

SAFETY OF HERBAL MEDICINE: A REVIEW

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ABSTRACT

Traditional medicine is a broad term encompassing health practices, approaches, knowledge and beliefs which incorporate herbal, animal and mineral based medicines, spiritual therapies, manual techniques and exercises, applied singularly or in combination to treat, diagnose and prevent illnesses or maintain well-being. There has been a lot of interest, today, in the traditional medicine for its potential contribution to health care. However, there are a lot of concerns about the traditional medicine in areas of efficacy, safety and quality. The efficacy and safety of any pharmaceutical product is determined by the compounds (desired and undesired) which it contains. The purpose of quality control is to ensure that each dosage unit of the drug product delivers the same amount of active ingredients and is, as far as possible, free of impurities. It is very important that a system of standardization is established for every plant medicine in the market because the scope for variation in different batches of medicine is enormous. Many medicinal herbs and pharmaceutical drugs are therapeutic at one dose and toxic at another. Interactions between herbs and drugs may increase or decrease the pharmacological or toxicological effects of either component. Synergistic therapeutic effects may complicate the dosing of long-term medications. The variety of novel herbal formulations like polymeric nanoparticles, liposomes, nanoemulsions, microsphere, has been reported using bioactive and plant extracts.

Keywords: Herbal medicines, safety and efficacy, standardization.

INTRODUCTION

Natural medicines provide valuable resources to meet the requirements for global health care at affordable prices. Therefore, safety and efficacy need to be proven in a comparable manner to conventional drugs. Evidence-based natural and western medicine may merge to a "one-world medicine" for the sake of all patients in industrialized and developing countries. In the present review, we discuss strategies for preservation of traditional knowledge on natural medicines, sustainability of medicinal herbs and natural products, and standardization and quality control. The objective of this study was to examine the methods used in systematic reviews of safety across a range of complementary therapies to assess the variation in approach and the potential for developing guidance on conduct and reporting. Herbal medicine, or phytotherapy, is the science of using herbal remedies to treat the sick. It therefore covers everything from medicinal plants with powerful

actions, The term phytotherapy was introduced by the French physician Henri Leclerc (1870-1955). Herbal medicine has come a long way since the days of the ancient 'herbalism'. The study of the use of medicinal plants is now a scientific subject, a field of medicine in the same way as chemotherapy, hydrotherapy, electrotherapy and others. Knowledge of medicinal plants and their uses has been recorded from antiquity¹⁻².

IMPORTANCE OF HERBAL MEDICINE

The points of thought are why common people divert to use the Ayurvedic, Chinese and other herbal medicines? Though it is used all over the world, in India, its use is much more because of their easy accessibility, no expert consultation required, are considered safe to use and also because primary health care services fall short of peoples' need both in qualitative and quantitative terms. We should make all these easily marketed ayurvedic, and other herbal medicines FDA approved and increase public

awareness about pros and cons of their uses. The common belief that anything natural is safe is not correct. Herbal Medicines are readily available in the market from health food stores without prescriptions and are widely used in India, China, USA and all over the world. According to recent survey the majority of people who use herbal medicines do not inform their physicians about their consumptions that can cause abnormal test results and confusion in proper diagnosis. However, natural medicines seem to be barely able to provide convincing alternatives to conventional western medicine for global health-care². Some reasons are

1) The knowledge of shamans and traditional healers is getting lost, since their oral traditions being handed down from generation to generation for thousands of years seem to be extinguished in modern times.

2) The traditional use of medicinal plants needs to be systematically investigated and standardized. People outside the field of phytotherapy that phytotherapy is inactive, because infectious diseases would otherwise not kill many millions of patients each year, which is striking and embarrassing at the same time for scientists working on natural medicines.

3) The rainforests and other biological habitats are getting extinguished with a breath-taking velocity. Half of the rainforest worldwide has already been destroyed during the past three decades. This has irreversible impact on drug development

4) Overharvesting of medicinal plants from the wild presents a severe problem of preserving many plant species endangered to be extinguished.

5) Global climate change may affect both the growths of medicinal plants as well as their constituents.

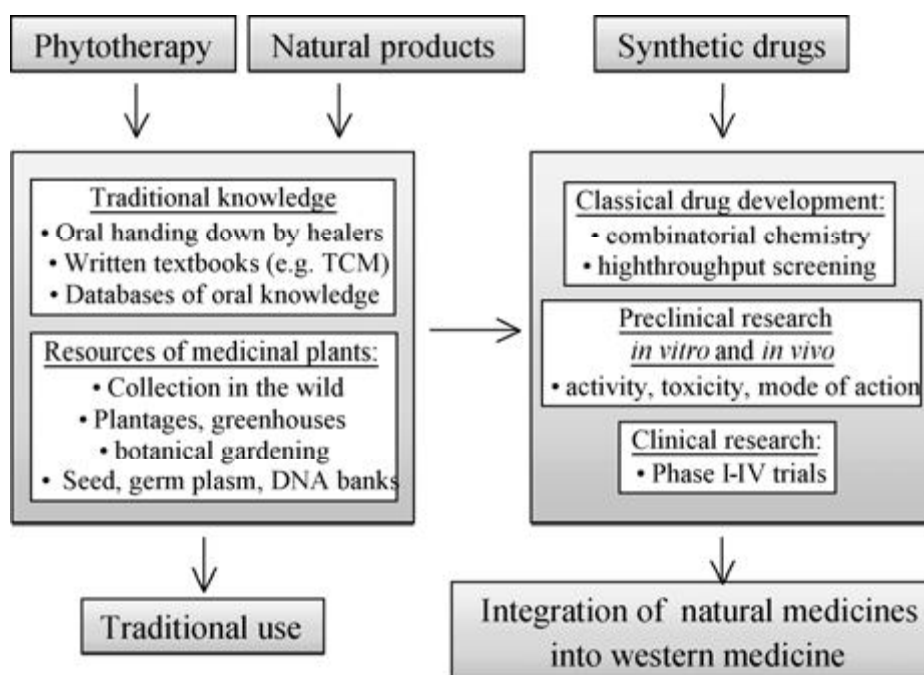


Fig. 1: Integration of natural medicines into western medicine

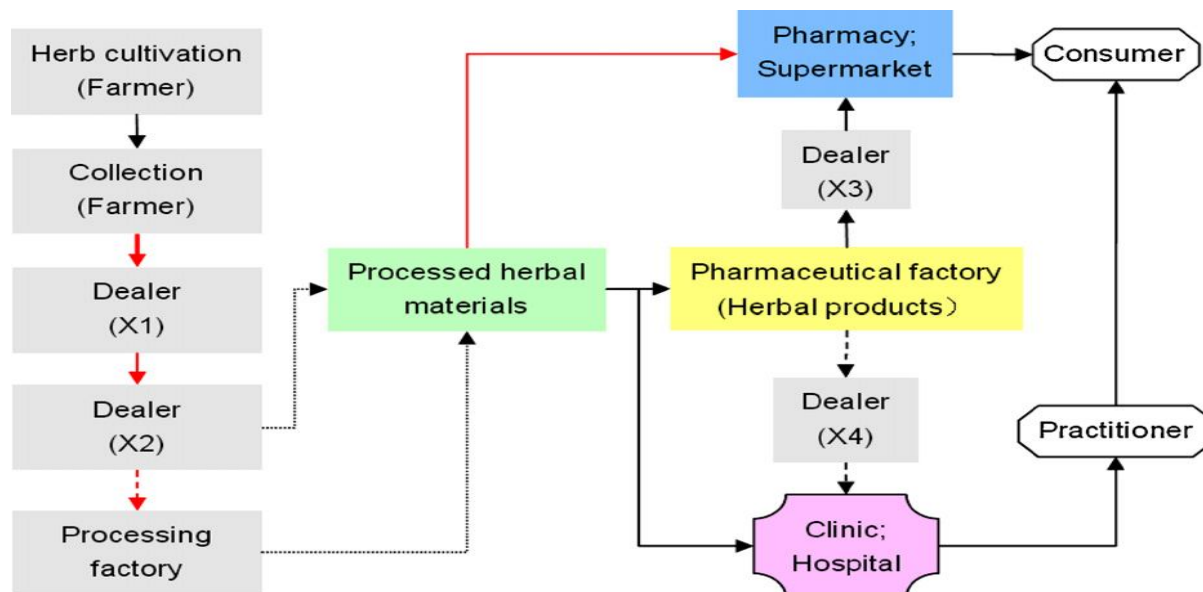


Fig. 2: Flow diagram of the traditional circulation of herbal medicines

TECHNIQUES IN EXTRACTION OF HERBALS

1. Supercritical fluid extraction (SFE)

Supercritical fluid extraction (SFE) is the most preferable process for the extraction of the bioactive chemical from the medicinal and aromatic plants. SFE has emerged as a highly promising technology for production of herbal medicines and nutraceuticals with high potency of active ingredients. SFE techniques have been found useful in isolating the desired phytoconstituents from the herbal extracts⁴.

2. Microwave-assisted extraction (MAE)

MAE technology includes the extraction of high-value compounds from natural sources including phytonutrients, nutraceutical and functional food ingredients and pharmaceutical actives from biomass. MAE finds utility in production of cost effective herbal extracts and helpful in extraction of carotenoids from single cells, taxanes from taxus biomass, essential fatty acids from microalgae and oilseeds, phytosterols from medicinal plants, polyphenols from green tea, and essential oils from various sources. Compared to conventional solvent extraction methods, Advantages of this technology include: (a) Improved product, -purity of crude extracts, stability

of marker compounds and use of minimal toxic solvents (b) Reduced processing costs, increased recovery and purity of marker compounds, very fast extraction rates, reduced energy and solvent usage.

3. Solid phase extraction (SPE)

SPE technique is applied for isolation of analytes from a liquid matrix and purified herbal extracts. This technique has many advantages such as: high recoveries of the analyte, concentration of analyte, highly purified extracts, ability to simultaneously extract analytes of wide polarity range, ease of automation, compatibility with instrumental analysis and reduction in organic solvent in comparison with more traditional sample preparation techniques. The solid-phase extraction was introduced for determining thirteen organochlorine pesticide residues including alpha-benzene hexachloride (BHC), betaBHC, gamma-BHC, delta-BHC, p,p'-dichloro-diphenyldichloroethylene (pp'-DDE), p,p'-dichloro-di-phenyldichloroethane (pp'-DDD), The organochlorine pesticides were extracted from herbs with mixed solvents of acetone and n-hexane by ultrasonic and cleaned up by Florisil solidphase extraction column. Solid phase extraction was used to prepare the test solution for

the analysis of aristolochic acid I and II in herbal medicines⁴.

Techniques in Herbal Drug Identification and Characterization

1. HPLC

Preparative and analytical HPLC are widely used in pharmaceutical industry for isolating and purification of herbal compounds. There are basically two types of preparative HPLC: low pressure HPLC (typically under 5 bar) and high pressure HPLC (pressure >20 bar). The important parameters to be considered are resolution, sensitivity and fast analysis time in analytical HPLC whereas both the degree of solute purity as well as the amount of compound that can be produced per unit time i.e. throughput or recovery in preparative HPLC. Vasicine, the major bioactive alkaloid of *Adhatoda vusica*, was estimated by HPLC in two polyherbal drug formulations - Shereeshadi Kashaya and Yastyadivati. Standardization of the Triphala (an antioxidant-rich herbal formulation) mixture of *Emblica officinalis*, *Terminalia chebula* and *T. belerica* in equal proportions has been reported by the HPLC method by using the RP18 column with an acidic mobile phase.

2. High performance thin layer chromatography (HPTLC)

TLC is the common fingerprint method for herbal analysis. Four species of herbal medicines were identified easily by TLC of the resins. With this technique, authentication of various species of *Ginseng* and *Radix Puerariae* is possible, as well as the evaluation of stability and consistency of their preparations from different manufactures. HPTLC fingerprint is mainly used to study the compounds with low or moderate polarities, but Di et al. established a fingerprint of fungal polysaccharide acid hydrolyzates by using automated multiple development. HPTLC technique is widely employed in pharmaceutical industry in process development, identification and detection of adulterants in herbal product and helps in identification of pesticide content, mycotoxins and in quality control of herbs and health foods. A Chandanasava known

to be effective in karsya (malnutrition) was standardised by organoleptic study, physico-chemical analysis, TLC and HPTLC⁶.

3. Liquid chromatography- mass spectroscopy (LCMS)

LC-MS has become method of choice in many stages of drug development. Chemical standardization of an aqueous extract of the mixture of the 20 herbs provided 20 chemical compounds serving as reference markers using LC-MS. Further, LC-MS analysis of aminoglycosides showed that these drugs are highly soluble in water, exhibited low plasma protein binding, and were more than 90% excreted through the kidney. Further this technique helps in analysis of aminoglycosides in plasma samples with ion pairing chromatography. Two HPLC methods, one combined with a photodiode array detector (LC/UV) and another with mass spectrometry (LC/MS), were reported for the analysis of aristolochic acid I and II in herbal medicines.

4. Gas chromatography (GC) and gas chromatography-mass spectroscopy (GC-MS)

GC-MS instruments have been used for identification of large number of components present in natural and biological systems. The identification and quantification of chemical constituents present in polyherbal oil formulation (Megni) consisting of nine ingredients, mainly *Myristica fragrans*, *Eucalyptus globulus*, *Gaultheria procumbens* and *Mentha piperita* was analyzed by GCMS method⁷.

5. Supercritical fluid chromatography (SFC)

SFC permits the separation and determination of a group of compounds that are not conveniently handled by either gas or liquid chromatography. SFC has been applied to a wide variety of materials including natural products, drugs, food and pesticide. SFC enables the resolution of unknown components and known markers such as azadirachtin A and B, salannin, and nimbin in neem seed extracts.

6. Capillary electrophoresis (CE)

Researchers evaluated the importance of CE for quality control of herbal medicinal products. Several CE studies dealing with herbal medicines have been reported and two kinds of medicinal compound i.e. alkaloids and flavonoids have been studied extensively. The methodology of CE was established to evaluate one herb drug in terms of specificity, sensitivity and precision, and the results were in agreement with those obtained by the HPLC method.

7. Thermal analysis of herbal drugs

Thermogravimetric analysis (TGA), differential thermal analysis (DTA) and differential scanning calorimetry (DSC) have been employed to study any 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 ethanol in herbal formulations such as asavas and arista. TGA and DTA analysis of mercury based Indian traditional metallic herbal drug Ras-sindoor indicated the presence of mercury sulphide based on a sharp peak at 354o C which corresponded to melting temperature of mercury sulphide.

8. X-ray powder diffractometry (X-RPD)

This technique is used to identify minerals, crystalline materials and metallic based herbal formulations. The tin based herbal drug Vanga Parpam was estimated by XRD and the intense sharp diffraction peaks clearly confirmed the presence of high crystallinity in Vanga Parpam. XRD analysis of metallic based Indian traditionally medicine Ras-sindoor 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.

9. Infrared spectroscopy

FTIR along with the statistical method principal component analysis (PCA) was applied to identify and discriminate herbal medicines for quality control in the fingerprint region 400-2000 cm^{-1} . The ratio

of the areas of any two marked characteristic peaks was found to be nearly consistent for the same plant from different regions, thereby, an additional discrimination method for herbal medicines. PCA clusters herbal medicines into different groups, clearly showing that IR method can adequately discriminate different herbal medicines using FTIR data. Near-infrared spectroscopy technique has been used for rapid determination of active components, species, geographic origin, special medicinal formula, on-line quality control, identification of counterfeit and discrimination of geographical origins of Chinese herbal medicines⁶⁻⁹.

CLASSIFICATION OF HERBAL MEDICINE

Based on their origin evolution and the forms of current usage-

Category 1: Indigenous herbal medicines

Historically used in a local community or region and is very well known through long usage by the local population in terms of its composition, treatment and dosage. Detailed information on this category of TM, which also includes folk medicines, may or may not be available.

Category 2: Herbal medicines in systems

Medicines in this category have been used for a long time and are documented with their special theories and concepts, and accepted by the countries. Ayurveda, Unani and Siddha.

Category 3: Modified herbal medicines

These are herbal medicines as described above in categories 1 and 2, except that they have been modified in some way—either shape, or form including dose, dosage form, mode of administration, herbal medicinal ingredients, methods of preparation and medical indications. They have to meet the national regulatory requirements of safety and efficacy of herbal medicines.

Category 4: Imported products with a herbal medicine base

This category covers all imported herbal medicines including raw materials and products. Imported herbal medicines must be registered and marketed in the countries of origin. The safety and efficacy data have to be submitted to the national authority of the importing country and need to meet the requirements of safety and efficacy of regulation of herbal medicines in the recipient country¹¹.

Requirement for Assessment Of Safety Of Herbal Medicine**1. Safety category**

A drug is defined as being safe if it causes no known or potential harm to users. There are three categories of safety that need to be considered, as these would dictate the nature of the safety requirements that would have to be ensured.

Category 1: safety established by use over long time

Category 2: safe under specific conditions of use (such herbal medicines should preferably be covered by well-established documentation)

Category 3: herbal medicines of uncertain safety (the safety data required for this class of drugs will be identical to that of any new substance).

2. Specific requirements for assessment of safety of four categories of herbal medicines

Category 1: Indigenous herbal medicines If the medicines in this category are introduced into the market or moved beyond the local community or region, their safety has to be reviewed by the established national drug control agency. If the medicines belong to safety category 1, safety data are not needed. If the medicines belong to safety category 2, they have to meet the usual requirements for safety of herbal medicines. Medicines belonging to safety category 3, i.e. 'herbal medicines of uncertain safety', will be identical to that of any new substance.

Category 2: Herbal medicines in systems The medicines in this category

have been used for a long time and have been officially documented. Review of the safety category is necessary. If the medicines are in safety categories 1 or 2, safety data would not be needed. If the medicines belong to safety category 3, they have to meet the requirements for safety of 'herbal medicines of uncertain safety'.

Category 3: Modified herbal medicines

The medicines have to meet the requirements of safety of herbal medicines or requirements for the safety of 'herbal medicines of uncertain safety', depending on the modification.

Category 4: Imported/exported products with a herbal medicine base

Exported products shall require safety data, which have to meet the requirements for safety of herbal medicines or requirements for safety of 'herbal medicines of uncertain safety', depending on the safety requirement of the importing/recipient countries¹⁰⁻¹³.

Regulatory Issue of Herbal Medicine

According to European Union definitions, herbal medicinal products (medicines) are "medicinal products containing as active ingredients exclusively plant material and/or vegetable drug preparations. 'Herbal drug technology includes all the steps that are involved in converting botanical materials into medicines, where standardization and quality control with proper integration of modern scientific techniques and traditional knowledge will remain important. All countries where medicinal plants and traditional medicines are used are aware of the need for regulating the use of these medicinal substances. There is a need for countries to regulate the use of medicinal plants because there is a growing interest in herbal medicines in the population of these countries¹⁵.

constituents of herbal medicinal product

It can be categorise into several groups which may be relevant for analytical and therapeutic purpose. From therapeutic point of view three group of constituents

are groups of interest active ingredient, active markers, negative markers and the fourth one is analytical (inactive) markers are of interest if no constituents of therapeutic relevance have been identified for special herbal drugs.

- 1) Constituent with known clinical activity (active principle)
- 2) Constituent with known pharmacological activity (active markers)

3) Constituent relevant for quality control (analytical markers)

4) Accompanying constituent like low amount of inorganic salts, sugars, amino acids (inert substances)

5) Constituent with potential negative impact (allergens, toxins)

6) Matrix substance usually not soluble (cellulose, lignins)

Herbal Medicinal Products Categorization Herbal drugs with known clinically active principles

Senna leaf	sennosides
Horse chestnut	seed aescins
Milk thistle fruit	silibinin
Kava rhizome kava	lactones
Aloe	aloin

Herbal drugs with known pharmacologically active markers

Hawthorn leaf with flower oligomeric	procyanidines
Ginkgo leaf flavone glycosides,	terpene lactones
Garlic bulb alliin,	Allicins
St. John's Wort herb hyperforin,	Hypericin
Asian ginseng	ginsenosides

Other herbal drugs with analytical markers

Valerian root	valerenic acids
Echinacea herb	caffeic acids
Siberian ginseng	lignan glycosides
Balm leaf	rosmarinic acid
Nettle root	scopoletin

Quality, Purity and Efficacy of Herbal Medicine

The efficacy and safety of any pharmaceutical product is determined by the compounds (desired and undesired) which it contains. The purpose of quality control is to ensure that each dosage unit of the drug product delivers the same amount of active ingredients and is, as far as possible, free of impurities. As herbal medicinal products are complex mixtures which originate from biological sources, great efforts are necessary to guarantee a constant and adequate quality. By carefully selecting the plant material and a standardized manufacturing process the pattern and concentration of constituents of herbal medicinal products should be kept as constant as possible as this is a prerequisite for reproducible therapeutic

results. With the increasing use of herbal products, particularly in the United States, the future worldwide labelling practice for herbal products should adequately address quality aspects.

According to the world health organisation WHO definition of the herbal medicine contain plant parts or plant material in the crude or processed state as active ingredient and may contain excipient. European medicines evaluation agency define herbal medicinal product that are containing exclusively herbal drugs. These are unprocessed state which are used for a medicinal or pharmaceutical purpose .herbal drug preparation are commutated powdered herbal drugs, extracted tinctures, fatty or essentials oils, extra juices, processed resins, gums so forth prepared from herbal drugs and

preparation whose production involve a fractionation , purification or concentration process. Based on EMEA and WHO quality guidance the herbal drugs or preparation in its entirety must be considered as the active ingredient. Therefore the great effort must be made to ensure quality, purity and efficacy for the herbal product¹⁴.

Drug Product Quality

As defined by the American pharmaceutical association and academy of pharmaceutical science (1968)-

1. The active ingredient labelled on the package should be contained in the respective tolerance range
2. The same amount of the active ingredient should be contain in each dose unit and each batch
3. The drug should be devoid of impurities
4. The drug should retain its active ingredient and efficacy until its usage
5. The drug shall release the active ingredient on the usage in such a way that they are bio available.

Parameters Affect Product Quality

A particular challenge in reviewing safety data on Herbal Medicinal Product (HMPs) is the quality of products suspected to be linked to ARs, or those used in experimental investigations. Causality assessment of ARs, as well as the results of research on the inherent toxicity of HMPs, can be confounded by quality issues. Purity of the HMP may be compromised by the presence of weeds, dirt, pesticides and pollutants such as PCBs, toxic metals, radioactivity, bacteria, moulds and mycotoxins, processing impurities and solvent residues. Identity issues such as species substitution, misidentification or adulteration may also occur. Issues related to HMP quality have been reviewed. The high quality of the finished product requires not only ingredients that meet pharmacopoeial standards but also depend on such factors as manufacturing, packaging, labelling, and importation activities that comply with current GMPs. The WHO has published guidelines on the quality of herbal medicines with reference to contaminants

and residues, on Good Manufacturing Practices for herbal medicines.

1. Heavy Metal Content

The reasons for the presence of metals in HMPs are varied. Plants may accumulate heavy metals from the environment during growth, heavy metals may be intentionally added to products within specific traditional health paradigms such as Ayurveda, and contamination may occur through inadequate quality control. Even though traditional preparation methods for the addition of metals to herbs are intended to render these metals non-toxic, poisonings related to metal exposure have been reported. Whatever the route by which heavy metals such as lead, cadmium and arsenic become present in HMPs, the levels of these metals can be extremely high and poisonings have occurred

2. Microbial Contamination

Microbial contamination can occur during the collection and the processing of ingredients or finished products. Some microbial species are common in the environment, while others can be introduced due to poor quality control or hygiene practices. Microbial contamination of HMPs including the health implications has been reviewed. The potential microbial contamination of herbs can be increased by the use of manures in agriculture, including those which may contain toxic strains of *Escherichia coli*. The drying of herbs shortly after harvest lessens the potential for the growth of microorganisms. Similarly, fungal attack of plants can introduce mycotoxins in HMPs.

3. Plant Identity

The correct identification of plant material during collection and processing is critical for the quality of HMPs. Several cases of incorrect plant substitution or mis-identification have been reported in the literature. A number of *Aristolochia* species have been used in herbal medicines throughout the world as anti-inflammatory agents for gout, arthritis, rheumatism and chronic inflammatory skin diseases. Use of *Aristolochia* species in herbal medicines is no longer permitted in

many countries due to their content of aristolochic acids which have been shown to be nephrotoxic, carcinogenic and mutagenic.

4. Adulteration

One of the greatest risks to human health related to HMPs arises from economically motivated adulteration. Such adulteration can occur through the addition of undeclared pharmaceutical drugs or, in illicit attempts to evade detection of adulteration, their analogues. Examples of HMP types commonly adulterated include sleep aids that have been adulterated with benzodiazepines such as estazolam or clonazepam weight loss products adulterated with sibutramine or fenfluramine, erectile dysfunction or sexual enhancement products adulterated with sildenafil, tadalafil, vardenafil, or their analogues, remedies for diabetes adulterated with glibenclamide, and body building products adulterated with androgenic steroids. Adulteration is always fraudulent and means "to make impure by adding extraneous, improper, or inferior ingredients". Instances of herbal medicines adulterated with orthodox drugs and plant materials have repeatedly been documented. Adulterations can be classified into three categories: addition of orthodox drugs to herbal medicines, substitution (use of fake or inferior plant materials), and addition of foreign materials (non-official herb parts, sands, metals). Adding substitutions and foreign materials to herbal drugs is usually aimed at maximizing profits by fraudulently increasing the weight or quantity of herbal materials. This usually occurs from the second to the fifth stage in the production process.

5. Pesticides

Pesticides include insecticides, fungicides, and herbicides. To some degree, residues of pesticides including their metabolites and/or degradation products will remain in plants, animals, or in the soil. Such residues have become a notable source of contamination for herbal medicines. The WHO and other organizations have established requirements to limit pesticide residues in herbal materials. Currently

parathyroid pesticides detected both in domestic and imported herbal materials, such as *Panax notoginseng* root, *Panax quinquefolium* root, and *Panax ginseng* root.

Standardisation of Herbal Medicine

A system to ensure that every packet of medicine that is being sold has the correct substances in the correct amount and will induce its therapeutic effect this is known as standardization. It is very important that a system of standardization is established for every plant medicine in the market because the scope for variation in different batches of medicine is enormous. Plant material may vary in its phytochemical content and therefore in its therapeutic effect according to different places of collection, with different times in a year for collection, with collection at the same time and places but in different years and with different environmental factors surrounding the cultivation of a particular medicinal plant. Adding to this variability is the fact that in herbal medicine several plants may be used together in the same preparation. This means that there should be a quality control test for the entire preparation to ensure quality of the product. World Health Organization (WHO) encourages, recommends and promotes traditional /herbal remedies in national health care programmes because these drugs are easily available at low cost, safe and people have faith in them. The WHO assembly in number of resolutions has emphasized the need to ensure quality control of medicinal plant products by using modern techniques and applying suitable standards¹¹.

Need of standardization

Substantial original documentation for the more organized systems of medicine still exists. Large expanses of local ethnic medicine, folklore, etc. Were passed on to the present generation only by word of mouth. Medical education was personalized to a small group of students or sometimes a single individual. Although several original codified texts like the Charak Samhita of exist with specific herbal formulas, the physicians down the

ages took liberty to modify these formulas according to prevailing local conditions or personalized them for individual patients. In course of time, though the name remained unchanged, the formula of the original preparation went through successive changes. This resulted in the same preparation having different compositions as well as different therapeutic indications. Thus any Traditional System of Medicine (TSM) is often crowded with duplication, confusing nomenclature of plants, accidental substitution of herbs, etc. due to these "transmission errors". There is no denying that the TSM that has been passed on to us from earlier generations is vastly different from the original works of the earliest authors⁷.

Strategies for Standardization and Quality Control

To establish international standards for natural medicines, the following measures are necessary:

- Correct identification of medicinal plants is of utmost importance since wrongly identified plants may contain poisonous ingredients.
- Standardization of production of Chinese herbal prescriptions by international quality guidelines such as Good Sourcing Practice (GSP) to guarantee authentication of medicinal plants, Good Agricultural Practice (GAP), Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), and Good Clinical Trial Practice (GCP).
- Processing procedures of herbal products have to be standardized.
- Chromatographic fingerprinting analysis can disclose the composition and concentration distribution of detectable ingredients.
- Quality control has not only the task to ensure proper composition of herbal prescriptions but also to avoid contamination with mycotoxins, pesticides, heavy metals, or other chemical toxins. Furthermore, faked herbal prescriptions with adulteration of drugs from western medicine, e.g., with glucocorticoids, have to be banned.

- Strengthening research on the physiological and pharmacological activity of herbal remedies.
- Basic pharmacological research to establish a scientific platform on the activity of medicinal products.
- Support from international collaborations of universities and pharmaceutical companies with scientists and clinicians worldwide.
- A seemingly striking contrast in the eyes of traditional healers is that traditional medicines have been applied for hundreds or thousands of years in patients. Therefore, it is not obvious why the activity of natural medicines should be first tested in cell lines *in vitro* or in mouse experiments *in vivo*. This apparent contradiction owes to the fact that western medicine first starts with preclinical research to elucidate the activity profile and the mode of action of novel compounds before a candidate drug enters clinical testing in patients

Steps Involved In Standardisation

Standardization of herbal drugs is not an easy task as numerous factors influence the bio efficacy and reproducible therapeutic effect. In order to obtain quality oriented herbal products, care should be taken right from the proper identification of plants, season and area of collection and their extraction and purification process and rationalizing the combination in case of polyherbal drugs.

The Standardization of crude drug materials includes the following steps-

Authentication

Each and every step has to be authenticated.

- a) Stage of collection.
- b) Parts of the plant collected.
- c) Regional status.
- d) Botanical identity like phytomorphology, microscopical and histological analysis (characteristic of cellwalls, cell contents, starch grains, calcium oxalate crystals, trichomes, fibers, vessels etc)

Various histological parameter studies are

- a) Leaf constant: - Palisade ratio, Vein islet number, Vein termination, Stomatal number and Stomatal index.
- b) Trichomes.
- c) Stomata.
- d) Quantitative microscopy.
- e) Taxonomical identity.
- f) Foreign matter.
- g) Organoleptic evaluation.
- h) Ash values and extractive values.
- i) Moisture content determination.
- j) Chromatographic and spectroscopic evaluation.
- k) Heavy metal determination.
- l) Pesticide residue.
- m) Microbial contamination.

The herbal formulation in general can be standardized schematically as to formulate the medicament using raw materials collected from different localities and a comparative chemical efficacy of different batches of formulation are to be observed. The preparations with better clinical efficacy are to be selected. After all the routine physical, chemical and pharmacological parameters are to be checked for all the batches to select the final finished product and to validate the whole manufacturing process¹⁶.

Stability Parameter

The stability parameters for the herbal formulations which include physical, chemical and microbiological parameters are as follow

1) Physical parameters include color, odour, appearance, clarity, viscosity, moisture content, pH, disintegration time, friability, hardness, flow ability, flocculation, sedimentation, settling rate and ash values.

2) Chemical parameters include limit tests, chemical tests, chemical assays etc. Chromatographic analysis of herbals can be done using TLC, HPLC, HPTLC, GC, UV, GC-MS and fluorimetry etc.

3) Microbiological parameters include total viable content, total mold count, total enterobacterial and their count. Limiters

can be utilized as a quantitative or semi quantitative tool to ascertain and control the amount of impurities like the reagents used during abstraction of various herbs, impurities coming directly from the manufacturing vessels and from the solvents etc.

Guidelines for Herbal Drug Standardisation 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. Reference 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. Reference to the pharmacological parameters, biological activity profiles, bitterness values, haemolytic 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.

Role Markers In Standardisation Of Herbal Drug

Scientifically validated and technologically standardized herbal medicines may be derived using a safe path of reverse pharmacology approach based on traditional knowledge database. This may play a vital role in drug discovery, development and therapeutics, in addition to dealing with a typical Western bias against Ayurveda. Correct identification and quality assurance of the starting

material is, therefore, an essential prerequisite to ensure reproducible quality of herbal medicine, which contributes to its safety and efficacy. Selection of chemical markers is crucial for the quality control of herbal medicines, including authentication of genuine species, harvesting the best quality raw materials, evaluation of post harvesting handling, assessment of intermediates and finished products, and detection of harmful or toxic ingredients. Chemical fingerprinting has been demonstrated to be a powerful technique for the quality control of herbal medicines. According to regulatory guidelines and pharmacopoeias macroscopic and microscopic evaluation and chemical profiling of the botanical materials is used for quality control and standardization⁸⁻⁹.

Markers are categorized in to two classes

(1) DNA markers are reliable for informative polymorphisms as the genetic composition is unique for each species and is not affected by age, physiological conditions as well as environmental factors. DNA can be extracted from fresh or dried organic tissue of the botanical material; hence the physical form of the sample for assessment does not restrict detection.

(2) Chemical markers generally refer to biochemical constituents, including primary and Secondary metabolites and other macromolecules such as nucleic acids.

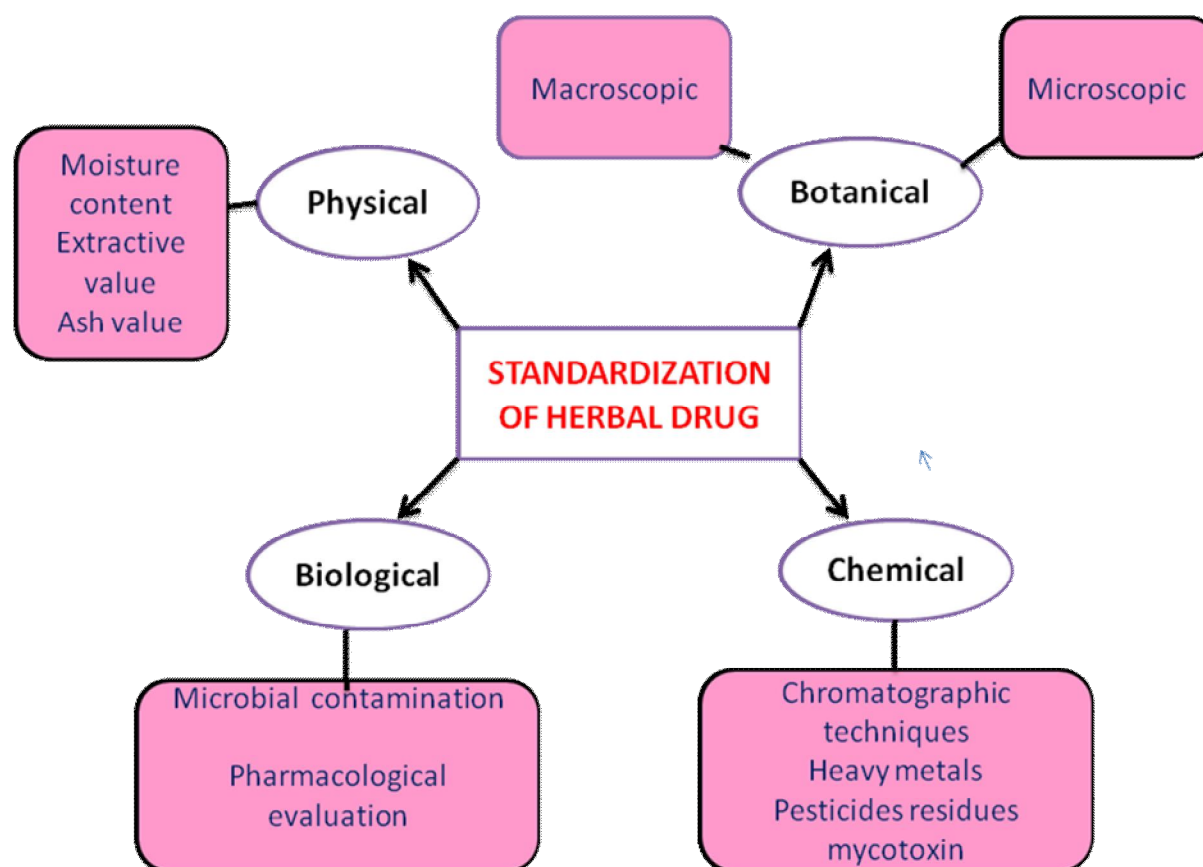


Fig. 3: Overview of standerdization methods of herbal medicine

LABELLING OF HERBAL MEDICINE

The primary source of information on herbal products is the product label. Currently, there is no organization or government body that certifies an herb or a supplement as being labeled correctly.

Certain information such as “the product has been manufactured according to Pharmacopoeia standards,” listing of active ingredients and amounts, directions such as serving quantity (dosage) and frequency of intake of the drug, must be

included on the labels of all herbal products and packages. The label should also indicate the method of extraction and relative amount of macerate and menstruum used, and possible side effects. In addition to the above information, the label should include the name and origin of the product, its intended use, net quantity of contents, other ingredients such as herbs and amino acids, and additives, for which no daily values have been established, storage conditions, shelf life or expiry date, warnings, disclaimer, and name and address of manufacturer, packer or distributor.

Validation of Herbal Product

The validation of herbal products is a major public health concern both in developed and resource-poor countries, where a fake businesses selling adulterated herbal medicines are common. In this regard, there is no control by the government agencies, despite the existence of certain guidelines in some individual countries and those outlined by the WHO. It is feasible that the introduction of scientific validation would control the production of impure or adulterated herbal products and would eventually ensure their rational use. This could also lead to the regulation of the industry so that only qualified physicians and health providers are allowed to prescribe the medication. Several of the principal pharmacopeias contain monographs outlining standards for herbal drugs. The major advantage of an official monograph published in a pharmacopeia is that standards are defined and available, and that the analytical procedures used are fully validated. 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, 1994–2001), the International Conference on Harmonization (ICH), and the US Food and Drug Administration (FDA) provide a framework for performing such validations. In general, 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. 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.

Impact of Novel Technologies

Modernization of traditional natural medicines implies the use of novel high-tech methods. Some recent technical developments are fascinating. It can be expected that they contribute to the progress of natural product and phytotherapy research in the years to come. Some of the exciting developments in this field will be discussed in this review.

Remote sensing and GPS/GIS to map medicinal plant locations

Remote sensing provides a new method to monitor all kinds of medicinal plant resources, e.g. wild or cultivated medicinal plants, rare or common species, as well as species in special ecological environments. As an example, modern high technologies of community ecology, statistics, 3S technologies (remote sensing RS, geographic information system GIS, global positioning system GPS) and computer information systems are being used in a national Chinese monitoring and protection system for Chinese medicinal resources.

Authentication of medicinal plants by barcode DNA

Standardization of medicinal herbs is sometimes challenged by misidentification of processed materials. The efficacies of therapeutic applications are critically dependent on the use of genuine materials. Methods for verification of medicinal herbs, based on variable sites of the rDNA internal transcribed spacer (ITS), represent a solution to this problem. DNA bar-coding provides a definitive means of authentication and for conducting molecular taxonomy studies.

Hollow fiber extraction

Hollow fiber solid-liquid phase microextraction (HF-SLPME) can be used

for the determination of natural products in medicinal plant samples. The procedure has some advantageous features, e.g. reduced risk of cross-contamination and carry-over problems due to disposable, single-use fibers. The method allows a very effective and enriched recuperation of an analyte into one single extract. The method shows good linearity, repeatability, low limits of detection and excellent enrichment.

Systems biology

Metabolomics now plays a considerable role in phytotherapy. Plants produce a huge array of chemicals, far more than are produced by most other organisms. Together with mRNA microarrays, metabolomic analyses, particularly transcriptome proteome coexpression network analyses represent a powerful tool box. This strategy can be used for the identification of genes involved in specific molecular pathways which determine the response of diseased cells and tissues to herbal preparations. The so-called “-omics” technologies are particularly valuable for the evidence-based development of new phytotherapeutics¹⁴.

Future Prospectuses

It is estimated that nearly three fourths of the herbal drugs used worldwide were discovered following leads from local medicine. According to WHO about 25% of modern medicines are descended from plants first used traditionally. Many others are synthetic analogues built on prototype compounds isolated from plants. Almost, 70% modern medicines in India are derived from natural products. The basic uses of plants in medicine will continue in the future, as a source of therapeutic agents, and as raw material base for the extraction of semi-synthetic chemical compounds such as cosmetics, perfumes and food industries. Popularity of healthcare plant-derived products has been traced to their increasing acceptance and use in the cosmetic industry as well as to increasing public costs in the daily maintenance of personal health and well being. Recently even developed countries,

are using medicinal systems that involve the use of herbal drugs and remedies. Undoubtedly the demand for plant-derived products has increased worldwide. The demand is estimated to grow in the years to come fuelled by the growth of sales of herbal supplements and remedies.

Herb-Drug Interaction

Many medicinal herbs and pharmaceutical drugs are therapeutic at one dose and toxic at another. Interactions between herbs and drugs may increase or decrease the pharmacological or toxicological effects of either component. Synergistic therapeutic effects may complicate the dosing of long-term medications—eg, herbs traditionally used to decrease glucose concentrations in diabetes¹ could theoretically precipitate hypoglycaemia if taken in combination with conventional drugs. Herbal medicines are ubiquitous: the dearth of reports of adverse events and interactions probably reflects a combination of under-reporting and the benign nature of most herbs used. Experimental data in the field of herb drug interactions are limited, case reports scarce, and case series rare. This lack of data is also true of drug drug interactions: published clinical studies are mainly case reports (controlled trials are scarce, since the random assignment of patients to trials that examine unintended effects is not ethical). Clinicians must ask patients about their use of herbs in a non-judgmental, relaxed way: a disapproving manner will ensure only that a patient will conceal further use. The patient should be treated as a partner in watching out for adverse reactions or interactions, and should be told about the lack of information on interactions and the need for open communication about the use of herbal remedies. Formulation, brand, dose, and reason for use of herbs should be documented on the patient's charts and updated regularly. Patients with clotting disorders, those awaiting surgery, or those on anticoagulant therapy should be warned against the concurrent use of ginkgo, danshen, dong quai, papaya, or garlic⁶.

Table 1: Intended Uses of Common Herbal Medicines

Herbal Medicine	Intended Uses
Ginseng	Tonic capable of invigorating users physically, mentally and sexually, also used for dealing with stress.
Ginkgo Biioba	Mainly to sharpen mental focus in other wise healthy adults and also in people with dementia; improvement of blood flow in the brain and peripheral circulation;
Garlic	To lower cholesterol levels and blood pressure; prevention of heart attack
Ginger	Prevention of motion sickness, morning sickness and Nausea

Table 2: Common Drug herb interactions

Herbal Product	Interacting Drug	Comments
Ginseng	Thenzelzine	Toxic symptoms e.g. headache insomnia and irritability
Ginkgo Biioba	Aspirin	Bleeding, can inhibit PAF
Garlic	Warfarin	Increased effectiveness of Warfarin; bleeding

Applications of Novel Drug Delivery System for Herbal Formulations

Over the past several years, great advances have been made on development of novel drug delivery systems (NDDS) for plant actives and extracts. The variety of novel herbal formulations like polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsions, microspheres, transfersomes, and ethosomes has been reported using bioactive and plant extracts. The novel formulations are reported to have remarkable advantages over conventional formulations of plant actives and extracts which include enhancement of solubility, bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery, and protection from physical and chemical degradation⁷.

(1) Liposome

The liposomes are spherical particles that encapsulate a fraction of the solvent, in which they freely diffuse (float) into their interior. They can have one, several or multiple concentric membranes. Liposomes are constructed of polar lipids which are characterized by having a lipophilic and hydrophilic group on the same molecules Milk thistle (*Silybum marianum*) is one of the few herbal drugs whose excellent pharmacological profile

readily lends itself to proof of clinical efficacy.

(2) Nanoparticles

Nanoparticles and nanoemulsions are colloidal systems with particles varying in size from 10 nm to 1000 nm. The nanospheres have a matrix type structure in which the active ingredient is dispersed throughout (the particles), whereas the nanocapsules have a polymeric membrane and an active ingredient core. Nanonization possesses many advantages, such as increasing compound solubility, reducing medicinal doses, and improving the absorbency of herbal medicines compared with the respective crude drugs preparations.

(3) Emulsions

Emulsion refers to a non-homogeneous dispersion system that is composed of two kinds of liquids unable to dissolve each other, and one of which disperses in the other one in a form of droplets. Generally, emulsion is composed of oil phase, water phase, surfactant and sub-surfactant. Its appearance is translucent to transparent liquid. Apart from its targeted sustained release, producing the herbal drug into emulsion will also strengthen the stability of the hydrolyzed materials, improve the penetrability of drugs to the skin and mucous, and reduce the drugs' stimulus to tissues. So far, some kinds of herbal drugs, such as camptothecin, *Brucea javanica* oil,

coixenolide oil and zedoary oil have been made into emulsion.

(4) Microspheres

Administration of medication via micro particulate systems is advantageous because microspheres can be ingested or injected and; they can be tailored for

desired release profiles and used site-specific delivery of drugs and in some cases can even provide organ-targeted release. So far, a series of plant active ingredients, such as rutin, camptothecin, zedoary oil, tetrandrine, quercetine and *Cynara scolymus* extract has been made into microspheres.

Table 3: Examples of Herbal Formulations

Type Of Formulations	Examples
Liposome	Quercetin liposomes, Paclitaxel liposome
Nanoparticles	Radix salvia miltiorrhiza nanoparticles, Berberine-loaded Nanoparticle
Emulsions	Docetaxel submicron Emulsion, Triptolide microemulsion
Microspheres:	Zedoary oil Microsphere, Rutin-alginate-Chitosan microcapsules

CONCLUSION

This review is an attempt to study the need of herbals in today's medication practice by considering with the classification of herbals, extraction and standardization methods, its quality, safety and efficacy of herbal product. It also gives us its wide future scope in NDDS and herbal drug interaction.

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