Review

HERBAL DRUG STANDARDIZATION: AN EXPLORATORY REVIEW

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ABSTRACT
There is increasing awareness in today's medical practice and general acceptability of the use of herbal drugs. Over 80% of the world population depends on herbal medicines and product for healthy living. This rise in the use of herbal product has also given rise to various forms of misuse and adulteration of the products leading to disappointment of consumers' and manufacturers' and in some cases fatal consequences. This review seeks to inform stakeholders in herbal medicine on 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 and standardization of herbal medicines and products were also discussed.

KEY WORDS – Herbal drugs, Standardization, validation and Good agricultural/Manufacturing practices

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INTRODUCTION

The use of herbs as medicine is the oldest form of healthcare and in all cultures throughout history herbs as a medicine has been used [1]. For a healthy life early people depend on nature and since that time humanity has depended on the plant resources for food, clothing, shelter, and medicine to cure various diseases. 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 optimal results. Even in ancient cultures, tribal people collected information on herbs and developed well-defined herbal pharmacopeias. Some sixty thousand years ago physical evidence of the use of herbal remedies has been found in a burial site of a Neanderthal man uncovered in 1960 in a cave in northern Iraq [2].

In the twentieth century, the herbal lore of native people develops pharmacopeia of scientific medicine. 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 medicine is still a central part of their medical system.

Throughout the world medicinal plants are widely distributed but most abundantly in tropical countries. It is estimated that about 25% of all modern medicines are directly or indirectly derived from higher plants [3-16]. Thus, herbal medicine has led to the discovery of a number of new drugs, and non-drug substances.

HERBAL MEDICINE

An herb is a plant or part of a plant valued for its medicinal and aromatic qualities. Herbs are biosynthetic chemical laboratories, producing a number of chemical compounds. Herbal remedies or medicines consist of portions of plants or unpurified plant extracts containing several constituents, which often work together synergistically. Herbal medicine is the use of herbs or herbal products for their therapeutic or medicinal value. They may come from leaves, roots, bark seeds, and flowers. They are eaten, swallowed, drunk, inhaled, or applied topically to the skin. Herbal products often contain a variety of naturally-occurring biochemicals from plants. 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.

During the past decade, there has been increasing interest in herbal medicines in both developing and developed countries. About 80% of the world's population, uses herbal medicine as their source of primary healthcare especially in the developing countries [17-19]. In the Western countries, people are attracted to herbal therapies for many reason, they believed that herbal medicines will help us live healthier lives. Individuals spend billions of dollars on herbal products who use them as home remedies and over-the-counter drugs. As such, the herbal medicines become the substantial proportion of the global drug market [5, 12, 8-10, 18, 20-22]. An individual must take the required dose over a certain length of time to achieve the desired benefit from herbal preparations. Although it is generally believed that most herbal medicines are safe for consumption, some herbs like most biologically active substances could be toxic with undesirable side effects [23]. There is a problem in the availability and quality of the raw materials because the active principles are diverse and may be unknown. In many countries, herbal products are launched into the market without proper scientific evaluation, and without any toxicological studies. Consumers can buy herbal products without a prescription and might not recognize the potential hazards in an inferior product [24].

SCOPE OF QUALITY CONTROL AND STANDARDIZATION OF HERBAL MEDICINES

Generally, all medicines, should fulfill the basic requirements of being safe and effective whether they are synthetic or of plant origin, [25-30] The term "herbal drugs" denotes plants or plant parts that have been converted into phytopharmaceuticals by means of simple processes involving harvesting, drying, and storage [31].

Standardization of herbal formulations is essential in order to assess quality of drugs, based on the concentration of their active principles, physical, chemical, phyto-chemical, standardization , and In-vitro, In-vivo parameters. The quality assessment of herbal formulations is of paramount importance in order to justify their acceptability in modern system of medicine. Specific standards would lead to the process of prescribing a set of characteristics exhibited by the particular

herbal medicine worked out by experimentation and observations. Hence standardization is a tool in the quality control process.

Several problems not applicable to synthetic drugs often influence the quality of herbal drugs. For instance:

1. Herbal drugs contain 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 naturally and chemically variable.

5. The source and quality of the raw material are variable.

The methods of harvesting, drying, storage, transportation, and processing also affect herbal quality. At present for herbal preparations no official standards are available. Presently it is very difficult to identify the presences of all the ingredients in a formulation. Hence the first important task is to evolve such parameter by which the presence of all the ingredient can be identified, various chromatographic and spectrophotometric methods and evaluation of physicochemical properties can be tried 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

1. Modern system of medicine is based on sound experimentation data, toxicity studies and human clinical studies.
2. But, pharmacopoeial standards on raw material/ finished products are not available.
3. GMP for the herbal industry is not well defined nor is the barest minimum standards of medicinal plant products mentioned or regulated.
4. The lack of quality standards has resulted in mild to serious adverse effects ranging from hepatotoxicity to death. Hence herbal ingredients require tools for determining identity,purity,and quality and tools have to be technical sufficient, rapid and cost effective with GMP requirements.

Guidelines for the Standardization and quality control of herbal crude drugs:

Standardization and quality control of herbals is the process involved in the physicochemical evaluation of crude drug 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[28, 32-33].The procedure includes following studies:

1. Macroscopic and microscopic examination: Visual inspection provides the simplest and quickest means by which to establish identity, purity and quality and search of adulterants.

2. Foreign organic matter: This involves removal of organic matter other than source plant to get the drug in pure form.

3. Ash values: It is the indicative of contamination, substitution and adulteration in preparing the drugs. These are – 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: Amount of the active constituents present in crude drug material when extracted with specific solvent. There are following Methods for determination of Extractive value. a) Cold method b) Hot method c) Soxhlet method. 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.

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.

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.

Physical evaluation

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

Microscopic evaluation

Detail of cell structure and arrangement of the cells useful for differentiating similar species. Any water-soluble contents can be removed from the cells by soaking in water. Starch grains can be gelatinized by heating in water. Microscopic analyses of plants are invaluable for assuring 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. This covers screening, isolation, identification and purification of the chemical components. The chemical screening or tests may include colour reaction test, which help to determine the identity of the drug substance and possible adulteration.

Biological evaluation

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

Analytical methods

There is a need for appropriate analytical methods for determining identity, quality, and relative potency. There are many analytical methods available. However, it is often difficult to know which is the most appropriate to use, but critical among know analytical tools in monograph standardization is chromatography.

Chromatography

Chromatography is the science which studies the separation of molecules based on differences in their structure and/or composition. Chromatographic separations can be carried out using a variety of supports, including immobilized silica on glass plates (thin layer chromatography), very sensitive High Performance Thin Layer Chromatography (HPTLC), volatile gases (gas chromatography), paper (paper chromatography), and liquids which may incorporate hydrophilic, insoluble molecules (liquid chromatography).

High performance thin layer chromatography (HPTLC) is an enhanced form of thin layer chromatography (TLC). A number of enhancements can be made to the basic method of thin layer chromatography to automate the different steps, to increase the resolution achieved and to allow more accurate quantitative measurements. It allows for the analysis of a broad number of compounds both efficiently and cost effectively. With HPTLC, the same analysis can be viewed collectively in different wavelengths of light thereby providing a more complete profile of the plant than is typically observed with more specific type of analysis.

Quantitative analysis

The most appropriate quantitative analytical method with accompanying chromatograms is desirable. The primary goal of the methods is to provide validated methods to be used to quantify the compounds most correlated with pharmacological activity or qualitative markers.

Control of starting material

Control of the starting materials is essential in order to ensure reproducible quality of herbal medicinal products [34-37]. The following points are to be considered in the control of starting materials:

1. Inter- or intra-species variation: There are considerable variations in different plants, for which the primary and secondary metabolite also varies considerably. These all variations are genetically controlled which is related to the country of origin for that particular species.

2. Environmental factors: The quality of a herbal ingredient can be affected by environmental factor like climate, altitude and other conditions under which it was cultivated. This result in major variations in the herbal ingredients present in some specific species of plants.

3. Time of harvesting: For some herbs the optimum time of harvesting should be specified as it is known that the concentrations of constituents in a plant can vary during the growing cycle or even during the course of a day. Therefore time of harvesting has a great role to play.

4. Plant part used: Usually the active constituents vary between plant parts and it is not uncommon for an herbal ingredient to be adulterated with parts of the plant not normally utilised. In addition, plant material that has been previously subjected to extraction and is therefore 'exhausted' is sometimes used as adulterants to increase the weight of a batch of herbal ingredient.

5. Post-harvesting factors: Treatment of the collected herbal raw materials like storage, transport etc. can greatly affect the quality of herbal ingredient. Storage conditions and processing treatments can greatly affect the quality of an herbal ingredient. Inappropriate storage after harvesting can result in microbial contamination, and processes such as drying may result in a loss of thermo-labile active constituents.

Good agricultural/Manufacturing practices

Quality control and the standardization of herbal medicines also involve several other steps like source and quality of raw materials, good agricultural practices and good manufacturing practices. These practices play a pivotal role in guaranteeing the quality and stability of herbal preparations [21-22, 30, 33, 38-41].

The quality of a plant product is determined by the prevailing conditions during growth, and accepted Good Agricultural Practices (GAP) can control this. These include seed selection, growth conditions, fertilizers application, harvesting, drying and storage. In fact, GAP procedures are integral part of quality control.

Factors such as the use of fresh plants, age and part of plant collected, period, time and method of collection, temperature of processing, exposure to light, availability of water, nutrients, drying, packing, transportation of raw material and storage, can greatly affect the quality, and hence the therapeutic value of herbal medicines. Apart from this, factors such as the method of extraction, contamination with microorganisms, heavy metals, and pesticides can alter the quality, safety, and efficacy of herbal drugs. Using cultivated plants under controlled conditions instead of those collected from the wild can minimize most of these factors [21, 42-43]. Sometimes, the active principles are destroyed by enzymes processes that continue for long periods from collection to marketing, resulting in a variation of composition. Thus, proper standardization and quality control of both the raw material and the herbal preparations should be conducted.

Contaminants of herbal ingredients

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

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

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

3. Microbial contamination: Aerobic bacteria and fungi are normally present in plant material and may increase due to faulty growing, harvesting, storage or processing. Herbal ingredients, particularly those with high starch content, may be prone to increased

microbial growth. Pathogenic organisms including Enterobacter, Enterococcus, Clostridium, Pseudomonas, Shigella and Streptococcus have been shown to contaminate herbal ingredients. It is essential that limits be set for microbial contamination and the European Pharmacopoeia now gives non-mandatory guidance on acceptable limits [44].

4. Pesticides: Herbal ingredients, particularly those grown as cultivated crops, may be contaminated by DDT (dichlorodiphenyltrichloroethane) or other chlorinated hydrocarbons, organophosphates, carbamates or polychlorinated biphenyls. Limit tests are necessary for acceptable levels of pesticide contamination of herbal ingredients. The European Pharmacopoeia includes details of test methods together with mandatory limits for 34 potential pesticide residues [44].

5. Fumigants: Ethylene oxide, methyl bromide and phosphine have been used to control pests which contaminate herbal ingredients. The use of ethylene oxide as a fumigant with herbal drugs is no longer permitted in Europe [44].

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

7. Radioactive contamination: There are many sources of ionization radiation, including radionuclides, occurring in the environment. Hence, a certain degree of exposure is inevitable. [40 , 45-46].

8. Other contaminants: As standards increase for the quality of herbal ingredients it is possible that tests to limit other contaminants such as endotoxins and mycotoxins will be utilized to ensure high quality for medicinal purposes [44].

FACTORS AFFECTING THE QUALITY CONTROL OF HERBAL DRUGS

Microscopic evaluation

Quality control of herbal drugs has traditionally been based on the appearance and identifying small fragments of crude or powdered herbs, and detection of foreign matter and adulterants. A primary visual evaluation, can be used to ensure that the plant is of the required species, and that the right part of the plant is being used. 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 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 [45].

Foreign matter

Herbal drugs should be made 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 [38-39, 41]. Macroscopic examination can be helpful to determine the presence of foreign matter, although, microscopy in certain special cases is indispensable (for example, starch deliberately added to "dilute" the plant material). Furthermore, when foreign matter consists, for example, of a chemical residue, TLC is often needed to detect the contaminants [8, 45, 47].

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 [45].

Heavy metals

Contamination by toxic metals can either be accidental or intentional. 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 be dangers for the health of the user and should therefore be limited [45 , 27 , 46]. 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, straight forward 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 [30]. Instrumental analyses have to be employed when the metals are present in trace quantities, in admixture, or 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) [47].

Microbial contaminants and aflatoxins

Medicinal plants may be associated with a broad variety of microbial contaminants, represented by bacteria, fungi, and viruses. 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 pharmacopeias, as well as, in the WHO guidelines [40, 48]. Materials of vegetable origin tend to show much higher levels of microbial contamination than synthetic products .The presence of fungi should be carefully investigated and/or monitored, since some common species produce toxins, especially aflatoxins. Aflatoxins in herbal drugs can be dangerous to health even if they are absorbed in minute amounts [40]. Aflatoxin-producing fungi sometimes build up during storage [46]. Procedures for the determination of aflatoxin contamination in herbal drugs are published by the [40]. After a thorough clean-up procedure, TLC is used for confirmation.

Pesticide residues

Even though there are no serious reports of toxicity due to the presence of pesticides and fumigants, it is important that herbs and herbal products are free of these chemicals or at least are controlled for the absence of unsafe levels [46]. Herbal drugs are liable to contain pesticide residues, which accumulate from agricultural practices, such as spraying, treatment of soils during cultivation, and administering of fumigants during storage. However, it may be desirable to test herbal drugs for broad groups in general, rather than for individual pesticides. Many pesticides contain chlorine in the molecule, which, for example, can be measured by analysis of total organic chlorine. Samples of herbal material are extracted by a standard procedure, impurities are removed by partition and/or adsorption, and individual pesticides are measured by GC, MS, or GC-MS. Some simple procedures have been published by the WHO and the European Pharamacopoeia has laid down general limits for pesticide residues in medicine [28, 45, 48-49].

Analytical methods

The best strategy is to follow closely the pharmacopoeia definitions of identity, purity, and content or assay. Valuable sources for general analytical procedures are included in the pharmacopeias, in guidelines published by the WHO [40, 45]. Additional information, especially on chromatographic and/or spectroscopic methods can be found in the general scientific literature. The plant or plant extract can be evaluated by various biological methods to determine pharmacological activity, potency, and toxicity.

A simple chromatographic technique such as TLC may provide valuable additional information to establish the identity of the plant material. This is especially important for those species that contain different active constituents. Qualitative and quantitative information can be gathered concerning the presence or absence of metabolites or breakdown of products [45]. TLC fingerprinting is of key importance for herbal drugs made up of essential oils, resins, and gums, which are complex mixtures of constituents that no longer have any organic structure. It is a powerful and relatively rapid solution to distinguish between chemical classes, where macroscopy and microscopy may fail. Chromatograms of essential oils, for example, are widely published in the scientific literature, and can be of invaluable help in identification. The instruments for UV-Visible determinations are easy to operate, and validation procedures are straightforward but at the same time precise. HPLC is the preferred method for quantitative analysis of more complex mixtures. Though the separation of volatile components such as essential and fatty oils can be achieved with HPLC, it is best performed by GC or GC-MS. The quantitative determination of constituents has been made easy by recent developments in analytical instrumentation. Recent advances in the isolation, purification, and structure elucidation of naturally occurring metabolites have made it possible to establish appropriate strategies for the determination and analysis of quality and the process of standardization of herbal preparations. Classification of plants and

organisms by their chemical constituents is referred to as chemotaxonomy.

TLC, HPLC, GC, quantitative TLC (QTLC), and high-performance TLC (HPTLC) can determine the homogeneity of a plant extract. Over-pressured layer chromatography (OPLC), infrared and UV-Visible spectrometry, MS, GC, liquid chromatography (LC) used alone, or in combinations such as GC-MS and LC-MS, and nuclear magnetic resonance (NMR), electrophoretic techniques, especially by hyphenated chromatographic techniques, are powerful tools, often used for standardization and to control the quality of both the raw material and the finished product. The results from these sophisticated techniques provide a chemical fingerprint as to the nature of chemicals or impurities present in the plant or extract [26]. Based on the concept of photo equivalence, the chromatographic fingerprints of herbal medicines can be used to address the issue of quality control. Methods based on information theory, similarity estimation, chemical pattern recognition, spectral correlative chromatograms (SCC), multivariate resolution, the combination of chromatographic fingerprints and chemometric evaluation for evaluating fingerprints are all powerful tools for quality control of herbal products.

Validation

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.

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 [50]. 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. 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 [50].

CONCLUSION

Plant materials are used throughout the developed and developing world as home remedies, in over-the-counter drug products, and as raw material for the pharmaceutical industry, and they represent a substantial proportion of the global drug market. Certain herbs have become popular over the years, but the general public, medical practitioners and the media still have a poor understanding of safe and effective use of herbal medicine. Therefore, it is essential to establish recognized guidelines for assessing their quality. The need for standardization of herbals is now very essential given the global acceptance of herbal products as remedies for various diseases and ailments.

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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