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Research Article

REVIEW ON HERBAL DRUG FORMULATION AND STANDARDIZATION

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Abstract

Herbal formulations contain an active herbal substance in combination with one or more herbal preparations. Herbal formulation are obtained by subjecting herbal substances to treatment such as extraction, distillation, expression, fractionation, purification, concentration. These are the preparations being prepared with the use of modern methods by using powder form of herbal drugs and its derived products. Quality standardization of herbal preparation is a fundamental requirement of herbal drugs industry dealing with Ayurvedic and herbal products. Nowadays newer and advanced methods are available for the standardization of herbal drugs like the combination of chromatographic and spectrophotometric methods, biological assays, use of biomarkers in fingerprinting etc. Bioassay can play an important role in the standardization of herbal drugs and can also become an important quality control method as well as for proper stability testing of the product. There is great need to improve quality standards of herbal formulations as its increasing demand by the peoples. In this review the study of various methods of conventional standardization of herbal drugs stated with the recent approaches of standardization methods. By that way we can explore in future the use of herbal drug preparation with its promising quality standards.

Keywords: Herbal drug, herbal formulation, Extraction, Standardization, Evaluation.

INTRODUCTION

Herbal drugs

The term "herbal drugs" denoted by means of plant or part of plants that have been converted into phytopharmaceuticals by simply means of processes involving collection or harvesting, drying and storage. Finished herbal products that contain active ingredients such as aerial and underground parts of plant or other plants material or combinations thereof, whether in the crude state or as plant preparations. Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products. In some countries herbal medicines 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 entire, fragmented or powdered. Herbal materials include, in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting with honey, alcoholic beverages or other materials. 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 beverages 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.

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However, finished products or mixture herbal products to which chemically defined active substances have been aded, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be herbal. Herbal medicines are used very commonly in various health practices. Traditional Medicines like Chinese medicine, Ayurveda, Unani, Naturopathy, Osteopathy and Homeopathy [1,2].

Advantages of herbal drugs

1. Low cost of production.
2. They may have fewer side effects.
3. Effective with chronic condition.
4. Wide spread availability.

Disadvantages of herbal drugs

1. Lack of dosage instruction.
2. Poison risk associated with wild herbs.
3. Can interact with other drugs.
4. Inappropriate for many condition.
5. Some are not safe to use.

Unit Operations/Stages Involved In Herbal Formulations [3,4]

There are several methods or operation involved in obtaining the herbal extract or bioactive phytoconstituents and these depend to some extent on the particular part of the plant which is being used. The main objective of each process is to obtain the extract in a pure state and free from any contaminating materials which may affect the odor, the physicochemical or pharmacological properties of the final formulation.

Grinding

The selected plant material is dried and subjected to powdering with the help of a hammer mill or disc pulverizer which has

built in sieves. This will help to disintegrate the organ, tissue and cell structure of the plant material so that the medicinal ingredients present therein are exposed to the solvents with which it is to be extracted.

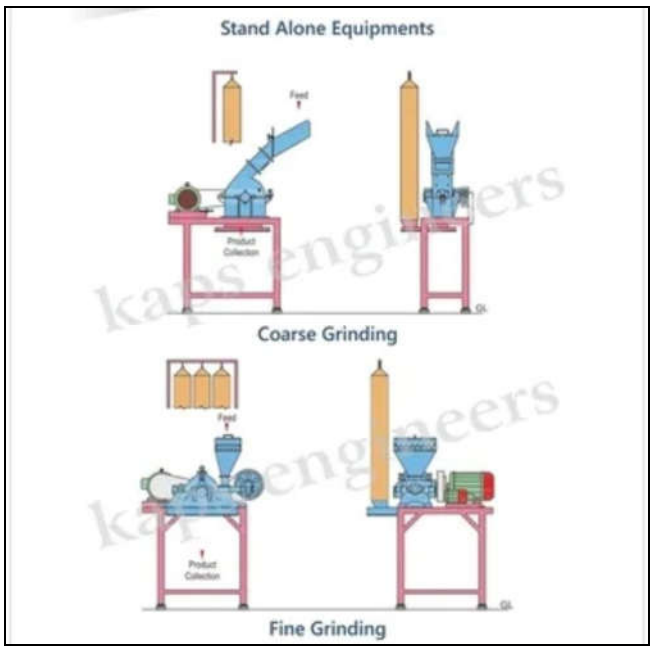

Figure 1. Grinding of herbal drugs

Extraction

This involves the separation of medicinally active principles from the plant material with the help of a suitable solvent. It could be hot aqueous extraction (decoction), cold percolation or solvent extraction using soxhlet extractor.

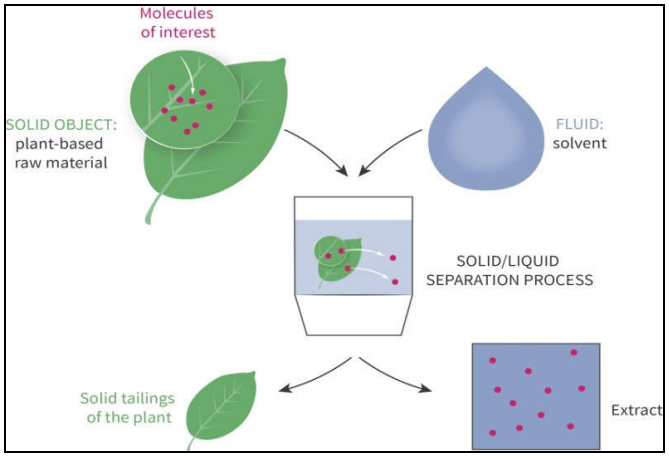

Figure 2. Extraction of herbal drugs

Filtration

Filtration**,** the process in which solid particles in a liquid or gaseous fluid are removed by the use of a filter medium that permits the fluid to pass through but retains the solid particles. Either the clarified fluid or the solid particles removed from the fluid may be the desired product. In some processes used in the production of phytochemicals, both the fluid filtrate and the solid filter cake are recovered. This technique entails the separation of the extract so obtained from the marc (exhausted plant material) by allowing it to trickle into a hold tank through the built-in false bottom of the extractor which is covered with a filter cloth.

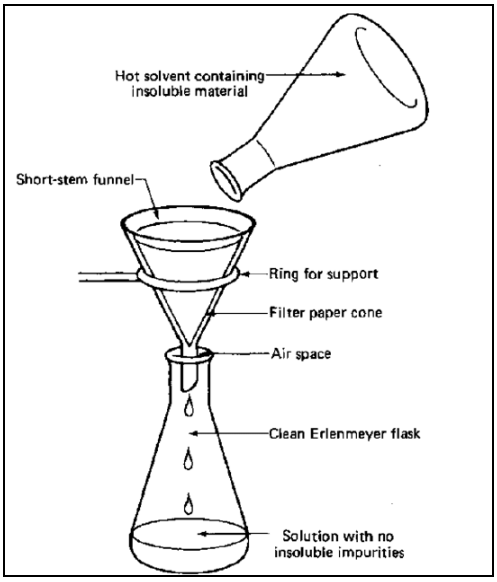

Figure 3. Filtration of herbal drugs

Concentration

The liquid extract so obtained is fed into a wiped film evaporator and concentration is carried out under vacuum to get concentrated extract.

Spray drying

The concentrated extract is subjected to a spray drier with the help of a high pressure pump at a controlled feed rate to get dry powder.

Distillation

This process is used for the preparation of oils of geranium, neroli, lavender, chamomile, lemon grass, etc. It is one of the oldest methods used to obtain oil from plants. It is essentially a heat process, the heat being used to drive the oil from the plant tissue. The plant or part of a plant being used must be in such a condition that steam and water will readily penetrate it. Garlic oil extracted by distillation in boiling water consists of dimethylsulfides, diallylsulfides, methyl allyl sulfides, and others, which have all been shown to process biological properties such as antioxidant effects. However, it lacks bactericidal and antithrombotic activity. It is known that the processing of garlic and onion into extracts, essence and dehydrated foods leads to the formation of products with significantly different physicochemical and biological characteristics 29. Essential oils as complex natural mixtures of volatile secondary metabolites can be isolated from plants by hydro or steam distillation (citrus peel oils).

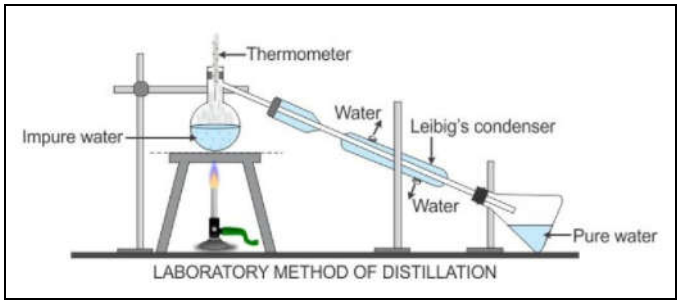

Figure 4. Distillation of herbal drugs

Expression

This is use for example in citrus oils. Expression means that the oils are expressed or pressed out of the peel of the almost ripe fruit, usually by using powerful hydraulic presses enclosed in a hollow cylinder, the walls of which are perforated like a sieve to allow the juice and oils to escape as the pressure is applied. The expressed liquid is of a milky appearance and is allowed to stand for several hours during which time the oil floats to the surface and can be separated and finally filtered. Essential oils which are complex natural mixtures of volatile secondary metabolites can also be isolated from plants by expression (citrus peel oils).

Standardization of herbal formulation

According to WHO standardization and quality control of herbals is the process involved in the physicochemical evaluation of crude drug covering aspects, such as selection and handling of crude material, safety, efficacy and stability assessment of finished product, documentation of safety and risk based on experience, provision of product information to consumer and product promotion. Standardization of herbal formulations is imperative in order to measure of satisfactory herbs, especially based on the amount of their lively principles, Physicochemical, phyto-chemical, standardization, and in-vitro, in-vivo research. The quality categorisation of herbal formulations is of predominant essentiality in order to confirm their acceptability in traditional system of medicine. One of the major problems faced by the herbal industry is the inconvenience of stiff quality control profiles for herbal formulations. In India, the department of Ayush, Government of India, launched a central scheme to develop a standard operating procedures for the manufacturing process to develop pharmacopoeial standards for Ayurveda medicines. The subject of herbal drug standardization is considerably broad and deep. World Health Organization (WHO) motivate, suggest and encourage traditional/herbal remedies in natural health care programmes because these medicines are easily available at low cost, safe and people have belief in them. WHO specific recommendations for assessments of the safety, efficacy and best of natural drug treatment as a prerequisite for global harmonisation are utmost importance. Hence, standardization is a most important aspect for establishing the quality and/or efficacy of Ayurvedic formulation or any other multiple ingredient herbal formulation [5].

Need of Standardization of Herbal drug

Modern system of medicine is based on sound experimental data, toxicity studies and human clinical studies. But, Pharmacopoeial standards on raw material / finished products are not available. cGMP for herbal industry are not well defined nor are the barest minimum standards of medicinal plant products maintained or regulated. The lack of quality standards has resulted in mild to serious adverse effects ranging from hepatic 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. Standardization 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 and rationalizing the combination in case of polyherbal drugs [6].

Conventional Methods For Standardization Of Crude Drug

Standardization of herbal raw drug includes passport data of raw plant drugs. It includes medico- botanical survey, identification, botanical authentification, macroscopic, examination. Testing of drugs as per approved Pharmacopoeial testing protocol- Fully pharmacognostical profile, Identification by various chromatographic techniques, Assessment of purity by physico-chemical profile, Assessment of strength by active marker or assay estimation and Safety by heavy metal profiling, microbiological limit test analysis, aflatoxins analysis, pesticides residue and biological activity19. Macroscopic identity of medicinal plant materials is based on sensory evaluation parameters like shape, size, colour, texture, odour and taste while microscopy involves comparative microscopic inspection of powdered herbal drug. Further, advances in microscope technology have increased the accuracy and capabilities of microscopy as a mean of herbal crude material identification due to the implication of light and scanning electron microscopes (SEM) in herbal drug standardization. The phytochemical evaluation for standardization purpose includes the following- Preliminary testing for the presence of different chemical groups, quantification of chemical groups of interest (e.g., total alkaloids, total phenolics, total triterpenic acids, total tannins), establishment of fingerprint profiles, multiple marker-based fingerprint profiles and quantification of important chemical constituents [7].

Organoleptic Evaluation

Organoleptic assessment method is the study of medicament using system. It refers to the techniques of analysis like physical, organoleptic and special features, such as: touch, texture, etc. evidently, the starting sight of the plant or plant extract is so specific that it tends to identify itself. If this is not sufficient, may be the plant or extract has a specific odour or taste. Organoleptic analysis constitute the effortless, yet the most human form of analysis. The fractured surfaces in cinchona, quillia, and cascara barks and quassia wood are important characteristics. Aromatic odor of umbelliferous fruits and sweet taste of liquorices are the examples of this type of evaluation where odor of drugs depends upon the type and quality of odorous principles (volatile oils) present [8].

Microscopical Evaluation

It involves detailed examination of the drugs and it can be used to identify the organized drugs by their known histological characters. It is mostly used for qualitative evaluation of organized crude drugs in entire and power forms with help of microscopic. Using microscope detecting various cellular tissues, trichomes, stomata, starch granules, calcium oxalate crystals and aleuronic grains are some of important parameters which play important role in identification of certain crude drugs standardization Starch and hemicelluloses is identified by blue color with iodine solution, All lignified tissues give pink strain with phloroglucinol and HCl etc. mucilage is stained pink with ruthenium red can be used to distinguish cellular structure. Microscopic evaluation also includes study

of constituents in the powdered drug by the use of chemical reagents. Quantitative aspects of microscopy includes study of stomata number and index, palisade ratio, vein-islet number, size of starch grains, length of fibres etc which plays a very important role in the identification of drug.

Chemical Evaluation

The chemical evaluation includes qualitative chemical tests, quantitative chemical tests, chemical assays, and instrumental analysis. The segregation, purification, and identification of active constituents are chemical methods of evaluation. Qualitative chemical tests include identification tests for various phytoconstituents like alkaloids, glycosides, tannins, etc. Most of drugs have definite chemical constituents to which their biological or pharmacological activity is attributed. Qualitative chemical test are used to identify certain drug or to test their purity.

- Evaluation test of resin, Acid value, sulphated ash
- Evaluation test of balsams: acid value, saponification value, bester values.
- Evaluation test of volatile oils : acetyl and ester values
- The qualitative chemical tests are useful in identification of chemical constituents and detection of adulteration.[9]

Chromatographic and Spectroscopic Analysis

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

Physical Evaluation

Physical methods are mostly used in crude plant evaluation for determination of the solubility, specific gravity, optical rotation, viscosity, refractive index, melting point, water content, degree of fibre elasticity, and other physical character of the crude material.

Biological Evaluation

The plant or extract can then be evaluated by various biological methods to determine pharmacological activity, potency, and toxicity. The biological evaluation would serve better than the physical and chemical evaluation for drugs that could not be satisfactorily assayed by these last two methods. Moreover, this is an important method, the crude drugs are considered important only because of their biological effects and this evaluation would conclude the effect These assays are conducted by determining the amount of drug of known potency required to produce a definite effect on suitable test animals or organs under standard conditions. Reference standard are used in certain bioassay procedures to minimize errors.

Who Guidelines For Quality Standardized Herbal Formulations [10]

1. Quality evaluation of crude drugs material, plant preparations and finished formulation.
2. Stability evaluation and shelf life study.
3. Safety evaluation; documentation of safety or toxicological studies.
4. Evaluation of efficacy by pharmacognostic information's and biological activity evaluations.

The herbal formulation must be standardized on the basis of active principles along with the chromatographic fingerprints (TLC, HPTLC, HPLC, and GC).

Potential hazardous contaminants and residues in herbal medicines Chemical contaminants

Toxic metals and non-metals: contamination of crude material with toxic substances such as arsenic can be attributed to many causes. These include environmental pollution, soil composition and fertilizers. This contamination of the raw material leads to contamination of the formulation during various stages during the manufacturing process. Radioactive Contaminants Dangerous contamination may be the consequence of a nuclear accident or may arise from other sources. WHO, in close collaboration with numerous other worldwide organisations, has developed guidelines for use in the event of worldwide contamination by means of radionuclides resulting from a primary nuclear accident. Example of such radionuclides include long-lived and short-lived fission products, actinides and activation products. In general the nature and the intensity of these Radionuclides.

Biological Contaminants

Microbiological contamination: Herbs and herbal material normally carry a large number of bacteria and moulds, often originating in soil or derived from manure. While a large range of bacteria and fungi form the naturally occurring microflora of medicinal plant. Aerobic spore forming bacteria frequently predominate. Current practice of harvesting, production, transportation and storage may cause additional contamination and microbial growth. Proliferation of microorganism may results from failure to control the moisture level of herbal medicines during the transportation and storage, as well as from failure to control the temperature of liquid forms and finished herbal products. Microbial contamination may also occur through handling of materials by personnel who are infected with pathogenic bacteria during harvest/ collection, post-harvest processing and the manufacturing process. This should be controlled by implementing best practice guideline such as GACP and GMP. Parasitic Contamination: parasites such as protozoa and nematode, and their ova, may be introduced during cultivation and may cause zoonosis, especially if uncomposted animal excreta are used. Contamination with parasites may also arise during processing and manufacturing if the personnel carrying out these processes have not taken appropriate personal hygiene measure.

Recent approaches in standardization fof herbal drug

Chromatographic Fingerprinting and Marker Compound Analysis: A chromatographic fingerprint of an Herbal Medicine (HM) is a chromatographic pattern of the extract of some common chemical components of pharmacologically active and or chemical characteristics. This chromatographic profile should be featured by the fundamental attributions of "integrity" and "fuzziness" or "sameness" and "differences" so as to chemically represent the HM investigated. It is suggested that with the help of chromatographic fingerprints obtained, the authentication and identification of herbal medicines can be accurately conducted(integrity) even if the amount and/or concentration of the chemically characteristic constituents are not exactly the same for different samples of this HM (hence,

"fuzziness") or, the chromatographic fingerprints could demonstrate both the" sameness" and "differences" between various samples successfully. Thus, we should globally consider multiple constituents in the HM extracts, and not individually consider only one and/or two marker components for evaluating the quality of the HM products. However, in any HM and its extract, there are hundreds of unknown components and many of them are in low amount. Moreover, there usually exists variability within the same herbal materials. Hence it is very important to obtain reliable chromatographic fingerprints that represent pharmacologically active and chemically characteristic components of the HM [11-14].

Supercritical fluid chromatography

In this method, compressed carbon dioxide (CO2) with small part of organic solvents (like methanol) are together used as the mobile phase, where major part is of carbon dioxide and minor is organic solvent; due to this ratio, the supercritical fluid chromatography (SFC) method is named as an alternative chromatography [15]. SFC method is an eco-friendly method as it utilizes very less quantity of organic solvents and the low viscosity of mobile phase as the pressure drop is less when compared with liquid chromatographic techniques. Lipid, flavonoid, phenolic, alkaloids, saponins, carbohydrates, and analysis of wide variety of analytes can be carried out with the SFC technique. The fat-soluble vitamin analysis is gaining more importance.SFC is also been noted as an unconventional method of sample preparation. It also finds application in large scale industries due to selective techniques and environment-friendly method [16].

Metabolomic Techniques

Metabolomics is a advanced emerging field of 'omics' research that is concerned with characterizing large numbers of metabolites using NMR, chromatography and mass spectrometry. It is commonly used in biomarker identification and the metabolic profiling of cells, tissues or organisms. The data processing challenges in this technique are quite unique and often require specialized (or expensive) data analysis software. Metabolomics has been used for identification of active phytoconstituents from herbal medicine. The greater potential of metabolomics has been reported in the development of active secondary metabolites from medicinal plants as novel or improved phytotherapeutic agents [17,18].

Chemometric Methods

Chemo metrics is a statistical approach to analyze instrument data, chemometrics often results in a faster and more precise Assessment of composition of a product or even physical or sensory properties. For example, composition (fat, fiber, moisture, carbohydrate) of dairy products or grain can be quickly measured using near infrared spectroscopy and chemometrics. Chemometrics can be used to speed methods development and make routine the use of statistical models for data analysis. Several chemometric approaches such as Computer Aided Similarity Evaluation (CASE) has been developed. All programs of chemometric algorithms for CASE are coded in METLAB5.3 based on windows. Data loading, removing, cutting, smoothing, compressing, background and retention time shift correction, normalization, peak identification and spectral matching, variation determination of common peaks/regions, similarity comparison, overly of sample classification and other data processes associated with the chromatographic fingerprint can be investigated with this software.

Differintial Pulse Polarography (DPP)

DPP can be used to study trace amounts of chemicals with very small detection limits on the order of 10-8 M. Some heavy metals, including lead, cadmium, zinc, copper and iron were successfully identified and determined by DPP. A DPP method has been for the determination of total hypericin in phytotherapeutic preparations in various buffer systems over the pH range 3.5–10.0[19].

X-Ray Powder Diffractrometry (XRD)

This technique is used to identify minerals, crystalline materials and metallic based herbal formulations. XRD analysis of metallic based Indian traditionally medicine Rassindoor indicated the presence of mercury sulphide which is represented by sharp peak. X-ray powder diffractometry data confirmed the formation of phospholipid complex with emodin, naringenin, quercetin, gallic acid [20].

Nuclear Magnetic Resonance

The combination of chromatographic separation technique with NMR spectroscopy is one of the most powerful and time saving method for the separation and structural elucidation of unknown compound and mixtures, especially for the structure elucidation of light and oxygen sensitive substances.

Thermal Analysis

Thermogravimetric analysis (TGA), differential thermal analysis (DTA) and differential scanning calorimetry (DSC) have been used to study different physical or chemical changes in various products including herbal drugs and also used to study preformulation or drug excipient compatibility. TGA may be operated under subambient conditions to analyse alcoholic content in various herbal formulations such as asavas and arista[21].TGA and DTA Analystical method are used to determine mercury based Indian traditional metallic herbal drug. It is also used in determination of metals present in Bhasma.

Conclusion

Herbals are traditionally considered harmless and increasingly being consumed by people as it has less side effects and comparable efficacy, better acceptability. Quality evaluation of herbal preparation is a fundamental requirement of industry and other organization dealing with ayurvedic and herbal products. The traditional approach towards standardization is insufficient for current herbal market and hence there is need for more advanced techniques for standardization. There are basically two techniques used for standardization these are chromatographic fingerprinting and DNA fingerprinting. The chromatographic fingerprinting is based on the chromatographic separation and identification of marker compound from other constituents. For quality approach of herbal drug formulation there is a great need of standardization by different reliable methods is stated in this current review study.

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