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Bottle Necks in Standardization of Traditional System of Medicines

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INTRODUCTION

In many developed countries popular use of Complementary and Alternate Medicine (CAM) is fuelled by concern about the adverse effects of chemical drugs, questioning of the approaches and assumptions of allopathic medicine and greater public access to health information. At the same time, longer life expectancy has brought with it-increased risks of developing chronic, debilitating diseases such as heart disease, cancer, diabetes and mental disorders. For many patients, CAM appears to offer gentler means of managing such diseases than does allopathic medicine.

Regulators wrestle with questions of safety and efficacy of traditional herbal medicines, while many industry groups and consumers resist any health policy developments that could limit access to TM (Traditional medicine)/CAM therapies. Reports of powerful immunostimulant effects for some traditional medicines raise hope among HIV-infected individuals, but others worry that the use of such cures will mislead people living with HIV/AIDS and delay treatment with proven therapies (WHO, 1978).

In general, however, increased use of TM/CAM has not been accompanied by an increase in the quantity, quality and accessibility of clinical evidence to support TM/CAM claims.

Herbal products are the most commonly used complementary and alternative therapies. The medical and research community is constantly searching for new natural agents. Natural products are now a multibillion-dollar industry in the developed countries and these products are used by millions of people annually. Consumers now regularly ask most pharmacists about the benefits of natural products in treating their medical conditions. Consumers are bombarded with recommendations from friends, family, television advertisements and magazine articles giving advice about natural remedies. Herbal products are widely perceived as being safe by patients because they are considered natural. Most medications before being offered to consumers undergo rigorous evidence-based clinical testing; this is not necessarily true for herbs. Consumers regularly use these products without the knowledge of their healthcare professionals (Eisenberg *et al.*, 1993, 1998). Therefore, it is important for developing better standardization techniques for traditional medicines. Plant species contain bewildering diversity of secondary metabolites. Accuracy in recording or observing the medicinal use of a plant, determining whether the ethno medical use can be demonstrated under scientific conditions in laboratory and/or chemical characterization of compounds and role of placebo effect are important issues that need to be verified in the development of drugs of plant (Kumar *et al.*, 2004, 2005).

STANDARDIZATION OF HERBAL MEDICINE OF TRADITIONAL SYSTEM OF MEDICINE

Herbal medicine has its basis in the traditional system of medicine like Ayurveda, Unani, Kambo, Malay Chinese system of medicine etc. These traditional systems of medicine have been used for centuries and have certain standard procedures for its preparation and standardization. The cultural aspects of herbalism in different countries and societies play an important role to see

the diversity of worldwide herbal use. In the traditional system of medicine like Ayurveda drugs are classified based on the Panca mahabhuta (Earth, water, fire, space and ether) is explained in association with its rasa (taste), guna (properties) and karma (action). The potency of the drug (veerya), target site (substratum), time of action (kala), stratagem (upaaya), targeted delivery with specific intention (abhipretha) are also expressed in the natural language which is associated with human cognitive processes, such as thinking and reasoning. Similarly all other traditional system of medicines has their own method of standardization for assuring quality most in human linguistic terms. This method of evaluation has to be taken into consideration in standardization of herbal medicine (Kumar *et al.*, 2004, 2005; Venugopal, 2001).

WHO Guidelines for Quality Standardized Herbal Formulations (WHO, 1978):

- Quality control of crude drugs material, plant preparations and finished products
- Stability assessment and shelf life
- Safety assessment; documentation of safety based on experience or toxicological studies
- Assessment of efficacy by ethnomedical informations and biological activity evaluations

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:

- Authentication (Stage of collection, parts of the plant collected, regional status, botanical identity like phytomorphology, microscopical and histological analysis, taxonomical identity, etc.)
- Foreign matter (herbs collected should be free from soil, insect parts or animal excreta, etc.)
- Organoleptic evaluation (sensory characters – taste, appearance, odor, feel of the drug, etc.)
- Tissues of diagnostic importance present in the drug powder
- Ash values and extractive values
- Volatile matter
- Moisture content determination
- 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). The quality of the drug can also be assessed on the basis of the chromatographic fingerprint
- Determination of heavy metals-e.g., cadmium, lead, arsenic, etc.
- 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
- 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 aflatoxins will produce serious side-effects if consumed along with the crude drugs (Table 1).
- 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

Table 1: Limits for microbial contamination

Microorganism	Finished product	Raw materials
<i>E. coli</i>	10 ¹	10 ⁴
Salmonella	-	-
Total aerobic bacteria	10 ⁶	-
Enterobacteria	10 ³	-

Aflatoxins should be completely removed or should not be present

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 are no chemical or analytical methods available. Therefore, biological-screening methods can be adopted for routine checkup 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 phytochemical 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 parameters for the herbal formulations which includes physical parameters, chemical parameters and microbiological parameters.

Physical parameters include color, appearance, odor, clarity, viscosity, moisture content, pH, disintegration time, friability, hardness, flowability, flocculation, sedimentation, settling rate and ash values.

Chemical parameters 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 mold count, total enterobacterial and their count. Limiters can be utilized as a quantitative or semiquantitative 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.

Chemical decomposition of substances present in the formulation also produces several toxic or impure compounds during storage in undesirable conditions. Contaminants may come directly from the atmosphere also. This include mainly dust, sulfur dioxide, H₂S, CO₂, arsenic, moisture, etc.

The guidelines set by WHO (Shrikumar *et al.*, 2004) can be summarized as follows:

- Reference to the identity of the drug. Botanical evaluation – sensory characters, foreign organic matter, microscopical, histological, histochemical evaluation, quantitative measurements, etc.
- Reference to the physiochemical character of the drug. Chromatographic profiles, ash values, extractive values, refractive index, polarimetric readings, moisture content, volatile oil content, etc.
- Reference to the pharmacological parameters. Biological activity profiles, bitterness values, haemolytic index, astringency, swelling factor, foaming index, etc.

- Toxicity details – heavy metals like cadmium, lead, arsenic, mercury, etc., Pesticide residues

$$\text{Maximum residue limits} = \frac{\text{Acceptable daily index} \times \text{body weight} \times \text{extraction factor}}{\text{Mean daily intake of drug} \times \text{safety factor} \times 100} \times \text{Therapeutic doses}$$

- Microbial contamination- Total viable aerobic count, pathogenic bacteria like enterobacteria, *E. coli*, salmonella, *Pseudomonous aeruginosa*, *Staphylococcus aureus*, etc. and presence of aflatoxins etc.
- Radioactive contamination

Modern herbal ayurvedic monographs: In the modern herbal ayurvedic monographs the standardization parameters are discussed in a comprehensive way. According to the modern ayurvedic monograph the quality control protocols include the following:

Title, synonyms, publications related to that plant, constituents present, analytical methods.

Descriptive evaluation: Description of the drug, phytomorphological, microscopical, organoleptic evaluations, foreign matter, foreign minerals, etc.

Physicochemical parameters: Identity: Physical and chemical identity, chromatographic finger prints, ash values, extractive values, moisture content.

Strength: Ethanol and water extractive values, volatile oil and alkaloidal assays, quantitative estimation protocols, etc.

Biological activity evaluation: Bitterness values, astringency, swelling factor, form index, hemolytic index, etc.

Toxicological evaluation: Pesticide residues, heavy metals, microbial contamination like total viable aerobic count, pathogens like *E. coli*, Salmonella, *P. aeruginosa*, *S. aureus*, Enterobacteria, etc.

Aflatoxins: The presence of aflatoxins can be determined by chromatographic methods using standard aflatoxins B₁, B₂, G₁, G₂ mixtures. Aflatoxin is a product of the microbial strain *Aspergillus flavus*.

Radioactive contaminants

Bottle backs of the existing methods are:

- Sensory evaluation: One cannot identify the adulterant in powdered drug. e.g., Flower bud of clove is substituted by mother clove and clove stalk which contains starch and sclereids, which is absent in bud, respectively
- Moisture content: It is not practicable method if drug contains other volatile substances like essential oil, ethers, esters etc.
- Total solid: Total solid content remain in range even after addition of impurity
- Tannin content: Tannin content of a drug can be maintained in range by adding adulterated or substandard drug

- The selected marker compound does not represent the wholesome nature of the plant
- The abundance of a particular compound depends on several factors ranging from seasonal to regional collection and ways of harvesting
- The formulations can always be spiked with markers thereby enhancing the chances for adulteration
- The concept of holistic approach of Ayurveda is not really met with these existing methods.

CONCLUSION

In modern method of analysis many sophisticated instruments like HPLC, HPTLC, U.V are used along with the characterization of compounds isolated. Now a day's importance is given on chemical constituents and negation of human cognitive processes such as thinking and reasoning which forms the core of traditional medicine. Does this justify the time tested traditional medicine? Imposition of standardization techniques using modern analytical methods will risk of loosing time tested medicine. With the world turning towards herbal medicine it is time to develop methods to standardize the traditional medicine with methods incorporating traditional and modern analytical method. Many small industries involved in preparation of herbal medicine are closing. The objective of United Nations Industrial Development Organization (UNIDO) for systematic utilization of the renewable natural resource for the benefit of the populace and increasing the industrial output will have serious set back. We will be risking the popular medicine in which most of people place faith with lack of proper standardization methods. There is need for development of techniques which includes both traditional methods of evaluation and modern methods of evaluation of traditional medicine. The coupling techniques like fuzzy logic, neural networks and accurate linguistic models along with modern analytic methods of analysis (Kumar and Bhatnagar, 2006). This will improve the quality of the drug and also motivates the traditional medicine practitioners to get more involved in the standardization process.

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