity of the herbal drugs. The fingerprint profiles serve as guideline to the phytochemical profile of the drug in ensuring the quality, while quantification of the marker compound/s would serve as an additional parameter in assessing the quality of the sample [2].

Several problems not applicable to synthetic drugs often influence the quality of herbal drugs. For instance:
1. Herbal drugs are usually mixtures of many constituents.
2. The active principle(s) is (are), in most cases unknown.
3. Selective analytical methods or reference compounds may not be available commercially.
4. Plant materials are chemically and naturally variable.
5. Chemo-varieties and chemo cultivars exist.
6. The source and quality of the raw material are variable.

The methods of harvesting, drying, storage, transportation, and processing (for example, mode of extraction and polarity of the extracting solvent, instability of constituents, etc.) also affect herbal quality [3].

NEED OF STANDARDIZATION:

It is the cardinal responsibility of the regulatory authorities to ensure that consumers get the medication, which guarantees purity, safety, potency and efficacy. The regulatory authorities rigidly follow various standards of quality prescribed for raw materials and finished products in pharmacopoeias, formularies and manufacturing operation through statutory imposed good manufacturing practices. These procedures logically would apply to all types of medication whether included in modern system of medicine or one of the traditional systems [4].

These have necessitated development of modern and objective standards for evaluating the safety, quality and efficacy of these medicines. People are also becoming aware of the potency and side effect. To gain public trust and to bring herbal product into mainstream of today health care system, the researchers, the manufacturers and the regulatory agencies must apply rigorous scientific methodologies to ensure the quality and lot to lot consistency of the traditional herbal products [5]. Need of Quality control and standardization of herbal products can be summarized as follows-

1. When traditional medicines were developed technology and concept of standardization was quite different.
2. During past thousand years dynamic process of evolution may have changed the identity of plant material.
3. Due to commercialization, supply of genuine raw material has become a challenge.
4. Properties of botanicals may have undergone change due to time and environmental factors [6].

Due to complex nature and inherent variability of the constituents of plant based drugs, it is difficult to establish quality control parameter and modern analytical technique are expected to help in circumventing this problem. Furthermore, the constituents responsible for the claimed therapeutic effects are frequently unknown or only partly explained. Most of the herbal formulations, especially the classical formulations of traditional medicine, are polyherbal. Even official standards are not available. The unique processing methods followed for the manufacture of these drugs turn the single drugs into very complex mixture, from which separation, identification and analysis of the components is very difficult [7].

SCOPE OF STANDARDIZATION:

Generally, all medicines, whether they are synthetic or of plant origin, should fulfill the basic requirements of being safe and effective [8, 9, 10, 11, 12, 13]. The term "herbal drugs" denotes plants or plant parts that have been converted into phytopharmaceuticals by means of simple processes involving harvesting, drying, and storage [14]. Hence they are capable of variation. This variability is also caused by differences in growth, geographical location, and time of harvesting.

At present no official standards are available for herbal preparations. Those manufacturers, who are currently doing some testing for their formulations, have their own parameters, many of which are very preliminary in nature. Presently it is very difficult to identify the presences of all the ingredients as claimed in a formulation. Hence the first important task is to evolve such parameter by which the presence of the entire ingredient can be identified, various chromatographic and spectrophotometric methods and evaluation of physicochemical properties can be tried to evolve pattern for identifying the presence of different ingredient. Wherever possible these methods can be applied for quantitative estimation of bioactive group of compounds like alkaloids, flavonoids, polyphenolic components or estimation of particular compound [15].

II. METHOD OF STANDARDIZATION:

According to WHO, standardization and quality control of herbals is the process involved in the physicochemical evaluation of crude drug covering aspects, such as selection and handling of crude material, safety, efficacy and stability assessment of finished product, documentation of safety and risk based on experience, provision of product information to consumer and product promotion which include physical, chemical and biological evaluation employing various analytical methods and tools [16, 17].

Physical evaluation

Each monograph contains detailed botanical, macro-scopic and microscopic descriptions of the physical characteristics of each plant that can be used to ensure both identity and purity. Each description is accompanied by detailed illustrations and photographic images which provide visual documentation of accurately identified material.

Microscopic evaluation

Full and accurate characterization of plant material requires a thorough physical examination. Microscopic analyses of plants are invaluable for assuring the identity of the material and as an initial screening test for impurities.

Chemical evaluation

This covers screening, isolation, identification and purification of the chemical components. Chemical analysis of the drug is done to assess the potency of vegetable material in terms of its active principles. The chemical screening or tests may include color reaction test, which help to determine the identity of the drug substance and possible adulteration.

Biological evaluation

Pharmacological activity of certain drugs has been applied to evaluate and standardize them. The assays on living animal and on their intact or isolated organs can indicate the strength of the drug or their preparations. These assays are known as Biological assays or Bioassay.

Analytical Methods

It helps in determining identity, quality and relative potency**.** The most important step in the development of analytical methods for botanical and herbal preparations is sample preparation. The basic operation includes steps such as pre- washing, drying of plant materials or freezedrying and grinding, to obtain a homogenous sample and often improving the kinetics of extraction of the constituents. In the pharmacopoeial monographs, method such as sonication, heating under reflux, Soxhlet extraction, and others are commonly used [18, 19]. However, such methods can be time-consuming, require the use of a large amount of organic solvent, and may have lower extraction efficiencies. To reduce or eliminate the use of organic solvents and improve the extraction processes, newer sample preparation methods, such as microwave-assisted extraction (MAE), supercritical fluid extraction (SFE), and accelerated solvent extraction (ASE) or pressurized liquid extraction (PLE) have been introduced for the extraction of targeted constituents present in plant materials.

Chromatography:

Separation of individual components from the herbal mixture is the key step to enable identification and bioactivity evaluation. Chromatography is a powerful analytical method suitable for the separation and quantitative determination of a considerable number of compounds, even from a complex matrix. These include paper chromatography (PC), thin-layer chromatography (TLC), gas chromatography (GC), HPLC, and capillary electrophoresis (CE).

TLC is used extensively in the phytochemical evaluation of herbal drugs because it enables rapid analysis of herbal extracts with minimum sample clean-up requirement, It provides qualitative and semi quantitative information of the resolved compounds. In TLC fingerprinting, the data that can be recorded using a high performance TLC (HPTLC) scanner includes the chromatogram, retardation factor (Rf) values, the color of the separated bands, their absorption spectra, λ max and shoulder inflection/s of all the resolved bands.

HPLC fingerprinting includes recording of the chromatograms, retention time of individual peaks and the absorption spectra (recorded with a photodiode array detector) with different mobile phases. Similarly, GLC is used for generating the fingerprint profiles of volatile oils and fixed oils of herbal drugs [20, 21].

HPTLC has been investigated for simultaneous assay of several components in a multicomponent formulation [22]. It has been well reported that several samples can be run simultaneously by use of a smaller quantity of mobile phase than in HPLC [23]. HPTLC technique is widely employed in pharmaceutical industry in process development, identification and detection of adulterants in herbal product and helps in identification of pesticide content, mycotoxins and in quality control of herbs and health foods [24].

LC-MS has become method of choice in many stages of drug development [25]. The chemical standardization of an aqueous extract of the mixture of the herbs provided chemical compounds serving as reference markers using LC-MS [26]. LC-NMR improves speed and sensitivity of detection and found useful in the areas of pharmacokinetics, toxicity studies, drug metabolism and drug discovery process. The online LC-NMR technique allows the continuous registration of time changes as they appear in the chromatographic run automated data acquisition and processing in LC-NMR improves speed and sensitivity of detection [27].

GC and GC-MS are unanimously accepted methods for the analysis of volatile constituents of herbal medicines, due to their sensitivity, stability and high efficiency. Especially, the hyphenation with MS provides reliable information for the qualitative analysis of the complex constituents [28].

Supercritical fluid chromatography is a hybrid of gas and liquid chromatography that combines some of the best features of each. SFC permits the separation and determination of a group of compounds that are not conveniently handled by either gas or liquid chromatography. SFC has been applied to a wide variety of materials including natural products, drugs, food and pesticide [29].

UV absorption has been the most commonly used detection method for the preliminary identification of the separated components. However, various other detectors, such as fluorescence (FD), flame ionization (FID), electron capture (ECD), refractive index (RI), and most recently, evaporative light scattering (ELSD), are also available for specific cases. Most of these detection methods allow the quantification of chemical compounds present in plant material or herbal product. The availability of high-speed computing and the appropriate software allows detection by using mass spectrometry (MS). This method not only allows the detection of component peaks of a mixture separated by chromatography but also in combination with UV (using a photodiode array detector), multistage MS and nuclear magnetic resonance spectrometry (LC–UV–MS–NMR), allows its molecular characterization [30, 31].

More recently, NMR metabonomics, in combination with chemometrics, especially principal component analysis (PCA) and simulated independent modeling of class analogy (SIMCA) algorithms, has been recognized as a very powerful tool to classify samples according to their total chemical composition. The resolution of high-field NMR can provide information in the orders of magnitude higher than of other fingerprinting technologies such as usual NMR spectrometry or HPLC. This is a non reductive fingerprinting method of the total chemical composition of samples [32, 33, 34, 35].

III. AUTHENTICATION AND REPRODUCIBILITY OF HERBAL INGREDIENTS:

The problems associated with unregulated herbal products highlight the major public health issues that can arise when their herbal ingredients have not been authenticated correctly. Herbal ingredients must be accurately identified by macroscopic and microscopic comparison with authentic material or accurate descriptions of authentic herbs [36]. It is essential that herbal ingredients are referred to by their binomial Latin names of genus and species; only permitted synonyms should be used. Even when correctly authenticated, it is important to realize that different batches of the same herbal ingredient may differ in quality due to a number of factors such as:

1. Inter or intra-species variation: The variation in constituents is mostly genetically controlled and may be related to the country of origin.
2. Environmental factors: The quality of an herbal ingredient can be affected by environmental factor like climate, altitude and other conditions under which it was cultivated.
3. Time of harvesting: For some herbs the optimum time of harvesting should be specified as it is known that the concentrations of constituents in a plant can vary during the growing cycle or even during the course of a day.
4. Plant part used: Active constituents usually vary between plant parts and it is not uncommon for an herbal ingredient to be adulterated with parts of the plant not normally utilized. In addition, plant material that has been previously subjected to extraction and is therefore 'exhausted' is sometimes used as adulterants to increase the weight of a batch of herbal ingredient.
5. Post-harvesting factors: Storage conditions and processing treatments can greatly affect the quality of an herbal ingredient. Inappropriate storage after harvesting can result in microbial contamination, and processes such as drying may result in a loss of thermo-labile active constituents.

GOOD AGRICULTURAL/MANUFACTURING PRACTICES:

Quality control and the standardization of herbal medicines also involve several other steps like source and quality of raw materials, good agricultural practices and good manufacturing practices. These practices play a pivotal role in guaranteeing the quality and stability of herbal preparations [37, 38]. The quality of a plant product is determined by the prevailing conditions during growth, and accepted Good Agricultural Practices (GAP) can control this. These include seed selection, growth conditions, fertilizers application, harvesting, drying and storage. In fact, GAP procedures are integral part of quality control.

Factors such as the use of fresh plants, age and part of plant collected, period, time and method of collection, temperature of processing, exposure to light, availability of water, nutrients, drying, packing, transportation of raw material and storage, can greatly affect the quality, and hence the therapeutic value of herbal medicines. Using cultivated plants under controlled conditions instead of those collected from the wild can minimize most of these factors [39, 40]. Sometimes, the active principles are destroyed by enzymic processes that continue for long periods from collection to marketing, resulting in a variation of composition. Thus, proper standardization and quality control of both the raw material and the herbal preparations should be conducted.

CONTAMINANTS OF HERBAL INGREDIENTS

Herbal ingredients of high quality should be free from insects, animal matter and excreta. It is usually not possible to remove completely all contaminants; hence specifications should be set in order to limit them.

1. Ash values: Incineration of an herbal ingredient produces ash which constitutes inorganic matter. Treatment of the ash with hydrochloric acid results in acid-insoluble ash which consists mainly of silica and may be used to act as a measure of soil present. Limits may be set for ash and acid-insoluble ash of herbal ingredients.

2. Foreign organic matter: It is not possible to collect an herbal ingredient without small amounts of related parts of plant or other plants. Standards should be set in order to limit the percentage of such unwanted plant contaminants.

3. Microbial contamination: Aerobic bacteria and fungi are normally present in plant material and may increase due to faulty growing, harvesting, storage or processing. Herbal ingredients, particularly those with high starch content, may be prone to increased microbial growth. Pathogenic organisms including Enterobacter, Enterococcus, Clostridium, Pseudomonas, Shigella and Streptococcus have been shown to contaminate herbal ingredients. It is essential that limits be set for microbial contamination and the European Pharmacopoeia now gives non-mandatory guidance on acceptable limits.

4. Pesticides: Herbal ingredients, particularly those grown as cultivated crops, may be contaminated by DDT (dichlorodiphenyltrichloroethane) or other chlorinated hydrocarbons, organophosphates, carbamates or polychlorinated biphenyls. Limit tests are necessary for acceptable levels of pesticide contamination of herbal ingredients. The European Pharmacopoeia includes details of test methods together with mandatory limits for 34 potential pesticide residues.

5. Fumigants: Ethylene oxide, methyl bromide and phosphine have been used to control pests which contaminate herbal ingredients. The use of ethylene oxide as a fumigant with herbal drugs is no longer permitted in Europe.

6. Toxic metals: Lead, cadmium, mercury, thallium and arsenic have been shown to be contaminants of some herbal ingredients. Limit tests for such toxic metals are essential for herbal ingredients.

7. Radioactive contamination: There are many sources of ionization radiation, including radionuclides, occurring in the environment. Hence, a certain degree of exposure is inevitable [42, 43, 44].

8. Other contaminants: As standards increase for the quality of herbal ingredients it is possible that tests to limit other contaminants such as endotoxins and mycotoxins will be utilized to ensure high quality for medicinal purposes [41].

IV. CONCLUSIONS:

The Indian herbal industry is growing in a tremendous rate. With the tremendous increase in traditional herbal therapy several concerns regarding the safety and quality of herbal medicines have also been observed. There is need for more advanced techniques of standardization. The advancement of analytical techniques will serve as a rapid and specific tool in the herbal research, thereby, allowing the manufacturers to set quality standards and specifications so as to seek marketing approval from regulatory authorities for therapeutic efficacy, safety and shelf- life of herbal drugs. The national health authorities should ensure that all herbal pharmaceutical product subject to their control are in conformity with quality, safety, efficacy and all premises and practices employed the manufacturing and distribution of these product comply with GMP standards so as to ensure the continued conformity of the products with these requirements until such time as they are delivered to the end user.

Quality control of herbal medicines has not only to establish reasonable analytical methods for analyzing the active constituents in herbal medicines, but many other factors should be concerned, such as pesticides residue, aflatoxins content, the heavy metals contamination, good agricultural practice (GAP), good manufacturing practice (GMP), etc. There is need for development of techniques which includes both traditional methods of evaluation and modern methods of evaluation. This will improve the quality of the drug and also motivates the practitioners to get more involved in the standardization process.

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