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APPROACHES TOWARDS STANDARDIZATION AND QUALITY ASSESSMENT OF HERBALS

S.S.SHUKLA,[1] SWARNLATA SARAF[2] AND S.SARAF[3]

Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur - 492010 C.G. (India)

Abstract: Nature always stands as golden marks to exemplify the outstanding phenomena of symbiosis. In the western world, people are becoming aware of the potency and side effect of synthetic drugs. There is an increasing interest in the natural remedies with a basic approach towards the nature. In India great deals of in depth knowledge exist among general public about the traditional use of herbal medicine. This is in addition to organized Indian system of medicine - Ayurveda. Which has already gained world wide attention. To ensure the safety and efficacy of herbal medicines; standardization and development of quality protocols for herbal medicines is extremely important. For the identification of medicinal plants and their constituents, WHO guidelines suggest the fingerprinting methods to meet the global standards of quality control of the herbal formulations. These new techniques and methods allow scientific study of the plant material and can guarantee global standards of the herbal products for national and international marketing and therapeutic use.

Keywords: Medicinal plants, Standardization, Quality control, Analytical technique.

Introduction

Medicinal plants and herbal medicines are enjoying their acceptance since the origin of mankind. They are time tested. Hindu saints and Vaidyas had their own parameters for testing the formulations. Since last few decades substitution/ adulteration is being done during manufacturing of some formulations. The substitution/ adulteration reveal itself that the "original medicinal plant / part" is replaced by spurious substance of same size and shape through it contains the cheaper variety of drug content. This results in cheating the consumers. In ancient time, every formulation had its own testing procedure.

For example, Ayurveda literature reveals that its own testing procedure for Banslochan (used in formulation called Sitopaladi churan), Banslochan is not easily fragile by hands and after washing with water it convert into transparent material.But in today's manufacturing such test procedure of ancient classics are not totally followed by most of the formularies.

Some Ayurvedic physicians and industry have developed their own procedure, mingle with old procedures to make a hybrid procedure for testing of their products that's why spurious raw material with low therapeutic importance is being mixed in some formulations. Hence, forth WHO and different regulatory bodies came into effect to solve problems associated with herbal formulations so that the consumers should not be cheated by the gray products. WHO have taken some steps to control these kind of adulteration. WHO has have adopted and generated some general methods for standardization and quality control of herbal products. At the same time WHO directed member countries to make their guidelines regarding the standardization of herbals. WHO have also suggested some recent techniques, instruments and parameters for the purpose of standardization and development of any herbal formulations. For the identification of plants and its constituents guidelines suggest the fingerprinting methods.

The herbal medicines are gaining popularity and acceptance in the developed countries due to the failure of the allopathic system of medicine in various chronic ailments. The adverse effects of chemical drugs are the another failure of allopathic system. Herbal formulations are well accepted in the world but they need standardization and quality control profiles to meet global standards. But due to complex nature and inherent variability of the

1. Research Scholar 2. Reader 3. Professor and Director

constituents of plant based drugs, it is difficult to establish the quality control parameters of herbal formulations.[1]

Herbal formulations show the number of problems when quality control aspect is considered. This is because of nature of the herbal ingredients and different secondary metabolites present therein. It is also due to variation in the chemical profile of the herbal due to intrinsic and extrinsic factors (growing, harvesting, storage and drying processes).[2,3,4]

There are two main important reasons for interest of development of standardization and quality aspect of the herbal products.

Firstly, the use of medicinal plants, as such as phyto-medicines, dietary supplements, food and beverage ingredients and traditional medicines.

Secondary, natural product continues remain as important source of new drug discovery. Quality is the sum of variable characteristics that significantly impact upon a product. For herbal medicines, such variable characteristics include the origin of the herb, botanical identity, purity, potency, stability and content of the marker compounds. Apart from these, good agriculture practices (GAP) and good manufacturing practices (GMP) are also important and directly assess the quality of the herbal products.[5, 6]

The task force appointed by the planning commission in June 1999, after studying the export market, suggested targets of Rs 3000 crores for 2005 and Rs 10,000 crores by 2050 for export of plant based herbal products. This is a challenging task.

To meet this challenge, standardization and quality assessment of herbal products as per international norms will be inevitable. Standardization of natural products is a complex task due to their heterogeneous composition, which is in the form of whole plant. To ensure reproducible quality of herbal products, proper control of starting material is utmost essential. The first step towards ensuring quality of starting material is authentication.[7]

Authentication of plant material

Majority of the crude drugs come from wild sources and it is collected by poor, illiterate tribal without any attention to botanical identification and authentications. At present very few official standards are available for herbal preparations. Manufactures have fixed their own parameters to identify the presences of all the ingredients as claimed in a formulation. Hence the first important task is to evolve such quality assessment parameter or quality parameter by which the presence of the entire ingredient can be identified. Various chromatographic and spectroscopic methods can be used for identification of different ingredient or phyto-constituents.[8]

Phyto-chemical variation

India has rich agro-climatic culture and ethnic biodiversity. There are many intrinsic factors, which govern the growth and medicinal quality of herbs. This is due to change in environmental factor which often leads to change in their bioactivity. Due to these inherent uncontrolable variations, standardization and QC becomes extremely important. Change in seasons, geographical variation, time of harvesting and age of plants, genetic factor (ploidy and variety), edaphic factors (soil pH, soil composition, macro and micro nutrients etc)[7] are also to be kept in view. Development of ASU drugs with proper efficacy has been undertaken by Department of AYUSH, ICMR and CSIR through Golden Triangle Programme utilizing traditional knowledge, latest safety, chemo-profiling and reverse pharmacology to arrive at standardized formulation with IPR, for placing at global market.[9]

Need of standardization [10 - 13]

1. Reproducible assays of the plant preparation generate confidence in the mind of the user and prescriber.
2. To ensure consistent quality of the preparation, the qualitative and quantitative chromatographic fingerprint on the basis of characteristic substance(s) for raw materials and finished products should be provided.
3. It is not just an analytical operation that ends with the identification and assay of an active principle and controls that are necessary to guarantee consistency of composition. The question of quality acquires greater relevance today than ever before.
4. Regulatory agencies and consumer groups on one hand and increasingly stringent quality norms for global positioning of the products on the other hand, demand that new materials and herbal

products there from, used for medicinal, nutritional and cosmetic purposes should be of consistent reproducibility; scientifically validated and supplemented by data on documented evidence of efficacy and safety.

5. Rapid advancement in the field of instrumentation where LOD and limits LOQ have routinely been upgraded to femto and atto levels, the chemical standardization of herbal products by hyphenated techniques (HPTLC, HPLC, LC/MS and LC/MS, GC/MS) has become more credible than biological evaluation of data.

6. The techniques are very useful for the characterization and quantification of the individual constituents in the plant extracts. LC/MS and GC/MS based multi component hyphenated methods allow the determination of the components in the mixture.

7. These techniques are sensitive, selective, fast with inexpensive clean up for sample preparation; where simultaneous separation as well as identification of the components in a mixture is possible. LC/GC performs the function of separation whereas MS performs the function of identification of the components in the mixture on the basis of molecular mass and fragmentation pattern. It gives us two dimensional information, the information from the UV/VIS or diode array detector in LC and FID/ECD/NPD detectors in GC is the first dimensional information in the form of retention time whereas the second dimension of information comes from the mass detector in the form of molecular mass and fragmentation pattern.

8. Techniques are very sensitive, selective and specific and allow the detection of the compounds even in picogram amounts. LC/MS has been playing a more significant role in plant medicine research.

9. This technique is capable of characterizing active components ranging from small molecules to macromolecules and recent scientific results and publications show that application of LC/MS has been rapidly expanding into the area of structure elucidation and characterization of active components, in addition to valuable quantitative analysis.

10. LC/MS methods are very useful in determining active components and their metabolites in pre-clinical studies. Studies on the metabolites of piperine, an alkaloid constituent of *Piper nigrum* and *Piper longum* led to the characterization of two metabolites in rat urine. These metabolites were characterized on the basis of LC/MS/MS and LC/NMR/MS/MS data.

Standardized Products

There is no harmonized definition of standardization. Standardized product ensures the batch to batch consistency of the finished product. This document assumes the definition of standardization used by NHPD. In some cases, standardization involves identifying specific chemicals (also known as markers) that can be used to manufacture a consistent product. The standardization process can also provide a measure of quality control of the product.[14]

Standardized Extracts

Standardized extract refers to product with a specifie minimum level or a specified range of one or more of biochemical constituents or marker compounds, while maintaining the total characterisics of a product containing plant material, algae, bacteria, fungi, or non-human animal material. It is achieved by characterizing and quantifying one or more biomarkers of either known pharmacological activity (medicinal or active compound) or unknown pharmacological activity. Biomarkers are classified as follows:

1. Active constituent: A known and acceptable therapeutically active biochemical component. This specific biochemical constituent can be adjusted by standardization to a level that is reproducible - either that naturally found in the plant or more concentrated in an extract.

2. Marker compound: When the active biochemical component is not known. The specified marker compound, which is characteristic of the natural health product, but does not contribute to therapeutic activity, is adjusted to serve an analytical purpose.

Marker compounds can be used to control batch-to-batch consistency of the finished product. It provides approach for standardization to manufacture the product to ensure that each batch contains the same amount of the marker component.

It is assumed that other chemical constituents in a given product will vary in proportion to the marker compound; if each batch contains the same standardized amount of marker, the content of other constituents will also be relatively consistent. Standardization of marker content can also be achieved by blending different batches of raw materials to achieve the target marker content.

According to the American Herbal Products Association (AHPA) guidelines, this is an excellent method for obtaining consistency. Some methods for identifying and quantifying selected marker or active constituents are available in, among other sources, the american herbal pharmacopoeia and therapeutic compendium or in the scientific literature. When no method exists for the specific product, or when improved technology allows for a more accurate and precise method, an alternative method may be used as long as it is validated according to Organization for Economic Co-operation and Development (OECD's), principles of good laboratory practices (GLP), International conference on Harmonization's (ICH) guidelines on validation of analytical procedures are submitted to AOAC international for validation.

Many manufacturers employ various production processes to manufacture health products containing extracts with target marker content, either by adjusting the extraction ratio and/ or adding fillers to achieve the targeted marker content. This practice may be appropriate in cases where it has been established that the marker is responsible for the pharmacological activity. The process of standardization as applied to products containing complex materials will facilitate consistency in quality of finished products in terms of quantity and potency. Presently, there are no universally accepted standards for the manufacturing of standardized extracts, however several monographs have been published and it is recommended that the analytical methods described in these monographs be used when available. Specifications for standardized products should include identity (e.g., chemo profile, multiple fingerprints), potency and strength (quantity), purity (incidental compounds/contaminants).

Manufacturing processes should be designed to ensure consistency, which requires control on both raw materials quality and manufacturing processes. Standardization does have advantages as indicated below; ensuring consistency confirmation of the correct content of extract/dosage unit positive control to indicate possible loss or degradation during manufacturing or shelf-life.[15,16]

Non-Standardized Extract

A non-standardized extract is made by soaking the plant, plant material, alga, bacterium, fungus, and non-human animal material in a liquid that removes specific compounds. The liquid can be used as is, or evaporated to make a dry non-standardized extract.

Herbal materials standardization

Standardization refers to measures taken to ensure that there is a consistent quantity of a defined marker compound within a herbal material. In order to achieve reproducible biological data in terms of safety and efficacy, it is recommended that the herbal material be standardized to the active ingredients when they are known or to specific markers when the actives are not yet known. Standardization is commonly achieved through blending different batches of the plant material. The assumption is that the content of the other constituents will also vary in proportion to the marker compound, and that if each batch contains the same amount of marker compound, other constituents will also be relatively consistent.[5, 17]

Certain authorities consider this method similar to adulteration, particularly if this is not declared on the product label and consequently this method of standardization is not encouraged.[4] It is difficult to quantify the market size of the traditional Indian system. Since most practitioners formulate and dispense their own recipes. The present annual turnover of product manufactured by large companies is estimated at approximately US $ 300 million compared to a turnover of approximately US $ 2.5 billions for modern drugs. According to the study on the attitude of allopathic medicine practitioners are relatively unfamiliar with Ayurvedic product even though some are practiced. They are willing to try an Ayurvedic product if its efficiency is scientifically proven and would try in ailments such as cough, cold, diarrhea, stomach problem, reproductive disease, liver & skin disease.[4]

Assessment of quality of herbal materials

Monographs exist for some of the commonly used and popular herbal medicines and the Indian Pharmacopoeia contains some monographs to which the respective herbs must comply. However where monographs are not available, quality assessment is usually based on the results of test procedures performed on the plant material itself. Such tests include analysis of the starting material, tests on microbial quality or contaminants such as pesticides and fumigation agents. Quantitative determination of marker compounds with known activity is also assessed as a quality criterion.[5]

Assessment of quality of herbal starting materials

An assessment of the quality of the starting material and excipients is required. Firstly, information on the site of collection, time of harvesting, stage of growth, drying and storage conditions should be documented and in the case of herbal drugs with constituents with known activity, assays of their content using validated methods are required. This content must be stated as a range in order to ensure reproducibility. Where the constituents are not known, suitable marker compounds may be selected and used. Generally, herbal materials must be tested for microbial contamination, pesticides and fumigation agents, toxic metals and other likely contaminants and adulterants. Acceptance criteria and limits exist but are diverse and appear to be lack of harmony on these (WHO, 1998). For instance, the limits for some pesticides published in the pharmacopoeia 1993 are more restrictive than the WHO limits. In addition, the limits specified for microbial contamination in the European Pharmacopoeia 2002 are more restrictive than the WHO 1998 limits.[18, 19]

Assessment of quality of herbal preparations

Guidelines require that the particulars of the characteristics, identification tests and purity tests for the product be established. These may include details of tests on the performance of the dosage form such as dissolution or infusion. Chemical fingerprints can be used to trace the stability of the herbal preparation. Since the whole herbal drug or preparation may be considered to be the active, a determination of the stability of a single marker compound may not be adequate; an analysis of the whole herbal material may be more appropriate. **Heigl and Franz**,[20] examined possible changes in the flavonoid pattern of common herbal drugs during long term and stress testing storage conditions used HPLC fingerprint comparisons to demonstrate differences in stability of individual flavonoid components. Such comparisons may allow determinations of substances present in the herbal preparations with respect to their stability and proportions, for quality purposes.[21]

Parameters for standardization of crude drug/ herbal medicines (As per WHO)

The following parameters are used for crude drugs/herbal medicines;[16]

1. Authentication (Stage of collection, parts collected, botanical identity like phytomorphology, microscopical and taxonomical identity, etc.)
2. Foreign matter
3. Organoleptic evaluation
4. Tissues of diagnostic importance present in the drug powder.
5. Ash values and extractive values.
6. Volatile matter
7. Moisture content determination
8. Chromatographic and spectroscopic evaluation. TLC, HPTLC, HPLC methods will provide qualitative and semi quantitative information about the main active constituents present in the crude drug as chemical markers in the TLC fingerprint evaluation of herbals (FEH).
9. Determination of heavy metals – e.g. cadmium, lead, arsenic, etc. **(Table 1).**
10. Pesticide residue – WHO and FAO set limits of pesticides, which are usually present in the herbs. Mainly pesticides like DDT, BHC, toxaphene, aldrin cause serious side-effects in human beings if the crude drugs are mixed with these agents **(Table 2).**
11. Microbial contamination – usually medicinal plants containing bacteria and molds are coming from soil and atmosphere. Analysis of the limits of *E. coli* and molds clearly throws light towards the harvesting and production practices. The substance known as afflatoxins will produce serious side-effects if consumed along with the crude drugs (**Table 3).**
12. Radioactive contamination – Microbial growth in herbals are usually avoided by irradiation.

Table 1. Limits for heavy/toxic metals

Sr. No.	Heavy/ Toxic Metals	As per WHO / FDA (Permissible limit)
1	Lead	10.0 ppm
2	Cadmium	0.30 ppm
3	Mercury	1.00 ppm
4	Arsenic	10.0 ppm

This process may sterilize the plant material but the radioactivity hazard should be taken into account. The radioactivity of the plant samples should be checked accordingly to the guidelines of International Atomic Energy (IAE) in Vienna and that of WHO.

Table 2. Limits for Pesticides residues

Sr. No.	Name of Pesticides/Insecticides	Limit as per FDA/ EP
1	Quinolphos	0.01 ppm
2	DDE	1.00 ppm
3	Alderin	0.05 ppm
4	Dieldrin	0.05 ppm
5	DDT	1.00 ppm
6	DDD	1.00 ppm
7	HCH (Hexa chlorocyclohexane)	0.30 ppm
8	Malathion	0.10 ppm
9	Parathion	0.30 ppm

Future of plant based medicines : Can India be a leader in the international market?

India exhibits remarkable outlook in modern medicines that are based on natural products besides traditional system of medicines. Almost, 70% modern medicines in India are derived from natural products. Medicinal plants play a central role not only as traditional medicines but also as trade commodities, meeting the demand of distant markets.

Ironically, India has a very small share (1.6%) of this ever-growing global market. To compete with the growing market, there is urgency to expeditiously utilize and scientifically validate more medicinal plants while conserving these species, which seems a difficult task ahead.

It is estimated that nearly three fourth of the plant-derived prescription drugs used worldwide were discovered following leads from local medicine. About 25% of modern medicines have descended from plants first used traditionally according to WHO. Many others are synthetic analogues built on prototype compounds isolated from plants.

Table 3. Permissible Limits of Microbial load and pathogens

Sr. No.	Microbial Load	Permissible Limit as per WHO		
		For contamination in the crude plant materials	For plant materials that have been pretreated (used as topical doses form)	For other plant materials for internal use
1	Total Viable Aerobic Count	-	$<10^7$cfu/g	$<10^5$cfu/g
2	*E.coli*	10^4/g	10^2/g	10/g
3	Total Yeast & mould count	10^5/g	10^4/g	10^3/g
4	Total enterobacteriaceae	-	10^4/g	10^3/g
5	*Salmonellae spp.*	-	none	none
6	*S.aureus*	absent	absent	absent
7	*Pseudomonas aeruginosa*	absent	absent	absent
8	*Coliforms*	absent	absent	absent
9	Afflatoxins	absent	absent	absent

* cfu/g = colony forming unit per grams Afflatoxins should be completely removed or should not be present.

Almost, 70% modern medicines in India are derived from natural products.[22]

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. In the dual role as a source of healthcare and income, medicinal plants make an important contribution to the larger development process. Though the efficacy of herbals requires development of quality consciousness in respect of the evaluation related evidences, supplying the demand for botanicals and herbals is a booming business. 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 according to several surveys. This means that scientists, doctors and pharmaceutical companies will be looking at countries like China, India, etc. for their requirements of medicinal plants. India needs a clear policy for such integration without compromise on the strategies that are science-based. Efforts are needed to establish and validate pharmaco-epidemiological evidence regarding safety and practice of plant based medicines.[23]

Conclusion

Standardization is a urgent need of the modern era for the purpose of safety and quality assurance measures so as to ensure supply of medicinal plant materials of good quality. However, irrespective of whether the plant is being used by the industry or by the rural community standardization of plant material is required. The decision on whether to collect plants from the wild or to cultivate it would depend on the feasibility of the approach for that particular species. After proper crude drug identification, WHO guidelines should be followed for collecting plant material in terms of proper season and climatic conditions, correct plant part, practices that are non-destructive and would prevent contamination from soil, toxic weeds or microbes. Post collection, appropriate processing and storage conditions are required to reduce drying time, detoxification to reduce side effects and to enhance therapeutic value of the plant material and to improve its shelf life.

Phytochemical standardization for identification of the plant material can be carried out by obtaining chemical fingerprint through chromatographic techniques in terms of a known marker compound or through bioassay guided fractionation or DNA fingerprinting techniques. Chromatographic and spectroscopic techniques proved its usefulness in isolation and proper identification of active constituents in the plant extracts. Biological screening plays a vital role in generating important efficacy and safety data to validate the claimed therapeutic potential of the plant before clinical trials are carried out. Hence, standardization involves the quality control of various factors affecting the therapeutic activity of a plant right from selection of the plant species to the formulation of the herbal drug so that it minimized batch-to-batch variation and meets standards of quality, safety, and efficacy.

S.No	Terms	Abbreviations
1.	ASU	Ayurveda, Siddha and Unani
2	CSIR	Council for Scientific and Industrial Research
3	DDD	Di-chloro-di-phenyl-di-chloro-ethane
4	DDE	Di-chloro-di-phenyl-di-chloro-ethylene
5	DDT	Dichloro-Diphenyl-Trichloroethane
6	FDA	Food drug administration
7	FAO	Food and Agricultural Organization
8	FID	Flame ionization Detector
9	GAP	Good agriculture practices
10	GC/MS	Gas chromatography/ Mass spectroscopy
11	GLP	Good laboratory practices
12	GMP	Good manufacturing practices
13	HCH	Hexa chlorocyclohexane
14	HPA	Herbal Products Association
15	HPLC	High Performance liquid chromatography
16	HPTLC	High Performance Thin layer chromatography
17	ICH	International conference on Harmonization's
18	ICMR	Indian council of medical research
19	IPR	Intellectual property right
20	LC/MS	liquid chromatography/ Mass spectroscopy
21	LOD	Limits of Detection
22	LOQ	limits of quantification
23	NHPD	Natural Health Products Directorate
24	NMR	Nuclear magnetic resonance
25	NPD	Nitrogen phosphorus detector
26	OECD's	Organization for Economic Co-operation and Development
27	UV/VIS	Ultra Voilet / Visible Spectrophotometer
28	WHO	World health organization

So an attempt has been done to make this review and to highlight the problems associated with herbal formulations and emphasize the recent development of the herbal formulations. So that the state of harmonization can be achieved and reincarnation of the pure herbal drugs can be done.

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Address for correspondence: Prof. (Dr). S. Saraf, Director, Iinstitute of Pharmacy, Pt. Ravishankar Shukla University, Raipur-492 010 Chhattisgarh (India). E- mail: shailendrasaraf@rediffmail.com

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