

## Quality control and evaluation of herbal drugs in modern era

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### Abstract

Standardization of herbal formulations is essential in order to assess of quality drugs. The quality of herbal drugs is the sum of all factors which contribute directly or indirectly to the safety, effectiveness and acceptability of the product. Now a day the field of herbal drugs and formulation is very fast and there is still lot to explore on the subject of standardization of these. The herbal medicines however, suffer from lack of standardization parameters. The main limitation is the lack of standardization of raw materials, of processing methods and of the finished products, dosage formulation, and the non-existence of criteria for quality control. It is necessary to introduce measures on the regulation of herbal medicines to ensure quality, safety, efficacy of herbal medicines by using modern suitable GMP standards.

**Keywords:** quality control, herbal drugs, medicinal plants & standardization

### Introduction

The traditional medicine is widely used for various human ailments. All plants in this planet are important because of its medicinal qualities. Traditional system of medicines has become significantly more popular all over the globe because of the effective and curative nature for chronic disease with less toxicity. Herbal medicines are not a simple task since many factors influence the biological efficacy and reproducible therapeutic effect <sup>[1, 2]</sup>. Standard herbal formulations are essential in order to assess of quality drugs, based on the concentration of their active principles, physico-chemical, phyto-chemical, In-vitro, and In-vivo parameters. The quality assessment of herbal formulations is paramount importance in order to justify their acceptability in modern system of medicine <sup>[3]</sup>. One of the major problems faced by the herbal pharmaceutical industry is the unavailability of rigid quality control profiles for herbal materials and their formulations <sup>[4]</sup>. Herbal drugs and product, the word "standardization" should encompass entire field of study from cultivation of medicinal plant to its clinical application. Plant material and herbal remedies derived from them represent substantial portion of global market and in this respect internationally recognized guidelines for their quality control are necessary. World Health Organization has emphasized the need to ensure quality control of medicinal plant products by using modern technique and by applying suitable parameters and standards.

### Standardization of Herbal Medicines

Generally, all medicines, whether they are synthetic or of plant origin, should be fulfill the basic requirements of being safe and effective <sup>[5, 6]</sup>. The term "herbal drugs" denotes plants or plant parts that have been converted into phyto pharmaceuticals by me simple processes involving harvesting, drying, and storage <sup>[7]</sup>. Hence they are capable of variation.

This variability is also caused by differences in growth, geographical location, and time of harvesting.

Standardization of herbal medicines is the set of standards or inherent characteristics, constant parameters, definitive qualitative and quantitative values that carry an assurance of quality, efficacy and safety. It is the process of developing and agreeing upon technical standard. 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 herbal medicine. Hence standardization is tools in the 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. 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 develop 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 develop 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, poly phenolic components or estimation of particular compound <sup>[8]</sup>.

### Need of quality control

Modern system of medicine is based on sound experimental data, toxicity studies and human clinical studies. But, Pharma copoeial 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 requirements. World health organization has set specific guidelines for the assessment of safety, efficacy and quality of herbal medicines. Quality control 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 of polyherbal drugs<sup>[9]</sup>.

### Quality control of herbal crude drugs – Processes and procedures

According to WHO<sup>[10, 11]</sup>, 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. Authentication- Each and every step has to be authenticated, area of the collection, parts of the plant collection, the regional situation, botanical identity, microscopic and histological analysis (characteristic features of cell walls, cell contents, starch grains, calcium oxalate crystals, hairs, fibers, vessels etc.) taxonomic identity, foreign matter, loss on drying, swelling index, foaming index, ash values, extractive values, chromatographic and spectroscopic evaluation, determination of heavy metals, pesticide residues, microbial contamination and radioactive contamination. The parameter stability of herbal formulations that includes pharma co gnostic parameters, physicochemical parameters, phyto-chemical parameters, microbiological assay and chromatographic analysis:

#### Pharmacognostic evaluation

It includes color, odor, taste, size, shape, micro scopical characters, and histological parameters.

#### Physico-chemical parameters

It includes foreign matter, total ash, acid-insoluble ash, swelling and foaming index, assay, extractive values, moisture content, viscosity, pH, Disintegration time, friability, hardness, sedimentation, alcohol content.

#### Chemical parameters

It includes limit tests, chemical tests etc.

#### Chromatographic and Spectroscopic Analysis

It includes TLC, HPLC, HPTLC, GC, UV, IR, AAS, FT-IR, LC-MS, and GC-MS etc.

#### 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<sup>[12, 13]</sup>.

### Current Regulations for Quality Control of Herbal Drugs

Several pharmacopoeias like Pharmacopoeia Committee, Chinese Herbal Pharmacopoeia, United States Herbal Pharmacopoeia, British Herbal Pharmacopoeia, British Herbal Compendium, and Japanese Standards for Herbal Medicine and the Ayurvedic Pharmacopoeia of India (API). Lay down monograph for herbs and herbal products to maintain their quality in their respective nations. World Health Organization (WHO) encourages, recommends and promotes traditional/herbal remedies in national healthcare programmers because these drugs are easily available at low cost, safe and people have faith in them. The WHO assembly in number of resolutions has emphasized the need to ensure quality control of medicinal plant products by using modern techniques and applying suitable standard<sup>[14, 15]</sup>.

### WHO Guidelines for Quality Control of 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's 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).

### Quality Control of Herbal Drugs

Quality can be defined as the status of a drug that is determined by identity, purity, content, and other chemical, physical, or biological properties, or by the manufacturing processes. Quality control is a term that refers to processes involved in maintaining the quality and validity of a manufactured product. 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<sup>[16]</sup>. In general, quality control is based on three important pharma copeial definitions: Identity- it should have one herb. Purity – it should not have any contaminant other than herb. Content or assay-the active constituents should be within the defined limits. It is obvious that the content is the most difficult one to assess, since in most herbal drugs the active constituents are unknown<sup>[17]</sup>. Identity can be achieved by macro and micro scopical examinations. Voucher specimens are reliable reference sources. Outbreaks of diseases among plants may result in changes to the physical appearance of the plant and lead to incorrect identification<sup>[18- 19]</sup>. At times an incorrect botanical quality with respect to the labeling can be a problem. Purity is closely linked with safe use of drugs and deals with factors such as ash values, foreign matter, and heavy metals. However, due to the application of improved analytical methods, modern purity evaluation

also includes microbial contamination, aflatoxins, radioactivity, and pesticide residues. Analytical methods such as photometric analysis, Thin layer chromatography (TLC), High performance liquid chromatography (HPLC), High performance thin layer chromatography (HPTLC), and Gas chromatography (GC) can be employed in order to establish the constant composition of herbal preparations. Content or assay is the most difficult area of quality control to perform, since in most herbal drugs the active constituents are unknown. Sometimes markers can be used. In all other cases, where no active constituents or marker can be defined for the herbal drug, the percentage extractable matter with a solvent may be used as a form of assay, an approach often seen in pharmacopeia<sup>[20, 21]</sup>. A special form of assay is the determination of essential oils by steam distillation. When active constituents or markers 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<sup>[22]</sup>.

#### **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 characteristic 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 characteristic 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. These are various approaches to the evaluation of safety of herbal medicines. 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 phytochemical and pharmacological studies. It is, however, safe to assume that, based on human experiences in various cultures, the use of toxic plant ingredients has already been largely eliminated and recent reports of toxicity could largely be due to misidentification and overdosing of certain constituents<sup>[23]</sup>.

#### **Toxicity Assessment**

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<sup>[24]</sup>. Toxicity assessment involves one or more of the following techniques- *In vivo* & *in vitro* techniques, cell line techniques, micro- array and other modern technique.

#### **Critical Factors Affecting the Quality Control of Herbal Drugs**

##### **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. A primary visual evaluation, which seldom needs more than a simple magnifying lens, can be used to ensure that the plant is of the required species, and that the right part of the plant is being used. At other times, microscopic analysis is needed to determine the correct species and/or that the correct part of the species is present. For instance, pollen morphology may be used in the case of flowers to identify the species, and the presence of certain microscopic structures such as leaf stomata can be used to identify the plant part used. 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<sup>[25]</sup>.

##### **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. Macroscopic examination can easily be employed to determine the presence of foreign matter. Furthermore, when foreign matter consists, for example, of a chemical residue, TLC is often needed to detect the contaminants [25, 20, 22].

### Ash Content

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. The second procedure measures the amount of silica present, especially in the form of sand and siliceous earth [25].

### Heavy Metals

Contamination by heavy metals 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 [26]. 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. A simple determination of heavy metals can be found in many pharmacopoeias and is based on color reactions with special reagents such as thioacetamide or diethyldithiocarbamate, and the amount present is estimated by comparison with a standard (WHO, 1988a). Instrumental analyses have to be employed when the metals are present in trace quantities, when the analyses have to be quantitative. Generally, the main methods commonly used are atomic absorption spectrophotometry (AAS), inductively coupled plasma (ICP) and neutron activation analysis (NAA) [27].

### Microbial Contaminants and Aflatoxins

Medicinal plants may be associated with a broad variety of microbial contaminants, represented by bacteria, fungi, and viruses. Inevitably, this microbiological background depends on several environmental factors and exerts an important impact on the overall quality of herbal products and preparations. Herbal drugs normally carry a number of bacteria and molds, often originating in the soil. Poor methods of harvesting, cleaning, drying, handling, and storage may also cause additional contamination, as may be the case with *Escherichia coli* or *Salmonella* spp. while a large range of bacteria and fungi are from naturally occurring microflora, aerobic spore-forming bacteria that frequently predominate. Laboratory procedures investigating microbial contaminations are laid down in the well-known pharmacopoeias, as well as, in the WHO guidelines [20]. Limit values can also be found in the sources mentioned. Generally, a complete procedure consists of determining the total aerobic microbial count, the total fungal count, and the total Enterobacteriaceae count, together with tests for the presence of *Escherichia coli*,

*Staphylococcus aureus*, *Shigella*, and *Pseudomonas aeruginosa* and *Salmonella* sp. The European Pharmacopoeia also specifies that *E. coli* and *Salmonella* spp. should be absent from herbal preparations.

### 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 [25].

### Validation

The validation of herbal products is a major public health concern both in developed and resource-poor countries. In this regard, there is no control by the government agencies, despite the existence of certain guidelines in some individual countries and those outlined by the WHO. If the herbal products are marketed as therapeutic agents, and irrespective of whether the products really have any positive effects to cure and reduce the severity of the disease, it is necessary to ensure scientific validation and periodic monitoring of the quality and efficacy by drug control administrators. Several of the principal pharmacopoeias contain monographs outlining standards for herbal drugs. The major advantage of an official monograph published in a pharmacopoeia is that standards are defined and available, and that the analytical procedures used are fully validated. This is of major importance, since validation can be a rather time-consuming process. Guidelines from the United States Pharmacopoeia (USPC, 1994 to 2001), 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 [28]. Also, of utmost importance is the availability of standards. For macroscopic and microscopic procedures in general this means that 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. 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<sup>[28]</sup>.

### Conclusions

This can be achieved only if the herbal products are evaluated and analyzed using sophisticated modern techniques of standardization such as UV-visible, TLC, HPLC, HPTLC, GC-MS and other methods. The assurance of the safety and efficacy of 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.

### References

- Muthamizhe SK, Prakash YG, Gopal V. Standardization of traditional medicine - Need and urgency. *Inter. J. of Phytotherapy*. 2013; 3(1):5-10.
- Bad jugar SB, Patil MB. Ethno medicines for Jaundice used in tribal areas of North Maharashtra. *Natural Product Radiance*. 2008; 7(1):79-81.
- Bauer R. Quality criteria and standardization of phyto pharmaceuticals: Can acceptable drug standard can be achieved. *Journal of Drug Information*. 1998; 32:101-110.
- Vaidya ADB, Deva sagayam TPA. Current status of herbal drugs in India: An overview. *J Clin Biochem*. 2007; 41(1):1-11.
- EMA. Guidelines on Quality of Herbal Medicinal Products/Traditional Medicinal Products. EMA/CVMP/81400 Review. European Agency for the Evaluation of Medicinal Products (EMA) London, 2005.
- WHO. General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine. World Health Organization, Geneva, 2002c.
- EMA. Quality of Herbal Medicinal Products Guidelines. European Agency for the Evaluation of Medicinal Products (EMA), London, 1998.
- Wani MS. Herbal medicine and its standardization. *Pharma. Info*. 2007; 1:6.
- Archana A, anubha K. Standardization of herbal drugs: an overview. *International research journal of pharmacy*. 2011; 12(2):56-60.
- WHO. Quality Assurance of Pharmaceuticals: A Compendium of Guidelines and Related Materials, Good Manufacturing Practices and Inspection. World Health Organization, Geneva, 1996a, 2.
- WHO. Guidelines for the Assessment of Herbal Medicines. WHO Technical Report Series, World Health Organization, Geneva, 1996b, 863.
- WHO. Quality Control Methods for Medicinal Plant Materials. World Health Organization, Geneva, 1992.
- Neeraj C, Bhupinder SS. An overview of advances in the standardization of herbal drugs. *J Pharm Educ Res*. 2011; 2(2):61-62.
- Rajini M, Kanaki NS. Phytochemical. Standardization of herbal drugs and poly herbal formulations. *Bioactive Molecules and Medicinal Plants*. 2008; 349-369.
- Mosihuzzaman M, Choudary MI. Protocols on safety, efficacy, standardization and documentation of herbal medicine. *Pure Applied Chemistry*. 2008; 80(10):2195-2230.
- Hylands P. New approaches for the quality control and standardization of plant delivered pharmaceutical and nutraceutical products. Oxford: Oxford Natural Products Publications, 2002.
- WHO. Quality Control Methods for Medicinal Plant Materials. World Health Organisation, Geneva, 1992.
- WHO. The International Pharmacopeia: Quality Specifications for Pharmaceutical Substances, Excipients, and Dosage forms, 3<sup>rd</sup> edn. World Health organization Geneva, 1988, 3.
- De Smet. PAGM. *Drug Information Journal*. 1999; 33:717-724.
- WHO. Guidelines for the appropriate use of Herbal Medicines. WHO Regional publications, Western pacific series, WHO Regional office for the Western Pacific, Manila, 1998, 3.
- WHO. Guidelines for the Assessment of Herbal Medicines. WHO Technical Report Series, No863. World Health Organization, Geneva, 1996.
- Sachan AK, Sachan NK, Kumar S, Sachan A, Gangwar SS. Evaluation and Standardization of Essential Oils for Development of Alternative Dosage Forms. *European Journal of Scientific Research*. 2010; 46(2):194-203.
- ICDRA. 6th International Conference on Drug Regulatory Authorities. World Health Organization, 1991.
- TDR. Operational Guidance: Information Needed to Support Clinical Trials of Herbal Products. UNICEF/UNDP/ WORLD Bank/WHO special program for Research and Training in Tropical Diseases (TDR), 2005.
- AOAC. Official Methods of Analysis of AOAC International, 18th edn. AOAC International, Gaithersburg, MD, 2005.
- De Smet PAGM, Keller K, Hansel R, Chandler RF. *Aristolochia species In: Adverse Effects of Herbal Drugs*. Springer-Verlag, Heidelberg, 1992, 1.
- Watson DG. *Pharmaceutical Analysis*. Churchill Livingstone, Edinburgh, 1999.
- De Smet PAGM, Keller K, Hansel R, Chandler RF. *Adverse Effects of Herbal Drugs*. Springer-Verlag, Heidelberg. 1997; 3:137-145