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STANDARDIZATION OF TRADITIONAL MEDICINE - NEED AND URGENCY

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ABSTRACT

The medicinal plants are the only economic source of a number well established and important drugs. The medicinal plants have enormous commercial potentials throughout the world. In addition, they are also the source of chemical intermediate needed for the production of some drugs. Although use of medicinal plant remedies is advantages, it does suffer some limitations. The main limitation is the lack of standardization of raw materials, of processing methods and of the final products, dosage formulation, and the nonexistence of criteria for quality control. Particularly in India, *Ayurveda, Siddha, Unani, Homoeopathy* etc. consists of large number of herbal remedies being used from ancient times and having the potential therapeutic claims. The medicaments however, suffer from lack of standardization parameters and proper documentation based on scientific screening procedures. Along with increased interest in herbal medicine there has been an explosion in the amount of literature on the subject and quality control is of utmost essential in this respect over the world. In the herbal boom worldwide, it is estimated that high quality phytomedicines will provide safe and effective medication. Recent advances in science and researches proves the use of modern sophisticated instrument is a necessary tool for making pure, tested, valuable natural drugs. This current review will enlighten, the standardization of plant drugs is necessary to produce quality medicines from the ancient medicine for the scientific world.

Key words: Standardization, Medicinal plants, Modern instrument, Phyto-medicine.

INTRODUCTION

Herbal medicine (or "herbalism") is the study and use of medicinal properties of plants [1]. Investigation of traditional medicine is very important for the welfare of rural and tribal communities for the treatment of conventional illness [2].

The departmentof *Ayurveda, Yoga, Naturopathy, Unani, Siddha* and *Homoeopathy* (AYUSH) is a part of the Ministry of Health & Family Welfare of the Government of India [3]. In recent years, plant derived products are increasingly being sought out as medicinal products, nutraceuticals and cosmetics and are available in health food shops and pharmacies over the counter as self-medication or also as drugs prescribed in the non-allopathic systems [4]. The traditional medicine is widely used for various human ailments. The usage of herbal medicine could be even traced right from the beginning of mankind. Man tried to know about the plants around him to satisfy his basic needs such as food, shelter and clothing. All plants in this planet are important because of its medicinal qualities. Traditional system of medicines has become significantly more popular all over the globe because of the effective and curative nature for chronic disease with less toxicity. The medicinal plant contains one or more active principles to cure the diseases

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[5]. Herbal medicines widely used in health-care in both developed and developing countries are complex chemical mixtures prepared from plants and are limited in their effectiveness because they are poorly absorbed when taken orally [6].

As per WHO definition, there are three kinds of herbal medicines: Raw plant material, processed plant material and medicinal herbal products. Herbal drugs are finished labelled products that contain active ingredients such as aerial or underground parts of plant or other plant material or combination thereof, whether in the crude state or as plant preparations. The use of herbal medicines has increased remarkably in line with the global trend of people returning to natural therapies [7]. According to an estimate of the World Health Organization (WHO), about 80% of the world population still uses herbs and other traditional medicines for their primary health care needs. The World Health Organization (WHO) has appreciated the importance of medicinal plants for public health care in developing nations and has evolved guidelines to support the member states in their efforts to formulate national policies on traditional medicine and to study their potential usefulness including evaluation, safety, and efficacy [8-10].

Herbal formulations have reached widespread acceptability as therapeutic agents for diabetics, arthritis, liver diseases, cough remedies, memory enhancers and adoptogens [11]. Owing to the medicinal properties attributed to a crude drug, it is necessary to maintain its quality and purity in commercial market. It is, however that the drugs in commerce are frequently adulterated and do not comply with the standards prescribed for authentic drug [12]. Most of the traditional systems of medicine are effective but they lack of standardization. So, there is a need to develop a standardization technique. Central Council of research in *Ayurveda* and *Siddha* has given preliminary guidelines for standardizing these conventional formulations. For the uniformity of batches in production of herbal formulations it is necessary to develop methods for evaluation. Standardization of drugs means confirmation of its identity and determination of its quality and purity. Initially the crude drugs were identified by comparison only with the standard description available. At present due to advancement in the chemical knowledge of crude drugs various methods like botanical, chemical, spectroscopic and biological methods are used for estimating active constituents present in the crude drugs in addition to its physical constants [13].

Market Importance and Use of Herbal Medicines in India

Medicinal plants are important for pharmacological research and drug development, not only when plant constituents are used directly as therapeutic agents, but also as starting materials for the synthesis of drugs or as models for pharmacologically active compounds. Regulation of exploitation and exportation is therefore essential, together with international cooperation and coordination for their conservation so as to ensure their availability for the future better utilization of these complementary systems of medicine. In India, there are currently about 250 000 registered medical practitioners of the Ayurvedic system (total for all traditional systems: approximately 291,000), as compared to about 700,000 of the modern medical system. In every Indian state, about one-third of the governmental medical posts are occupied by physicians who belong to the traditional systems [14].

Contaminants in herbal medicine

Potential contaminants of herbal medicines include microorganisms, microbial toxins, pesticides, fumigation agents, radioactivity, and the presence of toxic compounds of toxic metals .Some of these contaminants have been identified by the Committee for Proprietary Medicinal Products (CPMP) of the European Community (EC) for use in controlling the purity of herbal medications in the European Union (EU). The CPMP Guidelines highlight the need for good control of starting materials and the finished product and emphasize the importance of good manufacturing practice [15].

Substitution and misidentification of herbal substances

Risks associated with herbal medicine products were first reported for medicinal plants of the Asteraceae family, *Hypericin* and *Aristolochia* genus, and kava-kava. A number of cases of inadvertent or deliberate substitution of the constituents of Chinese herbal preparations are cited in the literature. For example, Siberian ginseng (*Eleutherococcus senticosus*), American ginseng (*Panax quinquefolium*), and Japanese ginseng (*Panax pseudo-ginseng*) have been substituted for Korean or Chinese ginseng (*Panax ginseng*). Sometimes the substitute has a much greater toxicity than the original material. Examples of substitution resulting in an adverse effect include reported cases of hepatitis with jin bu huan, renal fibrosis due to *Aristolochia fangchi*, and podophyllin poisoning due to *Podophyllum emod* [16].

Need for standardization

In recent years there is a spurt in the interest regarding survival of Ayurvedic forms of medication. In the global perspective, there is a shift towards the use of medicine of herbal origin, as the dangers and the shortcoming of modern medicine have started getting more apparent. It is the cardinal responsibility of the regulatory authorities to ensure that the consumers get the medication, which guaranteed the purity, Safety, potency and efficacy. This duty is discharged by regulatory authorities by rigidity following various standards of quality prescribed for raw materials and finished products

in pharmacopoeias controlling manufacturing formula through the use of formularies and manufacturing operation through statutory imposed "Good manufacturing practices".

Herbal products has been enjoying renaissance among the customers throughout the world. The quality of herbal medicine i.e. the profile of the constituents in the final product has implication in efficacy and safety. Due to complex nature and inherent variability of the constituents of the plant based drugs, it is difficult to establish quality control parameter and modern analytical technique are expected to help in circumventing this problem.

The quality control of crude drugs and herbal formulations is of paramount importance in justifying their acceptability in modern system of medicine. But one of the major problems faced by herbal drug industry is non-availability of rigid quality control profile for herbal material and their formulations.

The task of lying down standard for quality control of herbal crude drug and their formulation involves biological evaluation for particular disease area, chemical profiling of the material and lying down specification for the finished product. Therefore, in case of herbal drugs and product, the word "standardization" should encompass entire field of study from cultivation of medicinal plant to its clinical application.

Plant material and herbal remedies derived from them represent substantial portion of global market and in this respect internationally recognized guidelines for their quality control are necessary. WHO has emphasized the need to ensure quality control of medicinal plant products by using modern technique and by applying suitable parameters and standards. In order to overcome certain inevitable shortcoming of the Pharmacopoeial monograph other quality control measures must be explored [17].

Current regulations for standardization of herbal drugs

Several pharmacopoeias like Pharmacopoeia Committee, Chinese Herbal Pharmacopoeia, United States Herbal Pharmacopoeia, British Herbal Pharmacopoeia, British Herbal Compendium, Japanese Standards for Herbal Medicine and the Ayurvedic Pharmacopoeia of India (API) ., Lay down monograph for herbs and herbal products to maintain their quality in their respective nations. Government of India too has brought out Ayurvedic Pharmacopoeia of India, which recommends basic quality parameters for eighty common Ayurvedic herbal drugs. World Health Organization (WHO) encourages, recommends and promotes traditional/herbal remedies in national healthcare 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 standards [18].

History of important events in herbal drug standardization

- 1983- The first National Health Policy 1983 claims that India's is the richest source of herbs and the drugs should be standardized.
- 1995- A separate Department for Indian Systems of Medicine and Homeopathy (ISM&H) now known as AYUSH (Ayurveda, Yoga, Unani, Siddha, Homoeopathy) was established in March 1995 to promote indigenous systems.
- 1996-World Health Organization has recommended the drug control agency to regulate the quality and safety profile of herbal products.
- 1999-World Health Organization (WHO) had given a detail protocol for the standardization of herbal drugs comprising of a single content.
- 2002- The Indian Herbal Pharmacopoeia. Mumbai, Indian Drug Manufacturer's Association, 2002.
- 2002-Analytical approaches like Herboprint use three-dimensional HPLC and attempt to develop tools for activity-based standardization of botanicals
- 2003-Department of Indian Systems of Medicines & Homoeopathy (ISM&H) established in 1995 renamed into Department of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy (AYUSH)
- 2003- WHO Guidelines on good agricultural and collection practices (GACP) for medicinal plants. Geneva, Switzerland: World Health Organization; 2003.
- 2004- WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems.
- 2004-In Canada, the Natural Health Products Regulations (NHPR) [13] under the Food and Drugs Act came into force on 01 January 2004.
- 2005-National Policy on Traditional Medicine and Regulation of Herbal Medicines - Report of a WHO Global Survey
- 2007- WHO Guidelines for assessing quality of herbal medicines with reference to contaminants and residues. Geneva, Switzerland: World Health Organization; 2007.
- 2007- WHO Guidelines on good manufacturing practices (GMP) for herbal medicines. Geneva, Switzerland: World Health Organization; 2007.
- 2009- AYUSH department with collaboration with Quality Council of India introduced certification scheme for AYUSH drug products
- 2009- USP United States Pharmacopeia 32/National Formulary 27. Rockville, MD: The United States Pharmacopeial Convention; 2009.
- 2011-An EU directive passed in 2004 erects "disproportionate" barriers against herbal remedies by requiring them to be "licensed" before they can be sold. It

is called the Traditional Herbal Medicinal Products Directive (THMPD), Directive 2004/24/EC.

- 2011-Draft Guidance for Industry: Dietary Supplements: "New Dietary Ingredient Notifications and Related Issues". The document was published in the Federal Register on Tuesday, July 5, 2011 [18].

WHO Guidelines for Quality Standardized Herbal Formulations

1. The bioactive extract should be standardized on the basis of active principles or major compounds along with the chromatographic fingerprints (TLC, HPTLC, HPLC and GC). The standardization of crude drug materials includes the following steps:
2. Authentication (Stage of collection, parts of the plant collected, regional status, botanical identity like phyto-morphology, microscopical and histological analysis, taxonomical identity etc.)
3. Foreign matter (herbs collected should be free from soil, insect parts or animal excreta etc.)
4. Organoleptic evaluation (sensory characters – colour, taste, appearance, odour, feel of the drug etc.)
5. Tissues of diagnostic importance present in the drug powder.
6. Ash values and extractive values.
7. Volatile matter
8. Moisture content
9. 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. The quality of the drug can also be assessed on the basis of the spectroscopic fingerprint.

10. Determination of heavy metals – e.g. cadmium, lead, arsenic, etc.
11. Pesticide residue – WHO and FAO (Food and Agricultural Organization) set limits of pesticides, which are usually present in the herbs. These pesticides are mixed with the herbs during the time of cultivation. Mainly pesticides like DDT, BHC, toxaphene, aldrin cause serious side-effects in human beings if the crude drugs are mixed with these agents.
12. Microbial contamination – usually medicinal plants containing bacteria and moulds are coming from soil and atmosphere. Analysis of the limits of *E. coli* and moulds clearly throws light towards the harvesting and production practices. The substance known as aflatoxins will produce serious side-effects if consumed along with the crude drugs. Aflatoxins should be completely removed or should not be present.
13. Radioactive contamination – Microbial growth in herbals are usually avoided by irradiation. 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.

In order to obtain quality oriented herbal products care should be taken right from the proper identification of plants; season and area of collection, extraction, isolation and verification process.

Chemical and instrumental analyses are routinely used for analyzing synthetic drugs to confirm its authenticity. In the case of herbal drugs, however the scene is different especially for polyherbal formulation, as there is no chemical or analytical method available. Therefore biological-screening methods can be adopted for routine check up of herbal drugs and formulations. In the case of herbal drugs, the quality of raw materials and products can be furnished by regular pharmacognostic identifications and phyto-chemical analysis. The herbal formulations 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 process.

The stability parameter for the herbal formulations includes physical parameters, chemical parameters and microbiological parameters. Physical parameters include colour, appearance, odour, clarity, viscosity, moisture content, pH, disintegration time, friability, hardness, flow ability, flocculation, sedimentation, settling rate and ash values etc. Chemical parameter includes limit tests, extractive values, chemical assays, etc. Chromatographic analysis of herbals can be done using TLC, HPLC, HPTLC and GC, UV, Fluorimetry, GC-MS, etc.

Microbiological parameters include total viable content, total mould count, total enterobacteria 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, impurities from the solvents, etc.

Modern Techniques in herbal drug identification and Characterization

India can emerge as the major country and play the lead role in production of standardized, therapeutically effective ayurvedic formulation. India needs to explore the medicinally important plants. This can be achieved only if the herbal products are evaluated and analyzed using sophisticated modern techniques of standardization such as UV-visible, TLC, HPLC, HPTLC, GC-MS, spectrofluorimetric and other methods [19].

Thin layer chromatography (TLC)

Thin layer chromatography is simply known as TLC. It is one of the most popular and simple chromatographic technique used of separation of compounds. In the phyto-chemical evaluation of herbal drugs, TLC is being employed extensively for the following reasons:

1. It enables rapid analysis of herbal extracts with minimum sample clean-up requirement.
2. It provides qualitative and semi quantitative information of the resolved compounds.
3. It enables the quantification of chemical constituents [20].

High performance thin layer chromatography (HPTLC)

HPTLC fingerprint is mainly used to study the compounds with low or moderate polarities. 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. HPTLC technique was reported for simultaneous determination of Withaferin A and β-sitosterol-d-glucoside in four *Ashwagandha* formulations. *Syzygium jambolanum* was quantitatively evaluated in terms of stability, repeatability, accuracy and phytocconstituents such as glycoside (jamboline), tannin, ellagic acid and gallic acid by HPTLC. HPTLC was used for detection, monitoring and quantification of bacoside A & B in *Bacopa monnieria* and its formulations.

The standardization of *Cannabis stavia* was done by estimating the content of cannabinoidses in urine sample using HPTLC. HPTLC was used to estimate Withaferine A, a constituent of *Withania somnifera* in herbal extract and polyherbal formulations. HPTLC method has been reported for quantitative estimation of swetiamarin in different marketed polyherbal formulations and small fruits, big fruits and fresh fruits variety of *E. littorale*. Chandanasava known to be effective in karsya (malnutrition) was standardised by organoleptic study, physico-chemical analysis, TLC and HPTLC.

High performance liquid chromatography

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, and its content was found to be 18.1 mg/100 g in Shereeshadi Kashaya and 0.7 mg/100g in Yastyadivati. HPLC analysis of Senna leaves provided information about sennoside content, kaempferol-3-O-D-gentiobioside, aloeemodine-8-O-D-glucopyranoside, rhein8-O-D-glucopyranoside, torachrysone 8-O-D-glucopyranoside and isorhamnetine 3-O-D gentiobioside. 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**.** The combination of HPLC and LC/MS is currently the most powerful technique for the quality control of Chinese herbal medicine Gan-Cao (liquorice).

CONCLUSION

Medicinal plants are important in pharmacological research and drug development, not only when plant constituents are used directly as therapeutic agents, but also as starting materials for the synthesis of drugs or as models for pharmacologically active compounds. Regulation of exploitation and exportation is therefore essential, together with international cooperation and coordination for their conservation so as to ensure their availability for the future. As a whole, herbal medicines can have a risk of adverse effects and drug-drug and drug-food interactions if not properly assessed. Assessment of the safety and Quality of herbal products, therefore, is the first priority in herbal research.

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