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Review on standardization of herbal drug and formulation

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Abstract
Herbal drug technology is used for converting botanical materials into medicines, where Standardization is an important step for the establishment of a consistent biological activity, a consistent chemical profile, or simply a quality assurance program for production and manufacturing of herbal drugs. In below we are studying various WHO specific guidelines for the assessment of the safety, efficacy and quality of herbal medicines as a prerequisite for global harmonization are of outmost importance. An the overview covering various techniques employed in extraction and characterization of herbal medicines as well as herbal Nano medicines standardization is reported.

Keywords: Standardization, quality control, WHO guidelines

Introduction
The basic resources of medicines come from nature and they are used as medicaments from ancient time to present day. People around the world possess unique knowledge of the natural resources on which they depend, including tremendous botanical expertise. The traditional medicines cater about 85% of the world population for their health needs. It is essential to maintain safety, quality and efficacy of the plant and their products to avoid and serious health problems. Indian healthcare consists of medical pluralism and Ayurveda still remains dominant compared to modern medicine, particularly for treatment of a variety of chronic disease conditions. WHO defines traditional medicine as including diverse health practices, approaches, knowledge and beliefs incorporating plant, animal and/or mineral based medicines, spiritual therapies, manual techniques and exercises applied singularly or in combination to maintain well-being, as well as to treat, diagnose or prevent illness. WHO has provided some terms related to herbal drugs, according to their definitions. Standardization of herbal formulations is essential in order to assess of quality drugs, based on the concentration of their active principles, physical, chemical, phyto-chemical, standardization, and *In vitro*, *In vivo* parameters.

Standardization
In recent years, there has been great demand for plant derived products in developed countries. These products are increasingly being sought out as medicinal products, nutraceuticals and cosmetics4. In order to have a good coordination between the quality of raw materials, in process materials and the final products, it has become essential to develop reliable, specific and sensitive quality control methods using a combination of classical and modern instrumental method of analysis. Standardization is an essential measurement for ensuring the quality control of the herbal drugs. 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 [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. According to WHO guidelines, an herbal product needs to be standardized with respect to safety before releasing it into the market.

Herbal drug technology

Herbal drug technology involves conversion of botanical materials into medicines where standardization and quality control with proper integration of modern scientific techniques and traditional knowledge is employed, and various drug delivery technologies used for herbal drugs were reported. Conventional pharmaceutical products, herbal medicinal products may vary in composition and properties, and increasing reports of adverse reactions has drawn the attention of many regulatory agencies for the standardization of herbal formulations. In this context, correct identification and quality assurance is an essential prerequisite to ensure producible quality of herbal medicine, which contributes to its safety and efficacy [2].

Need of standardization

Modern system of medicine is based on sound experimental data, toxicity studies and human clinical studies. But, Pharmacopoeia standards on raw material / finished products are not available. cGMP for herbal industry are not well defined nor the barest minimum standards of medicinal plant products are maintained or regulated. The lack of quality standards has resulted in mild to serious adverse effects ranging from hepato toxicity to death. Hence, herbal ingredients require tools for determining identity, purity and quality and tools have to be technically sufficient, rapid and cost effective with GMP equirements. World health organization has set specific guidelines for the assessment of safety, efficacy and quality of herbal medicines. Standardization of herbal drug is not an easy task as numerous factors influence the bio efficacy, reproducible therapeutic effect. In order to obtain quality oriented herbal product care should be taken right from the proper identification of plants, season, area of collection, their extraction and purification and rationalizing the combination in case of poly herbal drugs.

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 plantmaterial.
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 [3].

The herbal raw material is prone to a lot of variation due to several factors, the important ones being the identity of the plants and seasonal variation (which has a bearing on the time of collection), the ectopic, genotypic and chemotypic variations, drying and storage conditions and the presence of xenobiotic. Environmental conditions such as sunlight, rainfall, altitude, temperature, soil, storage conditions as well as different harvesting procedures, time and method of collection, manufacturing processes such as selecting, drying, purifying, extracting, and genetic variability can create substantial variability in product quality and in the concentration of plant chemicals within different products. Ecological conditions like insect feeding, microbial infections may affect secondary metabolites and in turn chemical composition of the plant. Also different parts of same plant (example roots, stem and leaves) contain different concentration of chemical constituents. At the same time diurnal variations (for example paclitaxel, opium alkaloids) and seasonal changes also account for variability in herbal medicines. The therapeutic or toxic components of plant vary depending on the part of the plant used as well as stages of ripeness. Products from different manufacture vary considerably and it is not possible to control all the factors that affect the plants chemical composition [7]. 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. Many preparations are either liquid or semisolid. For such formulations it is very difficult to establish parameters for quality control. 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.

Conventional methods for standardization of crude drug

Standardization of herbal raw drug includes passport data of raw plant drugs. It includes medico- botanical survey, identification, botanical authentication, macroscopic, examination. Testing of drugs as per approved Pharmacopoeial testing protocol- Fully pharmacognostical profile, Identification by various chromatographic techniques, Assessment of purity by physico-chemical profile, Assessment of strength by active marker or assay estimation and Safety by heavy metal profiling, microbiological limit test analysis, aflatoxins analysis, pesticides residue and biological activity. Macroscopic identity of medicinal plant materials is based on sensory evaluation parameters like shape, size, colour, texture, odour and taste while microscopy involves comparative microscopic inspection of powdered herbal drug. Further, advances in microscope technology have increased the accuracy and capabilities of microscopy as a mean of herbal crude material identification due to the implication of light and scanning electron microscopes (SEM) in herbal drug standardization The phytochemical evaluation for standardization purpose includes the following- Preliminary testing for the presence of different chemical groups, quantification of chemical groups of interest (e.g., total alkaloids, total phenolic, total triterpenic acids, total tannins), establishment of fingerprint profiles, multiple marker-based fingerprint profiles and quantification of important chemical constituents [4].

Standardization and quality control of herbal crude Drugs – Processes and procedures

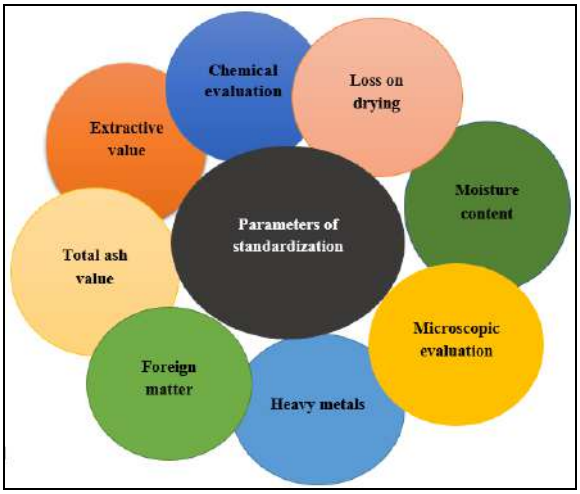
According to WHO (1996a and b, 1992), standardization and quality control of herbals is the process involved in the physicochemical evaluation of crude drug covering aspects, such as selection and handling of crude material, safety, efficacy and stability assessment of finished product, documentation of safety and risk based on experience, provision of product information to consumer and product promotion.

Attention is normally paid to such quality indices such as:

1. **Macro and microscopic examination:** For Identification of right variety and search of adulterants.
2. **Foreign organic matter:** This involves removal of matter other than source plant to get the drug in pure form.
3. **Ash values:** These are criteria to judge the identity and purity of crude drug – Total ash, sulphated ash, water soluble ash and acid insoluble ash etc.
4. **Moisture content:** Checking moisture content helps reduce errors in the estimation of the actual weight of drug material. Low moisture suggests better stability against degradation of product.
5. **Extractive values:** These are indicative weights of the extractable chemical constituents of crude drug under different solvents environment.
6. **Crude fibre:** This helps to determine the woody material component, and it is a criterion for judging purity.
7. **Qualitative chemical evaluation:** This covers identification and characterization of crude drug with respect to phytochemical constituent. It employs different analytical technique to detect and isolate the active constituents. Phytochemical screening techniques involve botanical identification, extraction with suitable solvents, purification, and characterization of the active constituents of pharmaceutical importance.
8. **Chromatographic examination:** Include identification of crude drug based on the use of major chemical constituents as markers.
9. **Quantitative chemical evaluation:** To estimate the amount of the major classes of constituents.
10. **Toxicological studies:** This helps to determine the pesticide residues, potentially toxic elements, safety studies in animals like LD50 and Microbial assay to establish the absence or presence of potentially harmful microorganisms [5].

The processes mentioned above involves wide array of scientific investigations, which include physical, chemical and biological evaluation employing various analytical methods and tools. The specific aims of such investigation in assuring herbal quality are as varied as the processes employed.

Parameter of Standardization



Microscopic evaluation

Quality control of herbal drugs has traditionally been based on the appearance and today microscopic evaluation is indispensable in the initial identification of herbs, as well as, in identifying small fragments of crude or powdered herbs, and detection of foreign matter and adulterants. Although this may seem obvious, it is of prime importance, especially when different parts of the same plant are to be used for different treatments. Stinging nettle (Urtica urens) is a classic example where the aerial parts are used to treat rheumatism, while the roots are applied for benign prostate hyperplasia [6]. Some Microscopic Identification test are given below

Table 1: microscopic identification test [2].

Sr.no	Name of constituents	Product For Test /Reagent	Result
1	Starch, Hemicellulose	T.s of crude drug +1drop of iodin solutions	Blue color
2	Muciulage	Ruthenium red	Pink color
3	Lignin	T.s of crude drugs +1 drop of phloroglucinol + 1 drop of HCL	Pink color

Chemical Evaluation

This includes the identification and Characterization of the crude drug in relation to the phytochemical component. It uses various analytical techniques to detect and isolate the active ingredients. Phytochemical screening techniques include botanical identification, extraction with suitable solvents, purification and characterization of active ingredients of pharmaceutical importance.

Foreign Matter

Herbal drugs should be made from the stated part of the plant and be devoid of other parts of the same plant or other plants. They should be entirely free from moulds or insects, including excreta and visible contaminant such as sand and stones, poisonous and harmful foreign matter and chemical residues. Animal matters such as insects and "invisible" microbial contaminants, which can produce toxins, are also among the potential contaminants of herbal medicines.

Heavy Metals

Contamination by toxic metals can either be accidental or intentional. Contamination by heavy such as mercury, lead, copper, cadmium, and arsenic in herbal remedies can be attributed to many causes, including environmental pollution and can pose clinically relevant dangers for the health of the user and should therefore be limited. The

potential intake of the toxic metal can be estimated on the basis of the level of its presence in the product and the recommended or estimated dosage of the product. This potential exposure can then be put into a toxicological perspective by comparison with the so-called Provisional Tolerable Weekly Intake values (PTWI) for toxic metals, which have been established by the Food and Agriculture Organization of the World Health Organization [7].

Radioactive contamination

Dangerous contamination, however, may be the consequence of a nuclear accident. The WHO, in close cooperation with several other international organizations, has developed guidelines in the event of a wide spread contamination by radionuclides resulting from major nuclear accidents. These publications emphasize that the health risk, in general, due to radioactive contamination from naturally occurring radio nuclides is not a real concern, but those arising from major nuclear accidents such as the nuclear accident in Chernobyl and Fukushima may be serious and depend on the specific radionuclide, the level of contamination, and the quantity of the contaminant consumed. Taking into account the quantity of herbal medicine normally consumed by an individual, is unlikely to be a health risk. Therefore, at present, no limits are proposed for radioactive contamination [6].

Ash Content

Table 2: Total ash (%w/v) of herbal drugs [2]

Sr.no	Drug	Total Ash(%w/v)	Acid insoluble ash(%w/v)
1	Agar	-	1.00
2	Bael	3.50	-
3	Cannabis	15.00	5.00
4	Ginger	6.00	1.7(water soluble ash

To determine ash content, the plant material is burnt and the residual ash is measured as total and acid-insoluble ash. Total ash is the measure of the total amount of material left after burning and includes ash derived from the part of the plant itself and acid-insoluble ash. The latter is the residue obtained after boiling the total ash with dilute hydrochloric acid, and burning the remaining insoluble matter.

WHO guidelines for quality standardized herbal formulations

1. Quality control of crude drugs material, plant preparations and finished products.
2. Stability assessment and shelf life
3. Safety assessment; documentation of safety based on experience or toxicological studies.
4. Assessment of efficacy by ethno- medical information and biological activity evaluations.

The bioactive extract should be standardized on the basis of active principles or major compounds along with the chromatographic fingerprints (TLC, HPTLC, HPLC, and GC). Generally, all medicines, whether they are synthetic or of plant origin, should fulfil the basic requirement of being safe and effective. The term 'herbal drugs' denotes plants or plant parts that have been converted into phyto pharmaceuticals by means of simple processes involving harvesting, drying and storage [1].

Quality Control of Herbal Drugs

Quality control is a term that refers to processes involved in maintaining the quality and validity of a manufactured product. In general, quality control is based on three important pharmacopeial aspects -

a. Identity or authenticity- it should have one herb
b. Purity – it should not have any contaminant other than herb
c. Assay or Content -the active constituents should be within the defined limits. Identity can be achieved by macro and microscopical examinations. In addition to this identity tests, which include simple chemical tests, eg. colour or precipitation and chromatographic tests are also necessary. These chemical and chromatographic tests help to provide batch to batch comparability and the chromatogram may be used as a 'fingerprint' for the herbal ingredient by demonstrating the profile of some common plant constituents such as flavonoids, alkaloids and terpenes. To prove identity and purity, criteria such as type of preparation, sensory properties, physical constants, adulteration, contaminants, moisture, ash content, and solvent residues have to be checked. Voucher specimens are reliable reference sources. A special form of assay is the determination of essential oils by steam distillation. When active constituents (e.g. sennosides in senna) or markers.

(e.g. alkydamides in Echinacea) are known, a vast array of modern chemical analytical methods such as ultraviolet/visible spectroscopy(UV/VIS), TLC, HPLC, HPTLC, GC, mass spectrometry, or a combination of GC and MS(GC/MS), can be employed.

Stability Assessment and Shelf Life

Prolonged and apparently uneventful use of a substance usually offers testimony of its safety. In a few instances, however, investigation of the potential toxicity of naturally occurring substances widely used as ingredients in these preparations has revealed previously unsuspected potential for systematic toxicity, carcinogenicity and teratogenicity.

Assessment of Quality

All procedures should be in accordance with good manufacturing practices. Crude Plant Material. The botanical definition, including genus, species and authority, description, part of the plant, active and characteristics constituents should be specified and, if possible content limits should be defined. Foreign matter, impurities and microbial content should be defined or limited. Voucher specimens, representing each lot of plant material processed, should be authenticated by a qualified botanist and should be stored for at least a 10-year period. A lot number should be assigned and this should appear on the product label.

Plant Preparations

The manufacturing procedure should be described in detail. If other substances are added during manufacture in order to adjust the plant preparation to a certain level of active or characteristics constituents or for any other purpose, the added substances should be mentioned in the manufacturing procedures. A method for identification and, where possible, assay of the plant preparation should be added. If identification of an active principle is not possible, it should

be sufficient to identify a characteristic substance or mixture of substances to ensure consistent quality of the preparation.

Finished Product

The manufacturing procedure and formula, including the amount of excipients, should be described in detail. A finished product specification should be defined to ensure consistent quality of the product. The finished product should comply with general requirements for particular dosage forms. Stability the physical and chemical stability of the product in the container in which it is to be marketed should be tested under defined storage conditions and the shelf-life should be established.

Safety Assessment

Herbal medicines are generally regarded as safe based on their long-standing use in various cultures. However, there are case reports of serious adverse events after administration of herbal products. In a lot of cases, the toxicity has been traced to contaminants and adulteration. However, some of the plants used in herbal medicines can also be highly toxic. As a whole, herbal medicines can have a risk of adverse effects and drug-drug and drug-food interactions if not properly assessed. Assessment of the safety of herbal products, therefore, is the first priority in herbal research

Assessment of Toxicity

Toxicity investigation will also be required because the analysis alone is unlikely to reveal the contributions to toxicity itself [8].

Assessment of Efficacy

Herbal medicines are inherently different from conventional pharmacological treatments, but presently there is no way to assess their efficacy other than by currently used conventional clinical trial methodologies, in which efficacy is conventionally assessed by clinical, laboratory, or diagnostic outcomes: Clinical outcomes include parameters such as improved morbidity, reduced pain or discomfort, improved appetite and weight gain, reduction of blood pressure, reduction of tumor size or extent, and improved quality of life. Laboratory /other diagnostic outcomes include parameters such as reduction of blood glucose, improvement of hemoglobin status, reduction of opacity as measured by radiological or imaging techniques, and improvement in electrocardiogram (ECG) findings. Standardization and Quality control of herbal drugs involve wide array of scientific investigations, which include physical, chemical and biological evaluation employing various analytical method and tools.

- **Physical Evaluation:** Each monograph contains detailed botanical, macroscopic and microscopic descriptions with detailed illustrations and photographic images which provide visual documentation of accurately identified material. A microscopic analysis assures the identity of the material and as an initial screening test for impurities.
- **Chemical Evaluation:** Chemical analysis of the drug is done to assess the potency of vegetable material in terms of its active principles. It covers screening, isolation, identification, and purification of the chemical components. It 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 animals and on their intact or isolated organs can indicate the strength of the drug or their preparations.
- **Analytical Methods:** It helps in determining identity

Summary

The need for standardization of herbals is now very essential given the global acceptance of herbal products as remedies for various diseases and ailments. The deployment of modern analytical tools in testing the various quality parameters for an effective quality control herbal product cannot be over emphasized. The assurance of the safety and efficacy of a herbal drug requires monitoring of the quality of the product from collection through processing to the finished packaged product. It is recommended that various government agencies should follow a more universal approach to herbal quality by adopting the WHO guidelines and also developing monographs using the various quality parameters outlined above.

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