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Standardization of herbal drugs: An overview

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Abstract
Many different types of medicinal herbs and their formulation have been used since time immemorial. Practical experience and several modern research works have clearly shown that therapy using medicinal plants is more esteemed than using synthetic chemicals. The world is rich in medicinal plants growing wild or cultivated, forming a huge natural and economical health which must be protected, increased for the development of economy, wealth of nation and health of people. The identification of purely active moiety is an important requirement for Quality control and dose determination of plant related dugs. Standardization of herbal drugs means confirmation of its identity, Quality and purity. Therefore, it is necessary to improve the safety of herbs and develop a certain quality control along with following WHO guidelines for herbal medicines.

Keywords: standardization, quality control, medicinal plants, WHO

Introduction

Medicinal plants play a key role in global health. Despite the great advances made by modern medicine in recent decades, plants still make a significant contribution to health care [1]. Even in ancient cultures, tribal people methodically collected information about herbs and developed well-defined herbal pharmacopoeias. Physical evidence of the use of herbal remedies was found about 60,000 years ago in the cemetery of a Neanderthal man discovered in 1960 in a cave in northern Iraq [2]. The Assembly of the World Health Organization shall assume its responsibilities for taking account of its law, policy formulation, regulations and national measures to ensure the use of safety and the effectiveness of traditional medicine [3]. The WHO has listed some terms related to herbal medicines according to its definitions. Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products. In some countries, herbal medicines may traditionally contain natural organic or inorganic active substances that are not of plant origin (for example, animal and mineral materials). Herbs include raw plant material such as leaves, seeds, stems, flowers, fruits, wood, bark, roots, rhizomes or other parts of the plant, which may be whole, crushed or powdered[4].Herbal materials include, fresh Juices, gums, fixed oils, essential oils, resins and dry powders of herbs[5].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 material sherbs [4].Finished herbal products consist of herbal preparations made from one or more herbs.However, finished products or mixture herbal products to which chemically defined active substances have been added, including synthetic compounds and/orisolated constituents from herbal materials, are not considered to be herbal(WHO guideline, 2000) [1].

The Need for Standardization of Herbal/Traditional Medicine

The main reason for standardizing herbal extracts is to achieve the greatest possible control in double-blind clinical studies. According to herbalist Bob Bruce, standardization has advantages. It produces a constantly strong product with guaranteed components. When you consider the quality of most commercial herbs, standardization will at least ensure that they contain something and that the right herb is used. Many herbalists look to the brighter side of standardized herbal products than to the quantum intake of more people, including doctors and pharmacists, who are accustomed to the consistency and percentage of active ingredients.

Standardization of Herbal Medicines

According to WHO (1996a ab, 1992), standardization and quality control of herbs is a process involving physico-chemical evaluation of a raw drug, which includes aspects such as raw material selection and handling, safety assessment, efficacy and stability of the finished product, safety and risk documentation based on experience, providing information about the product to the consumer and its promotion. During the manufacture, formulation, storage, packaging, transport and distribution of a medicinal product, it may change the efficacy, safety, stability, and therefore the standardization of herbal medicinal products is a necessity of an era for the actual process [6-9]. Phytochemical standardization consists of all possible information generated in relation to the chemical fractions present in the herbal medicinal product. Hence, purpose of standardization of herbal medicine includes the following:

1. Preliminary testing for the presence of different chemical Groups.
2. Quantification of chemical groups of interest (e.g., total alkaloids, total phenolics, total triterpenic acids, total tannins).Establishment of fingerprint profiles.
3. Multiple marker-based fingerprint profiles.
4. Quantification of important chemical constituents [1]

WHO Guidelines for Herbal Drugs Standardization and Evaluation

Techniques involved in standardization of crude drugs

1. Preliminary Evaluation- Sampling, Foreign determination, determination of total fiber.

2. Morphological Evaluation-Colour, odour, taste, size, shape, extra features.
3. Microscopical evaluation- Qualitative histological evaluation of types of tissues, quantitative assessement of palisade ratio, vein-islet, vein termination, stomatal index, stomatal number and Lycopodium spore method
4. Physical qualitative evaluation- Solublity refractive index, optical rotation, melting point, boiling point, density, viscosity, chromatographic and spectroscopic evaluation:
5. Physical quantitative evaluation- Ash values, Extractive values, Moisture contentand Volatile oil determination.
6. Chemical Evaluation-To dectect different classes of phytochemicals, quantitative determination of phyochemicals, assay
7. Biological Evaluation- Swelling Index, Hemolytic index, Bitterness value, Foaming index, Total tannins value
8. Toxicological Evaluation- Determination of pesticides, Determination of arsenic and heavy metals, Determination radioactive contamination, Determination of aflatoxins
9. Pharmacological Evaluation- Animal activity, Animal organ or tissue activity
10. Analytical Evaluation- Chromatographic-TLC, Paper, HPTLC, HPLC AND GC and spectroscopic evaluation.

Preliminary Evaluation

Sampling- It is important step because whole quality control is based on selecting sample from raw material or finished products. Foreign matter determination –Everything that is not a biological source of raw drugs is considered foreign matter. They must be completely free of insects or fungi, including visible and excluded contaminants such as stones, sand, harmful and toxic foreign bodies and chemical residues. Animal objects such as insects and invisible microbial contaminants that produce toxins as well as potential contaminants in herbal medicines [10-11].

Macroscopic evaluation can easily be used to determine the presence of contaminants, although microscopy, such as intentionally added starch to "dilute" plant material, is necessary in certain special cases.as insects and invisible microbial contaminants, which produces toxins, as well as the potential contaminants of herbal medicines. Macroscopic evaluation can easily used to determine the presence of foreign matter, although microscopy is essential in certain special cases for example starch intentionally added to “dilute” the plant material [12].

Total fiber determination

Extract 2 g of ground material with petroleum ether to remove fat. If fat content is below 1 % extraction may be omitted. After extraction with petroleum ether boil 2 g of dried material with 200 ml of sulphuric acid for 30 mins with bumping chips. Filter and wash with boiling water until washings are no longer acidic. Boil with 200 ml of sodium hydroxide for 30 mins. Filter and wash again with sulphuric acid, three 50 ml portions of water and lastly 25 ml alcohol. Remove the residue and transfer to ashing dish (pre weighed dish W1). Dry for two hours at 130± 2. Cool the dish in a dessicator and weigh W2. Ignite for 30 mins, at 600oC. Cool in a dessicator and reweigh (W3).

$$\text{Crude fiber content} = \frac{\text{Loss in Weight in Ignitation (W2-W1) - (w3-w1)}}{\text{Weight of sample}} * 100$$

Morphological Evaluation: Herbal drugs evaluation by size, shape color, odor, taste and particular characteristics like touch, texture etc. This is a technique of qualitative evaluation related to the study of morphological and sensory report of whole Drugs [13].

Microscopical evaluation: Microscopic evaluation of raw herbal medicines is necessary to identify crushed or powdered materials. It includes a detailed evaluation of herbal medicines and is used to identify medicines arranged on the basis of their known histological features. Measurement of leaf constants Surface constants can be measured, such as number of stomata, stomatal index, number of venous islets, number of vein terminations, Proportion of palisades. The number of stomata, the index of the stomata, is present in the upper and lower epidermis and is made by peeling the epidermal layer and then the clear layer is slowly held on a microscope slide, cut with a slide and then a drop of chloral hydrate is added to remove any chlorophyll. Microscope 45X. The Stomata are taken using a lucid camera attached to a microscope and the number of bronchi is calculated using formulas. The venous islet, venous end, palisade ratio is determined by cooking the leaf pieces in chloral hydrate for 15-20 minutes and then the leaf fragment is placed on a microscope slide and observed 45X for the venous islet, vein end and 5X for the palisade ratio [13].

Physical qualitative evaluation

Determination of total ash

About 2 grams of the drug is weighed and placed in the china dish and keep in incinerator and kept it for about 5-10 min at 450°C The remained ash is cooled and weighed and percentage of ash is calculated with dried drug.

Acid-insoluble ash: The ash remained in the total ash is taken in 25 ml of dil HCL and it is filtered, the residue remained on filter paper is Acid insoluble ash and the percentage is calculated with the dried crude drug.

Water soluble ash: The total ash is dissolved in 25 ml of distilled water and filter the ash solution, the remained ash is subtracted from the total ash gives the water soluble ash and percentage is calculated to the dried drug.

Determination of alcohol soluble extractive Weigh 5 gm of the drug and keep in contact with 100 ml of alcohol and kept for 24 hrs for maceration with intermittent shaking and it is filtered after 24 hrs and filtrate is evaporated to dryness and percentage of alcohol soluble extractive is calculated with the dried drug.

Determination of water soluble extractive It is same with the alcohol soluble extractive but the alcohol is replaced with water with chloroform as preservative

Determination of ether soluble extractive weigh 75 gm of the drug and prepare a thimble and the extracted with petroleum ether in soxhlet apparatus for 6 hrs and then the extract is allowed to evaporate the extract and calculate the percentage of drug.

Moisture content (loss on drying): Weigh 5 gm of the drug and place in the china dish and dried in the oven at 105°C for 5 hrs and weigh the drug continuously, with an interval of 1 hour until the two successive weights was not more than 0.01 gm.

Volatile oil content: Efficiency of several drugs is due to their odorous principle (volatile oils).Such crude drugs are standardized on the basis of their volatile oil contents. Weighed quantity of the drug is boiled with water in a round bottomed flask fitted with clevenger apparatus. The distillate collected is graduated into volatile oil. The amount thus obtained is recorded from the tube [14, 15].

Chemical Evaluation: This includes the identification and Characterization of the crude drug in relation to the phytochemical component. It uses various analytical techniques to detect and isolate the active ingredients. Phytochemical screening techniques include botanical identification, extraction with suitable solvents, purification and characterization of active ingredients of pharmaceutical importance [16, 17].

Biological Evaluation: Swelling Index test is very useful for materials with swelling properties, especially gums and mucilage, pectin and hemicelluloses.
Hemolytic index- Saponin have characteristics of frothing property and have ability to cause haemolysis when added to suspension of blood. The plants from caryophyllace, Aralaceae, Sapindaceae, Primulaceae contain saponin. it is determined by comparing with reference material saponin which have haemolytic activity in 1000 unit per gram.
Bitterness value- Bitter properties of the plants materials are determined the comparing the threshold bitter concentration of the materials with that of a dilute solution of quinine HCL. It stimulate the Gastric secretion.
Foam index- Saponin are high molecular weight containing phytoconstituents having detergent activity. The foaming ability of an aqueous decoction of plant materials is measured in term of foaming index.
Total tannins value -Tannins are present in the cell sap. It has astringent property. Tannin binds with proteins and turns into water insoluble materials and are resist to proteolytic enzymes [18-21].

Toxicological Evaluation
Determination of pesticides
WHO and FAO (food & agricultural Organisation) set limits of pesticides, which are usually present in the herbs. These are mixed with the herbs during the time of cultivation. Mainly pesticides like DDT, BHC, toxaphene, aldrin cause serious side effects in human beings. Determination of arsenic and heavy metals
Arsenic and heavy metals are even in trace amounts but they are dangerous removed from herbal drugs. Amount is estimated by matching the depth of colour with of standard stains.

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 tobe a health risk. Therefore, at present, no limits are proposed for radioactive contamination.

Aflatoxins determination: Aflatatoxins produced by the growth of mold *Aspergillus flavus* and have carcinogenic properties.B1, B2, G1 and G2 are highly dangerous contamination in any material of the plant origin [22, 23].

Pharmacological Evaluation: Some drugs have specific biological and pharmacological activity which is utilized for their evaluation. Actually this activity is due to specific type of constituents present in the plant extract. For evaluation the experiments were carried out on both intact and isolation organs of living animals. With the help of bioassays, strength of drug in its preparation can be evaluated [24].

Analytical Evaluation
Thin Layer Chromatography: Thin layer chromatography is a simple versatile method used in pharmaceutical analysis for both qualitative and quantitative evaluation of chemical constituents. Compared to other chromatographic methods, TLC has been associated with many advantages including use of simple equipments, short development time of 15 min to 1h, wide choice of stationary phases and quick recovery of separated constituents. Moreover, easy visualization of separated components by UV light makes TLC a method of choice for simple quick and easy analysis.

High Performance Liquid Chromatography: High performance liquid chromatography is one of the modern day applications highly utilized in separation and isolation of natural pharmaceutically active compounds including alkaloids and glycosides whose role in modern conventional medicine is undisputable. It is the most preferred method.

Gas Chromatography and Mass Spectrometry: Many biologically active chemical compounds are volatile there by making gas chromatography an important tool in quality control of herbal medicine. It has high sensitivity of detecting almost all the volatile and thermostable chemical compounds.
HPTLC-High-performance thin-layer chromatography (HPTLC) has been emerged as an important tool for the qualitative, semi quantitative, and quantitative phytochemical analysis of the herbal drugs and formulations. This includes developing TLC fingerprinting profiles and estimation of biomarkers. This review has an attempt to focus on the theoretical considerations of HPTLC and some examples of herbal drugs and formulations analyzed by HPTLC [25, 26].

Conclusion
A significant number of methods to authenticate crude drugs have been addressed here. Despite these challenges, there is a growing need for consumers and healthcare professionals to obtain reliable and up-to-date information on the safety and efficacy of medicinal plants. Macroscopic, microscopic, microbiological, physicochemical, phytochemical and chromatographic quality assurance mechanisms are needed for widely used herbal medicines. Ensuring the safety and efficacy of the herbal medicine requires monitoring the

quality of the product, from collection, through processing to the final packaged product. It is recommended that several government agencies follow a more universal approach to herb quality, adopt WHO guidelines and also develop monographs using the various qualitative parameters described above. This will strengthen the regulatory process and minimize quality degradation.

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