IAMJ

Review Article *International Ayurvedic Medical Journal* *ISSN:2320 5091*

STANDARDIZATION OF HERBAL DRUGS - 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 although most of these applications are not scientific. 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. The challenges are innumerable and enormous, making the global herbal market unsafe. Today physicians are totally depending upon the mediator's right from the drug collection to the manufacturing of the medicines. Some of *Ayurvedic* practitioners use traditional herbal preparations made by them for their treatment purposes. Our ancient books have mentioned many methods to standardize drug and also about adulteration. Now days, old methods are necessary but there are lots of limitations to these methods due to shortage or unavailability or limited source, adulteration, lack of knowledge of drug identification and adverse effects of drugs and need to be validated and updated. Herbal medicines are not a simple task since many factors influence the biological efficacy and reproducible therapeutic effect. So it is necessary to improve safety of herbal drugs by developing certain quality control parameters & by following the WHO guidelines for herbal medicines. This review seeks to enlighten the need to establish quality parameters for collection, handling, processing and production of herbal medicine as well as employ such parameters in ensuring the safety of the global herbal market. The processes of good quality assurance &standardization of herbal medicines at different stages were also discussed.

Keywords: Herbal drugs, Adulteration, Standardization, Quality, Safety, Efficacy

INTRODUCTION

The use of herbs as medicine is the oldest form of healthcare known to humanity and has been used in all cultures throughout history. Early humans recognized their dependence on nature for a healthy life and since that time humanity has depended on the diversity of plant resources for food, clothing, shelter, and medicine to cure myriads of ailments. Led by instinct, taste, and experience, primitive men treated illness by using plants, animal parts, and minerals that were not part of their usual diet. Primitive people learned by trial and error to distinguish useful plants with beneficial effects from those that were toxic or inactive, and also which combinations or processing methods had to be used to gain consistent and optimal results. Even in ancient cultures, tribal people methodically collected information on herbs and developed well-defined herbal pharmacopeias. The knowledge of plant based drugs developed gradually and was passed on, thus, laying the foundation for many systems of traditional medicine all over the world. In some communities' herbal medi-

cine is still a central part of their medical system. Medicinal plants are widely distributed throughout the world but most abundantly in tropical countries. It is estimated that about 25% of all modern medicines are directly or indirectly derived from higher plants.

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)

Herbs include crude plant material, such as leaves, flowers, fruit, seeds, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.

Herbal materials include, in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting or stir-baking with honey, alcoholic beverages or other materials.

Herbal preparations are the basis for finished herbal products and may include powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration, or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.

Finished herbal products consist of herbal preparations made from one or more herbs

They may come from any part of the plant but are most commonly made from leaves, roots, bark seeds, and flowers. Hence they are capable of variation. They are taken in the form of *churna*, *vati* (eaten, swallowed) *Kashaya*, *swarasa* or *asava arista* form (drunk), *nasya* (inhaled), or as *lepa* (applied topically to the skin). Herbal products often contain a variety of naturally-occurring bio-chemicals from plants, many of which contribute to the plant's medicinal benefits. Chemicals known to have medicinal benefits are referred to as "active ingredients" or "active principles" and their presence depends on a number of factors including the plant species, the time and season of harvest, the type of soil, the way the herb is prepared, etc.

Quality Control and Standardization of Herbal Medicines – Concept and Scope

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.

Herbal product cannot be considered scientifically valid if the drug tested has not been authenticated and characterized in order to ensure reproducibility in the manufacturing of the product. The quality assurance is also required during cultivation, harvesting, primary processing, handling, storage, packaging, and distribution. Therefore, there has been introduced a set of criteria and guidelines by WHO to be followed at each step as an integral part of quality control standards:

1. **Good Agricultural and cultivation Practices**
2. **Good storage practices**
3. **Good manufacturing practices**
4. **Good laboratory Practices**

The main objective of these guidelines is to contribute to the quality assurance of medicinal plant materials used as the source for herbal medicines, which aims to improve the quality, safety and efficacy of finished herbal products and minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.

Herbal formulations

At present standard parameters available for herbal preparations are not mere satisfactory due to several reasons. For e.g. Presently it is very difficult to identify the presences of all the ingredients as claimed in a formulation. Those manufacturers, who are currently doing some testing for their formulations, have their own parameters and SOP's many of which are very preliminary in nature. Some manufacturers use the term standardization incorrectly to refer to uniform manufacturing practices, but following a recipe is not sufficient for a product to be called standardized. 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.

Need for standardization:

In the global perspective, there is a shift towards the use of medicine of herbal origin, as the dangers and the shortcoming of modern medicine are getting more apparent. It is the cardinal responsibility of the regulatory authorities to ensure that consumers get the medication, which guarantees **purity, safety, potency and efficacy.**

Aim & Objectives:

To describe the importance, concept, processes and the parameters required for the Standardization of herbal drugs

Materials and Methods (2):

WHO Guidelines for Quality Standardized Herbal Formulations (3)

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.

Caraka clearly described the Parameters to be assessed for a drug to be standardized in *Vimana sthana* 8 th chapter where the concept of quality, safety and efficacy was explained elaborately (4)

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Prakriti- Namarupavijnana-Pharmacognosy

Gunaha- *Rasa, Guna, Veerya, Vipaka.*

Drug properties- physical &chemical & Pharmacological properties

Prabhava- Pharmacotherapeutic effect- Pharmacodynamics & Pharmacokinetics

Desha - Geographical area – Distribution, cultivation, Place of collection etc.

Grihita–collection practices

Nihitam–storage practices

Upaskrita–manufacturing process

Matra – Dose

Ritu– collection & cultivation time

Yukta – Method of collection- Area, Time & Soil

Nihitha– Storage & Preservation- Bheshjagara

Upaskrita –Pharmaceutical processing of formulations

Matra - Selection & fixation of specific dose

Yukta – Logical interpretation and application

Vyadhi–Indication in specific disease

vidhisyapurushasya – Similar to clinical trials

Doshaapakarsha &Upashamana- Act on particular *dosha* can be known by pathological test how much reduced or increased

Generally, all medicines whether they are synthetic or of plant origin, should be pure, safe and effective. In general, quality control is

based on three important pharmacopeial definitions

1. Identity- it should have one herb
2. Purity – it should not have any contaminant other than herb
3. Content or assay-the active constituents should be within the defined limits.

Assessment of quality

All procedures should be in accordance with good manufacturing practices.

- ✓ Crude plant material
- ✓ Plant preparations
- ✓ Finished product

Assessment of 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

Assessment of Safety: The toxic effects of herbal preparation may be attributed mainly to the following: Inherent toxicity of plant constituents and ingredients and Manufacturing malpractice and contamination. Evaluation of the toxic effects of plant constituents of herbal formulation requires detailed phyto-chemical and pharmacological studies.

Assessment of toxicity: Toxicity investigation will also be required because the analysis alone is unlikely to reveal the contributions to toxicity itself. In assessing toxicity of an herbal medicine, the dose chosen is very important. Toxicity assessment involves one or more of the following techniques- In vivo techniques, in vitro techniques, cell line techniques, micro- array and other modern technique Standardization techniques to adequately model toxicity.

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:

The parameters to be assessed for the standardization of the raw drug covering the purity, safety, and efficacy aspects are:

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 value:** helpful in determining the quality and purity of crude drugs, especially in powder form. The objective of ashing vegetable drugs is to remove all traces of organic matter, which may otherwise interfere in an analytical determination.

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.

METHODS OF STANDARDISATION OF AYURVEDIC MEDICINES

1) Raw material standardization.
2) In process standardization
3) Finished product standardization.

1. Raw material standardization:

This includes authentification process in which following points should be considered. Area of the collection, parts of the plant collection, the regional situation, botanical identity, microscopic and histological analysis, taxonomic identity, Foreign matter, Loss on drying, swelling index, foaming index, ash values and extractive values, Chromatographic and spectroscopic evaluation, Determination of heavy metals, pesticide residues, Microbial contamination, Radioactive contamination.

2. In process standardization:

SOP's – it should have the manufacturing procedure in detail, if other substances are added during manufacture in order to adjust the plant preparation. 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.

3. Final product

Prepared drug should possess standard nature of characteristics. The manufacturing procedure and formula, including the amount of recipients, 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. The processes 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.

Analytical Specifications of Herbal Formulations followed as per requirement and form of the medicine: (5)

1. Description, Colour, Odour
2. Total – ash
3. Acid – insoluble ash
4. Water & Alcohol-soluble extractive
5. Viscosity
6. Refractive index
7. Specific gravity at 250 C.
8. Alcohol content Test for methanol.
9. Total acidity.
10. Non reducing and reducing sugar
11. PH
12. Total sugar content
13. Loss on drying at 105 ^{o}C
14. Particle size (80-100 mesh for *Churna*; 40-60 mesh for *Kvathachurna*)
15. Weight variation
16. Disintegration time -Not more than 15 min
17. Identification TLC/HPTLC/GLC
18. Assay
19. Test for heavy/Toxic metals: Lead,Cadmium, Mercury, Arsenic
20. Microbial contamination: Total bacterial count, Total fungal count
21. Test for specific Pathogen: E. coli, Salmonella spp. S.aureus, Pseudomonas aeruginosa
22. Pesticide residue: Organochlorine pesticides, Organophosphorus pesticides, Pyrethroids
23. Test for Aflatoxins (B1,B2,G1,G2)

Results and Discussion:

Different techniques involved in standardization of crude drugs

1. Organoleptic / Macroscopic Evaluation
2. Microscopic Evaluation
3. Physical Evaluation
4. Chemical Evaluation
5. Biological Evaluation
6. Toxicological Evaluation

Steps Involved in Standardization of Raw Materials

1. Pharmacognostic evaluation: It includes color, odor, taste, texture, size, shape, microscopical characters, and histological parameters.

2Physico-chemical parameters: It includes foreign matter, Disintegration time, total ash, friability, acid-insoluble ash, hardness swelling and foaming index flow capacity, assay, flocculation, successive extractive values sedimentation, moisture content, alcohol content, Viscosity, pH etc.

3. Chemical parameters: It includes limit tests, chemical tests etc.

4. Chromatographic and spectroscopic analysis: It includes TLC, HPLC, HPTLC, GC, UV, IR, FT-IR, AAS, LC-MS, GC-MS, fluorimetry etc.

5. Microbiological parameters: It includes the full content of viable, total mould count, total coliforms count. Limiters can be used as a quantitative tool or semi-quantitative to determine and control the amount of impurities, such as reagents used in the extraction of various herbs, impurities ships directly from the manufacturing and solvents etc.

WHO Guidelines for Quality Standardized Herbal formulations (6)

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). The standardization of crude drug materials includes the following steps:

1. Authentication (Stage of collection, parts of the plant collected, regional status, botanical identity like phyto-morphology, microscopical and histological analysis, taxonomical identity etc.)
2. Foreign matter (herbs collected should be free from soil, insect parts or animal excreta etc.)
3. Organoleptic evaluation (sensory characters – colour, taste, appearance, odour, feel of the drug etc.)
4. Tissues of diagnostic importance present in the drug powder. e. Ash values and extractive values.
5. Moisture content
6. Volatile matter
7. Determination of heavy metals e.g. cadmium, lead, arsenic, etc.
8. Chromatographic and spectroscopic evaluation: TLC, HPTLC, HPLC methods will provide qualitative and semi quantitative information about the main active constituents present in the crude drug. The quality of the drug can also be assessed on the basis of the spectroscopic fingerprint.
9. Pesticide residue: WHO and FAO (Food and Agricultural Organization) set limits of pesticides, which are usually present in the herbs. These pesticides are mixed with the herbs during the time of cultivation. Mainly pesticides like DDT, BHC, toxaphene, aldrin cause serious side-effects in human beings if the crude drugs are mixed with these agents.
10. Microbial contamination: Usually medicinal plants containing bacteria and moulds are coming from soil and atmosphere. Analysis of the limits of E. coli and moulds clearly throws light towards the harvesting and production practices. The substance known as aflatoxins will pro-

duce serious side-effects if consumed along with the crude drugs. Aflatoxins should be completely removed or should not be present.

11. Radioactive contamination: Microbial growth in herbals is usually avoided by irradiation. This process may sterilize the plant material but the radioactivity hazard should be taken into account. The radioactivity of the plant samples should be checked accordingly to the guidelines of International Atomic Energy (IAE) in Vienna and that of WHO.

Validation: By definition, **validation** is the process of proving that an analytical method is acceptable for its intended purpose for pharmaceutical methods. Guidelines from the United States Pharmacopeia (USPC, 1994 to 2001), the International Conference on Harmonization (ICH), and the US Food and Drug Administration (FDA) provide a framework for performing such validations.

Generally, validation investigations must include studies on specificity, linearity, accuracy, precision, range, detection, and quantitative limits, depending on whether the analytical method used is qualitative or quantitative). Also, of utmost importance is the availability of standards. For macroscopic and microscopic procedures- reliable reference samples of the plant must be available. A defined botanical source (e.g. voucher specimens) will normally solve this problem. Standards for chromatographic procedures are less easy to obtain. Characteristic plant constituents, either active or markers, are seldom available commercially.

Sometimes an LC-MS approach can be referred to as a mode of characterization. Going one step further, after isolation of such a compound, elucidations to prove its definite structure will not be easy. The method often employed is to use readily available compounds that behave similarly in the chosen chromatographic systems, and to calculate retention values and/or times towards these compounds as a standard. Qualitative chemical examination is designed to detect and isolate the active ingredients. TLC and HPLC are the main analytical techniques commonly used. In cases when active ingredients are not known or too complex, the quality of plant extracts can be assessed by a “fingerprint” chromatogram

Labelling: The quality of consumer information about the product is as important as the finished herbal product. Information or warning on the label helps to reduces the risk of inappropriate uses and adverse reactions. The primary source of information on herbal products is the product label. Contents of label and its Rules are prescribed and to be followed as per the Drug & Cosmetic Act Rules 1945(7). The information such as “name of the drug, manufacturer, batch number, any special category of scheduled drugs if used, date of expiry if any and assurance that the product has been manufactured according to Pharmacopoeia standards,” listing of active ingredients and amounts, directions such as serving quantity (dosage) and frequency of intake of the drug, must be on the label.

Currently, there is no organization or government body that certifies herb or a supplement as being labelled correctly. Studies of herbal products have shown that consumers have less than a 50% chance of actually getting what is listed on the label, and published analyses of herbal supplements have found significant differences between what is listed on the label and what is in the bottle.

The word “standardized” on a product label is no guarantee of higher product quality, since there is no legal definition of the word “standardized.” Consumers are often left on their own to decide what is safe and effective

for them and the lack of consistent labelling on herbal products can be a source of consumer frustration.

Table 1 Brief over view of the process of standardization

Standardization of Herbal Raw drugs	Norms to be followed during standardization	Standardization of Herbal formulations
1 Passport data of raw plant drugs **2** Correct taxonomic identification and authentication **3** Study on the medicinal part: stem, bark, etc. **4** Collection details: location, stage and development, time storage etc. **5** Organoleptic evaluation of raw drug **6** Microscopic and molecular examination **7**Chemical composition **8** Biological activity of whole plant **9** Shelf life of raw drugs -	GSL (Good survey of literature) GAP (Good agricultural practices) GCP (Good clinical practices) GHP (Good harvesting practices) GLP (Good laboratory practices) GMP (Good manufacturing practices) GMT (Good marketing techniques)	Follow define GMP. Toxicity evaluation Chemical profiling Pharmaco dynamics Pharmacokinetics Dosage Stability Presentation and packing Therapeutic merits

CONCLUSION

In spite of the great advances observed in modern medicine in recent decades, plants still make an important contribution to health care. Lack of availability of medicinal plant species, adulteration, dependence on the mediators for the manufactured products, preparation of medicine in the name of traditional medicine together cope up to emphasize the need for standardization right from the identification of the plant, collection the raw material to the manufacturing of the herbal compound in suitable form and marketing i.e Total quality Management. The need for standardization of herbals is now very essential considering the global acceptance of herbal products as remedies for various diseases and evidence is emerging on the dangers of indiscriminate use of certain herbs. The assurance of the quality, safety and efficacy of an 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. This will strengthen the regulatory process and minimize quality breach.

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Source of Support: Nil
Conflict Of Interest: None Declared

How to cite this URL: T Mahesh Babu Et Al: Standardization Of Herbal Drugs - A ReviewInternational Ayurvedic medical Journal {online} 2017 {cited January, 2017} Available from: http://www.iamj.in/posts/images/upload/269_277.pdf