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Standardization and Quality Evaluation of Herbal Drugs

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ABSTRACT

In recent years most, people throughout world are turning to use medicinal plant and herbal product in healthcare system. the use of herbal product as medicine by the basis of history. The identification of pure active ingredient is an important requirement for Quality and dose determination of plant related dugs. Therefore, evaluation of the parameters based upon chemical, physical, microbiological, therapeutic and toxicological studies can serve as an important tool in stability studies. Standardization of herbal drugs means confirmation of its identity, Quality and purity. The present overview covers the standardization parameters with their standards value of some herbal drugs.

Keywords: Herbal medicine, Standardization, Quality control, evaluation, WHO Guidelines.

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Introduction:

Herbal products have been used since long times as medicinal drug for the treatment of a numerous diseases. Medicinal plants have played important role in world health. In malice of the great advances observed in modern drug in recent times, plants still make an important contributing to health care (Calixto *et al.,* 2000). Herbal products have been our single most popular source of medicines. Each plant is like factory capable of synthesizing infinite number of highly complex and unusual chemical substances whose structures could otherwise escape the mind forever (Kinghorn, 2002). There are at least 120 different chemical substances originated from plants that are considered as important drugs currently in use in the world, while several other drugs are simple synthetic changes of the herbal products (Farooqi, 2001). WHO has delivered some terms related to herbal drugs, according to their definitions. Herbal medicines include *herbs, herbal materials, herbal preparations* and *finished herbal products*. In some countries herbal drug may contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (e.g. animal and mineral materials). Herbs include crude plant material, such as leaves, flowers, fruit, seeds, stems, wood, bark, roots, rhizomes or other plant parts, which may be enter, 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 substances may be processed by many local procedures, such as steaming, roasting or stir baking with honey, alcoholic drinks or other substance. Herbal preparations are the basis for finished herbal products and may include comminuted or 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 drinks and/or honey, or in other materials. Finished herbal products consist of herbal preparations made from one or more herbs. If more than one herb is used, the term “mixture herbal product” can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture herbal products to which chemically defined active substances added, including synthetic compounds and/or isolated constituents from herbal

substance, are not considered to be herbal. Herbal product is used very commonly in different health practices or therapies of Traditional Medicines like Chinese medicine, Ayurveda, Unani, Naturopathy, Osteopathy and Homeopathy. [1]

Quality Control:

Quality control is a term that refers to processes involved in continuing the quality and validity of a manufactured product tie in general, quality control is based and three important pharmacopeia 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 microscopical examinations. In addition to this identity tests, which include simple chemical tests, e.g. color or precipitation and chromatographic tests are also required. These substance and chromatographic tests help to provide batch to batch comparability and the chromatogram may be used as a 'fingerprint' for the product which demonstrating the profile of certain common herbal plant chemical constituents such as flavonoids, alkaloids and terpenes. To show identity and purity, such as type of preparation, sensory properties, physical constants, adulteration, contaminants, moisture, ash content, and solvent residues are checked. Example are reliable reference sources for Outbreaks of illness among the natural plants may result in changes to the physical appearance of the herbal plant and lead to incorrect identification, Purity are closely linked with safe use of drugs and deals with factors such as ash values, impurities and heavy metals. but due to the application of improved analytical methods and modern purity evaluation which contains microbial contaminate, aflatoxins, radioactivity, and pesticide residues. Analytical methods which is photometric analysis, Thin layer chromatography (TLC), High performance liquid chromatography (HPLC), High performance thin layer chromatography (HPTLC), and Gas chromatography (GC) can be used for found the constant composition of herbal product. Depending upon the active source of the preparation are known and unknown, different concepts such as "standardization" is important for them to establish relevant criteria for consistency. Content and assay are the very difficult area of quality control to perform, in the maximum herbal product are have unknown the active constituents. Sometimes markers can be used. In 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. 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. alkyd amides 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 used. [2]

Evaluation:

Physical Evaluation- Each monograph contains detailed botanical, macroscopic and microscopic descriptions with detailed examples and photographic images which provide visual documentation of correctly 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 helps to determine the identity of the drug substance and possible adulteration.

Table no.1

S.N.	Name of constituents	Identification test
1.	Resins	Sulphated ash Acid value
2.	Balsams	Saponification value Bester value Acid value
3.	Volatile oil	Ester value Acetyl value
4.	Gums	Methoxy determination Volatile acidity

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. [3]

Microscopic Evaluation:

It involves the detailed valuation of the herbal medicines and it is use for recognized the organized drugs based on their known histological characters. It is regularly used to qualitative analysis of established crud drugs in total and powder form with the help of microscope. The inner pseudo parenchyma cells are round and oval shape. They check protein and fixed oil. Crude drugs are microscopically identified by taking thin TS (Transverse section), LS (Longitudinal Section) in a bark, wood and leaf.

The various parameters included in microscopy are given bellow.

I. Stomata II. Trichomes III. Leaf Content IV. Quantitative Microscopy

Table no. 2

Sr.no.	Name of constituents	Test /Reagent	Result
1	lignin	T.S. of crude drug + 1drop of phloroglucinol+1drop of HCL	Pink color
2	mucilage	Ruthenium Red	Pink color
3	Starch, Hemicellulose	T.S. of crud drug + 1drop of iodine solution	Blue color

Microbiological parameters:

It includes the full content of viable, total mound 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 ship directly from the manufacturing and solvents.

Toxicological studies:

Toxicological studies important to decide whether a new drug should be modified for clinical use or not. Depending on the period of contact with animals to drug, toxicological studies may be of three types. acute, sub-acute and chronic. Toxicity depends not only on the dose of the substance but also on the toxic properties of the substance. The relationship between these two factors is important in the assessment of therapeutic dosage in pharmacology and herbalism

Acute toxicity: Acute toxicity is defined as the toxic effects produced by single exposure of drugs by any route for a short period of time. Acute toxicity studies in animals are considered necessary for any pharmaceutical intended for human use. The main objective of acute toxicity studies is to identify a single dose causing major adverse effects or life-threatening toxicity, which often involves an estimation of the minimum dose causing lethality. The studies are usually carried out in rodents and consist of a single dose. In pharmaceutical drug development, this is the only study type where lethality or life-threatening toxicity is an endpoint as documented in current regulatory guidelines to evaluate toxicity of a compound in animals' various routes may be used, but two most commonly used modes of administration for animals' studies are via intraperitoneal injection or the oral route.

Usually acute (single dose) toxicity study is carried out on laboratory animals by using high dose (enough to produce death or morbidity) of the substance in question and/or based on previous report on its toxicity or toxicity of structurally related compounds. Acute toxicity studies are commonly used to determine LD50 of drug or chemicals. The acute study provides a guideline for selecting doses for the sub-acute and chronic low dose study, which may be clinically more relevant.

Sub-acute toxicity: In sub-acute toxicity studies, repeated doses of drug are given in sub-lethal quantity for a period of 14 to 21 days. Sub-acute toxicity studies are used to determine effect of drug on biochemical and hematological parameters of blood as well as to determine histopathological changes.

Chronic toxicity: In chronic toxicity studies, drug is given in different doses for a period of 90 days to over a year to determine carcinogenic and mutagenic potential of drug. The parameters of chronic toxicity studies are same as that of sub-acute study. Multiple dose studies are necessary to assure the safety of natural products. On the other hand, clinical observations of acute assays are valuable tools to define the doses to be tested in multiple dose experiments, along with pharmacological studies in animals and in humans.

Pharmacopoeia standards

The identification, purity and quality of herbal drugs are determined by reference given in a pharmacopoeia. Pharmacopoeia prescribes like Analytical, physical and structural standards for the herbal drugs. The essential standards are given in pharmacopoeia shown in figure 1.

A significant identification and examination of crude drugs is important in processes of herbal formulation because of more diversity and changes in their chemical nature or characters.

To reduce this problem all pharmacopeias, have certain standards. Specific test for specific plant material is given below. Alkaloids content drageoir test, Fat content Acid value Iodine value, saponification value molish test carbohydrates Million tests Amino acid Volatile oil

Hemolytic activity Assay for Phosphate/Aluminum/ Camphor /Potassium /Lead/Iron/Gold/Calcium

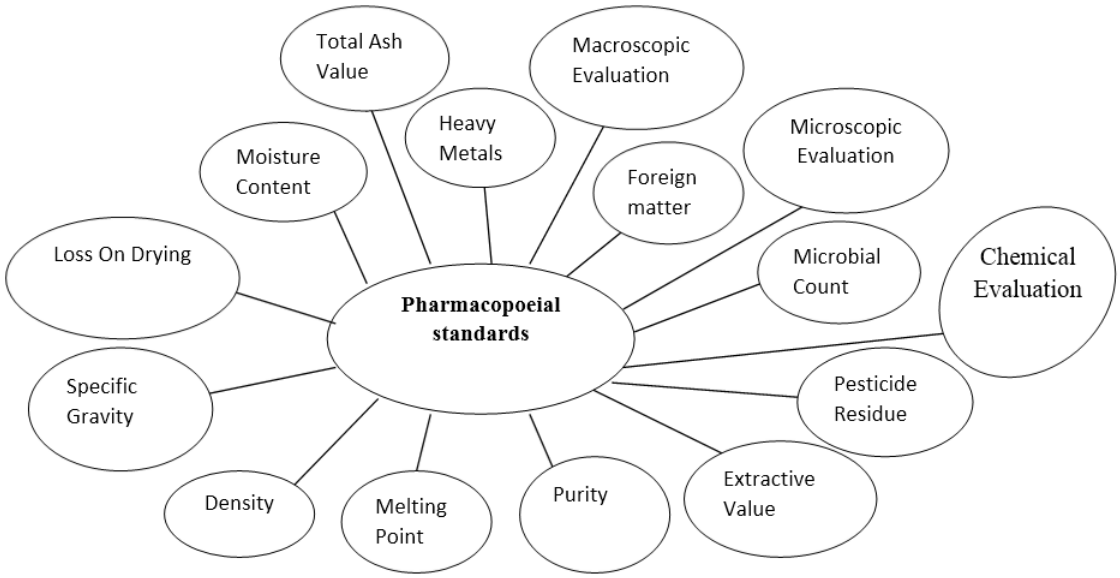

Figure no.1

Herbal Drug Standardization:

Standardization are a system that ensures an amount of quantity, quality & therapeutic effect of ingredients in each herbal medicine. Standardization of herbal drugs for Global competitiveness such a raw material needs to have authentic, physio-chemical standards, storage conditions, size and shape. Processing of raw material include material, energy inputs, operational uniformity, safety or occupational health, intermediate quality whereas finished product includes physio chemical properties, biological assay, storage stability, user safety *etc.* [4]

Methods of Standardization of Ayurvedic Medicines

1) Raw material standardization.

2) In process standardization

3) Finished product standardization.

1. Raw material standardization:

This includes authentication 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 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 enough 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 number 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 dosage forms. The processes involve 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.

Need for standardization:

The worldwide perspective, there is a shift towards the use of medicine from natural 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.**

WHO Guidelines

The subject of herbal drug standardization is massively wide and deep. The guidelines set by WHO can be summarized as follows: -

1. Reference to the identity of the drug. Botanical evaluation-sensory characters, foreign organic matter, microscopical, histological, histochemical evaluation, quantitative measurements etc.

2. Refers to the physicochemical character of the drug. Physical and chemical identity, chromatographic fingerprints, ash values, extractive values, moisture content, volatile oil and alkaloidal assays, quantitative estimation protocols etc.

3. A reference to the pharmacological parameters, biological activity profiles, bitterness values, hemolytic index, astringency, swelling factor, foaming index etc.

4. Toxicity details- pesticide residues, heavy metals, microbial contamination like total viable count, pathogens like *E. coli, Salmonella, P. aeruginosa, S. aureus, Enterobacteria* etc.

5. Microbial contamination.

6. Radioactive contamination. [5]

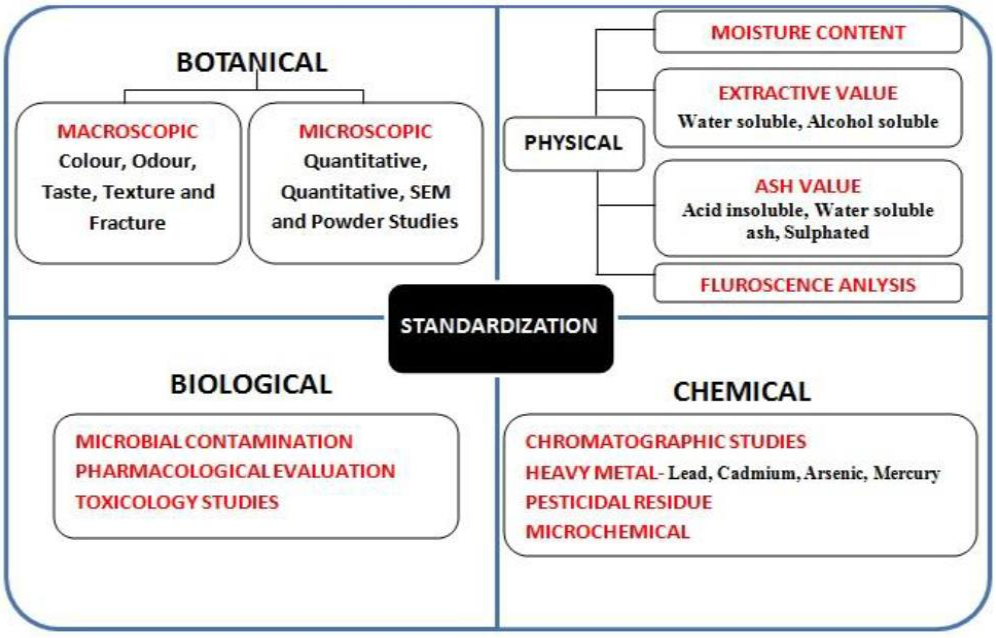

Figure no.2

Chromatography Techniques:

Common Methodology for Thin layer chromatography (TLC) Analysis Method

TLC (Thin layer chromatography): TLC is the most common, versatile method of choice for herbal analysis, and instrumental chromatography methods like GC and HPLC were also used. nowadays, TLC is still normally used for the analysis of herbal medicines since various pharmacopoeias such as Indian herbal pharmacopoeia, Ayurvedic pharmacopoeia; American Herbal Pharmacopoeia (AHP), Chinese drug monographs and analysis, Pharmacopoeia of the People's Republic of China, etc. Rather, TLC is used as a simply method of initial screening with a semi quantitative evaluation together with other chromatographic techniques as there is relatively less change in the simple TLC separation an herbal medicine than with instrumental chromatography. Thin-layer chromatography is a technique in which a solute undergoes distribution between two phases, a stationary phase acting through adsorption and a mobile phase in the form of a liquid. The adsorbent is a relatively thin, uniform layer of dry finely powdered material applied to a glass, plastic or metal sheet or plate. Glass plates are most commonly used. Separation may also be achieved based on partition or a combination of partition and adsorption, depending on the support, its preparation and its use with different solvent [Harborne ,1928; Stahl, 1969]. Identification can be affected by observation of spots of identical Rf value and about equal magnitude obtained, respectively, with an unknown and a reference sample chromatographed on the same plate. A visual comparison of the size and intensity of the spots usually serve for semi-quantitative estimation. TLC had the benefits of many-fold possibilities of detection in analyzing herbal medicines. In addition, TLC is rather simple and can be employed for multiple sample analysis. For each plate, more than 30 spots of samples can be studied simultaneously in one time. in thin-layer chromatography (TLC) the very important steps for a qualitative and quantitative analysis. Thus, the use of thin-layer chromatography (TLC) to analyze the herbal medicines is still popular. [6]

Common Methodology for HPTLC Analysis Method

The analysis method for estimation of quality of herbal drug. These are moving a fast towards an integrative and comprehensive way to tack the complex nature of herbal medicines. High-performance thin layer chromatography (HPTLC) is one of the complicated instrumental techniques for qualitative and quantitative analysis of the herbs and herbal medicines. when establishing as new analytical procedure, always starts with wide literature survey i.e. primary information about the physicochemical characteristics of sample and nature of the sample (structure, polarity, volatility, stability and solubility). It involves considerable trial and error procedures. General steps involved in HPTLC method are as follow:

Basic Steps:

- Selection of the stationary phase
- Mobile phase selection and optimization
- Sample Preparation and Application
- Chromatogram Development (separation)
- Detection

Advantages of HPTLC:

- Ability to analyze crude samples containing multi-components.
- The separation process is easy to follow especially with colored compounds.
- Several samples can be separated parallel to each other on the same plate resulting in a high output, time saving, and a rapid low-cost analysis.
- Choice of solvents for the HPTLC development is wide as the mobile phases are fully evaporated before the detection step.
- Two-dimensional separations are easy to perform. Stability during chromatography should be tested using two-dimensional development.
- Specific and sensitive color reagents can be used to detect separated spots (Dandruff reagent/Kidde reagent).
- HPTLC can combine and consequently be used for different modes of evaluation, allowing
- identification of compounds having different light-absorption characteristics or different colors.
- Contact detection allows radiolabeled compounds to be monitored and microbial activity in spots to be assessed.

Liquid Chromatography- Mass Spectroscopy (LC-MS)

LC-MS is a method for choice in many stages of drug development. Current advances technique is electrospray, thermo spray, and ion spray ionization this technique which employed unique advantages of high detection sensitivity and specificity, liquid secondary ion mass spectroscopy, later laser mass spectroscopy with 600 MHz offers accurate determination of molecular weight proteins, peptides. Isotopes pattern can be detected by this technique. [7]

MARKERS:

Markers may be chemically defined constituents of an herbal medicines which are employed for quality control purposes. whether they have any therapeutic activity or not. Markers may be calculating the amount of active ingredient in herbal medicine or preparation in the finished product. Marker compounds are pure, single isolated compounds, secondary metabolites mostly with terpenes, steroid, alkaloid, flavonoid aromatic hetero aromatic frameworks and glycosides having alcoholic, carbonyl, olefinic, acid, ester and amide functionalities highly useful for single crude drugs: May be not survive in multi herbal products. For quantitative studies, use of specific markers that can be easily analyzed to distinguish between types.

Genetic Marker

the genetic markers are a gene or DNA sequence with a known located on a chromosome and related with a gene or a quality. It can be described as a difference, which may be comes due to mutation or alteration in the genomic loci that can be observed. A genetic marker is a short DNA sequence, such as a sequence surrounding a single base-pair change (single nucleotide polymorphism SNP), or a long one, like minisatellites.

Some commonly used types of genetic markers are

- RFLP (or Restriction fragment length polymorphism)
- AFLP (or Amplified fragment length polymorphism)

- RAPD (or Random amplification of polymorphic DNA)
- VNTR (or Variable number tandem repeat)
- Micro satellite polymorphism
- SNP (or Single nucleotide polymorphism)
- STR (or Short tandem repeat)
- SFP (or Single feature polymorphism)

They can be further divided as dominant or codominant. Dominant markers used for analyzing many loci at one time, e.g. RAPD. A primer amplifying a dominant marker could amplify at many loci in one sample of DNA with one PCR reaction. Co-dominant markers are analyzing one locus at a time. A primer amplifying a co-dominant marker would yield one targeted product. [8]

Conclusion

The Indian medicinal industry is developing in a tremendous change. With the tremendous increase in traditional herbal treatment many companies regarding the safety, quality and efficacy of herbal drug has been observed. There are need for more advanced techniques of standardization. The advance analytical techniques will serve as a rapid and specific tool in the herbal medicine research, the manufacturers to set quality standards and specifications to find marketing approval from regulatory authorities for therapeutic efficacy, shelf- life and safety of herbal medicine. The national health organization should ensure that all herbal pharmaceutical drug product subject to their control. and conformity with quality, safety, efficacy and all premises and practices employed the manufacturing and distribution of these product are comply with GMP standards to ensure the conformity of the products with their requirements until they delivered to the end user. Quality control of herbal product have not only to establish reasonable analytical methods for analyzing the active ingredient in herbal medicines, but different factors should be affected such as pesticides residue, toxins content, the heavy metals contamination, good agricultural practice (GAP), good manufacturing practice (GMP), etc. There is the need for development of techniques which includes both traditional methods of evaluation and standardization. These are improving the quality of the herbal drug and inspire the practitioners to get involved in the standardization process and evaluation method.

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