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REVIEW ARTICLE

Quality Control Parameters for Medicinal Plants, an Overview

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ABSTRACT

Medicinal plants have been used in the Indian subcontinent since antiquity. History of herbal medicine is as old as history of mankind itself. It is time tested and widely used across globe. However, recent trends have been directed more towards maligning this rich heritage rather than exploiting its merits. Recent research papers published across globe have alarmed the world in a wrong direction towards propagation of herbal medicine, especially, Ayurveda. Spurious finished products are a consequence of inferior quality of raw materials used in their processing. Therefore, need of time is to abide by standard protocols laid for assuring quality of these raw materials i.e. medicinal plants. The present article deals in detail the background of standardizing medicinal plants in India and an in depth discussion on WHO protocols related to quality control of these herbal drugs.

KEYWORDS: Quality control, WHO

INTRODUCTION

Pharmaceutical research is aimed at meeting the medical needs of the population for whom appropriate therapeutic remedies are not available or at those that are available are unsafe for prophylactic use for various disorders. While meeting medical needs, research also has to ensure that market needs for such exist and that the product will command sales and profits proportionate to investments. In cases where there are mismatches between these two, the products suffer the status of orphan drugs. The selection of an appropriate R&D portfolio is a strategic management exercise for a company, which should take into account apart from medical needs, innovative potential for success and available resources.2000 edition of European monograph contains monographs on 152 crude drugs. Whereas in Indian Pharmacopoeia, 1996 edition, their number shrunk to 57 including only 12 crude drugs. Herbs are not included in essential drug list in India. Although, in Shanghai hospitals, 500 herbal drugs have found place in essential drugs list of about 1000, expenditure on drugs decreased from 67% of hospital budget in 1992 to 51% in 1996, growth rate of drug expenditure decreased from 23.4% to 0.3% for outdoor and from 28.2% to 2.4% for indoor patients, thereby approximate annual saving of 600 million US$ in 7 hospitals. WHO compiled an inventory of 21,000 plants used for medicinal purposes in 91 countries Less than 10,000 species have been investigated. In India, over 17,500 species are reported, many endemic. Traditional systems of medicine use 2,000; Ayurvedic medicines alone need 800 species, whereas folklore use of 8,000 plants has been reported. CSIR has screened about 4000 species but few other broad based studies have been carried out. Organized, codified and systematically arranged written traditions with conceptual philosophy and rationales like Ayurveda, Siddha, Unani and Amchi use almost 2000 plant species[1]. Globalization of complementary medicine is possible only by ensuring quality assurance of finished product. This will not only provide better patient compliance but also increase faith of users on alternative medicines. Quality assurance is possible only by following standard rules of drug preparation. Raw drug standardization holds key to quality of finished product. Lack of interest in laying quality control parameters has led to negligence of this valuable medical science. The major factor that determines actual quality of finished products is the raw material being used. Hence, instead of only testing the quality of finished product, efforts should be made to standardize raw materials. Comprehensive guidelines like those published by WHO, IUPAC[2] and certain inhouse developed techniques have been in vogue recently used to standardize herbal raw drugs.

INDIAN SCENARIO[3]:

As an outcome of the first Health Minister's Conference of 1946, a Committee under the Chairmanship of Lt. Col. R. N. Chopra was appointed in 1946 by the Government of India. It was the Chopra Committee that had first gone into the question of need for proper identification of Ayurvedic medicinal plants as available in the bazaar, control over collection and distribution of crude drugs and made positive recommendations for compilation of an Ayurvedic Pharmacopoeia. Thereafter, the Dave's Committee [1955] reiterated the recommendations for compilation of an Ayurvedic

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Pharmacopoeia. They, therefore had appointed a Committee for Standard and Genuine Ayurvedic Herbs and Drugs in 1955 and subsequently after receiving its report, appointed a second committee with fresh set of terms of reference, called the Committee for Standard Ayurvedic Herbs and Drugs in 1957 both under the Chairmanship of Vaidya Bapalal Shah, of which Professor A. N. Namjoshi was the Member Secretary. The Bapalal Committee had very elaborately recommended the compilation of the Ayurvedic Pharmacopoeia as an urgent prerequisite for effective control of Ayurvedic Drugs to ensure quality assurance. Finally Government of India appointed the "Ayurvedic Research Evaluation Committee", under the Chairmanship of Dr. K. N. Udupa (1958) which had strongly highlighted the urgency of the compilation of an Ayurvedic Pharmacopoeia.

The first Ayurvedic Pharmacopoeia Committee was constituted in 1962 under the Chairmanship of Col. Sir Ram Nath Chopra. The Committee was reconstituted in 1972 under the Chairmanship of Prof. A.N.Namjoshi to continue the work of compilation of the Ayurvedic Formulary of India as a pre-requisite for undertaking the work of Ayurvedic Pharmacopoeia of India. The Part I of Ayurvedic Pharmacopoeia of India consists of Vol-I, II, III, IV and V comprising respectively 80, 78, 100, 68 and 92 monographs prescribing standards for Ayurvedic single drugs of plant origin, which go into one or more formulations admitted to the Ayurvedic Formularies of India, Part-I and Part-II. The Part-II of the Ayurvedic Pharmacopoeia consists of official standards for 50 compound formulations present in the Ayurvedic Formulary of India Part-I and Part-II. The title of the monograph for each compound formulation is given in Sanskrit, as in the Ayurvedic Formulary of India. This is followed by the Definition, Formulation Composition, Method of preparation, a brief description of the compound formulation, standards for Identity and Purity in so far as they are reflected by microscopy and physico-chemical parameters. Other requirements such as tests for heavy metals, microbial content have also been prescribed. Information on therapeutic uses, dose, administration and storage is included. The raw material which complies with the standards of API was selected for developing standards for compound formulations. In a few cases, where such standards were not available, the collaborator developed them and used them as standards for that raw material. The monograph gives limits under assay, for any one constituent or group of constituents like total alkaloids or total volatile oils. In the case of water soluble or alcohol soluble extractives a minimum lower limit has been given. For impurities like Ash, Acid insoluble Ash etc, a maximum upper limit has been given. It is a well known fact that there is wide variation in such values for crude drugs of plant origin in respect of their chemical contents. Therefore, such variations had to be taken into consideration in laying down minimum and maximum standards for the compound formulations.

WHO GUIDELINES[4]:

The standardization of raw herbal drug materials includes following steps (Fig. 1):

1. Authentication
2. Foreign matter (herbs collected should be free from soil, insect parts or animal excreta, etc.)
3. Organoleptic evaluation (sensory characters – taste, appearance, odour, feel of the drug, etc.)
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
9. Determination of heavy metals – e.g. cadmium, lead, arsenic, mercury etc.
10. Pesticide residue
11. Microbial contamination
12. Afflatoxins should be completely removed or should not be present.
13. Radioactive contamination

CLASSICAL EVALUATION AS PER AYURVEDIC LITERATURES:

Classical therapeutical attributes like Rasa, Guna, Virya, Vipaka and Karma classical formulations, doses, storage conditions.

DISCUSSION:

It is generally believed that standardization of the plant material is not required when used by the rural communities for their primary health care. But, regardless of whether the medicinal plant is to be used by local communities or by industry, a systematic approach is required for a plant identified from traditional medicine, as is done in modern medicine. It is necessary to focus on all aspects of medicinal plant research: from cultivation, ethno-pharmacology, utilization, isolation and identification of active constituents to efficacy evaluation, pharmacology, safety, standardization, formulation and clinical evaluation[5]. In the absence of official standards published by Government for statutory purposes, Ayurvedic Pharmaceutical Industry in particular has been experiencing several handicaps in implementing in house

standards, as in any case, they need to comply with official standards.

The western countries did pass through the same phase over 150 years ago for their medicines, their characteristics, methods of preparation and identity, purity and strength. Research towards this end was vigorous and out of the scientific data contributed by the scientists in research institutes and industry, the pharmacopoeial monographs of drugs were drafted. As a result pharmacopoeiae of the western world show considerable uniformity in principles, approach and information. Thus, while for compilation of the British Pharmacopoeia, information and scientific data was available, for the compilation of the Ayurvedic Pharmacopoeia little information and published data existed and the Ayurvedic Pharmacopoeia Committee had to do a lot of spade work. The publication of the Ayurvedic Formulary of India and the Ayurvedic Pharmacopoeia of India would now enable the Government to implement the Drugs and Cosmetic Act, 1940 in respect of quality control for the Ayurvedic, Siddha, Unani drug manufacturers, distributed and sold in India, under a license granted by it. The Ayurvedic Pharmacopoeia Committee has laid down standards for single drugs based on experimental data worked out at the PLIM, Ghaziabad and in some of the units of the Central Council for Research in Ayurveda and Siddha. Published scientific literature on the subject, although scanty, has also been collected and included after due verification. Authentication is done on stage of collection, foreign matter, parts of the plant collected, regional status, botanical identity like phytomorphology, microscopical and histological analysis, taxonomical identity, etc. 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 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. For example, leaf can be standardized on parameters of leaf constants like palisade ratio, vein islet number, vein termination, stomatal number and stomatal index. Recently some steps have been taken in the direction of quantitative pharmacognosy by few researchers[6]. The main barrier in the wider acceptance of medicinal plants is the non-availability or inadequacy of standards necessary for assessment of their quality. The quality of the drug can also be assessed on the basis of the chromatographic fingerprint. 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 medicinal plants. GCMS studies are required for herbs having volatile contents. Determination of foreign matter, ash value, volatile matter, bitterness value, haemolytic activity, astringency, determination of tannins, foaming index etc. are important values which need consideration during quality control of herbs. Fluorescence studies (for identification of adulterants and spurious herbs), FTIR (for various functional groups), DNA fingerprinting are also widely used now a days.

Pesticides like Aldrin, DDT, Endodulfan, BHC, Lindane, Chordane, Dieldrin, Chlorpyrifros, Dimethoate, Malathion, Methyl parathion, Quinolphos, Cypermethrin are generally assessed in the medicinal plants. WHO and FAO (Food and Agricultural Organization) have 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. Therefore their evaluation is of importance to assure quality of finished product. Collection of medicinal plants should not be done from places that are prone to or close to sources of contamination such as areas where high levels of pesticides or other possible contaminants are used or found e.g. roadsides, drainages, mine tailings, garbage dumps and industrial facilities which may produce toxic chemicals or active pastures that may lead to microbial contamination. Other pesticides to be assessed are organic phosphates, carbamate insecticides and herbicides, dithiocarbamate fungicides, triazin herbicides, fumigation agents like ethylene oxide, methyl bromide, phosphine etc. API advocates assessment of pesticides like Dichorvos, Fonofos, Diazinon, Methyl-Parathion, Methyl-Pirimiphos, Methyl-Chlorpyrifos, Methidathion, Ethion, Carbophenothion, Azinphos-Methyl, Phosalon etc. Insecticides to be assessed are α – Hexachlorocyclohexane, Hexachlorobenzene, β – Hexachlorocyclohexane, Lindane, δ – Hexachlorocyclohexane, ε – Hexachlorocyclohexane, Hepatachlor, Aldrin, cis-Hepatchor-epoxide, o,p-'DDE, α – Endosulfan, Dieldrin, p,p-'DDE, o,p-'DDD, Endrin, β – Endosulfan, o,p-'DDT, Carbophenothion, p,p-'DDT, cis-Permethrin, trans-Permethrin, Cypermethrin, Fenvalerate and Deltamethrin. Only the chlorinated hydrocarbons and related pesticides (e.g. aldrin, chlordane, DDT, dieldrin,

HCH) and a few organophosphorus pesticides (e.g. carbophenothion) have a long residual action. Most other pesticides have very short residual actions. Therefore it is suggested that, where the length of exposure to pesticides is unknown, the medicinal plant material should be tested for the presence of organically bound chlorine and phosphorus, or the content of these two substances should be determined. Toxicity details of heavy metals like cadmium, lead, arsenic, mercury etc. is a pre requisite. Research article published by Saper *et al*[7] have created much hue and cry in the recent past over quality of finished products as alarming levels of heavy metals were found in various finished Ayurvedic formulations sold over the counters in America. Therefore, assessing heavy metals has become mandatory for all herbs. The recommended permissible limits for mercury, lead, cadmium and arsenic are 1 mg/kg, 10 mg/kg, 0.3 mg/kg and 3 mg/kg respectively[8]. Usually medicinal plants contain bacteria and moulds that come from soil and atmosphere. Analysis of the limits of *E. coli* and moulds clearly throws light towards the harvesting and production practices. Microbial contamination consists of total viable aerobic count, pathogenic bacteria like enterobacteria, *Escherichia coli* (certain strains), salmonella, *Pseudomonous aeruginosa*, Shigella, *Staphylococcus aureus*, etc.

LIMITS FOR MICROBIAL CONTAMINATION[9]: (AS PER WHO)

Different limits are set according to the use of the material and the material itself. For contamination of "crude" plant material intended for further processing (including additional decontamination by a physical or chemical process) the limits, adapted from the provisional guidelines established by an international consultative group , are given for untreated plant material harvested

UNDER ACCEPTABLE HYGIENIC CONDITIONS:

1. Escherichia coli, maximum 10^4/g
2. Mould propagules, maximum 10^5/g
for plant materials that have been pre-treated (e.g. with boiling water as used for herbal teas and infusions) or that are used as topical dosage forms:
1. Aerobic bacteria, maximum 10^7/g
2. Yeasts and moulds, maximum 10^4/g
3. Escherichia coli, maximum 10^2/g
4. Other enterobacteria, maximum 10^4/g
5. Salmonellae - none.

FOR OTHER PLANT MATERIALS FOR INTERNAL USE:

1. Aerobic bacteria, maximum 10^5/g
2. Yeasts and moulds, maximum 10^3/g
3. Escherichia coli, maximum 10/g
4. Other enterobacteria, maximum 10^3/g
5. Salmonellae, none.

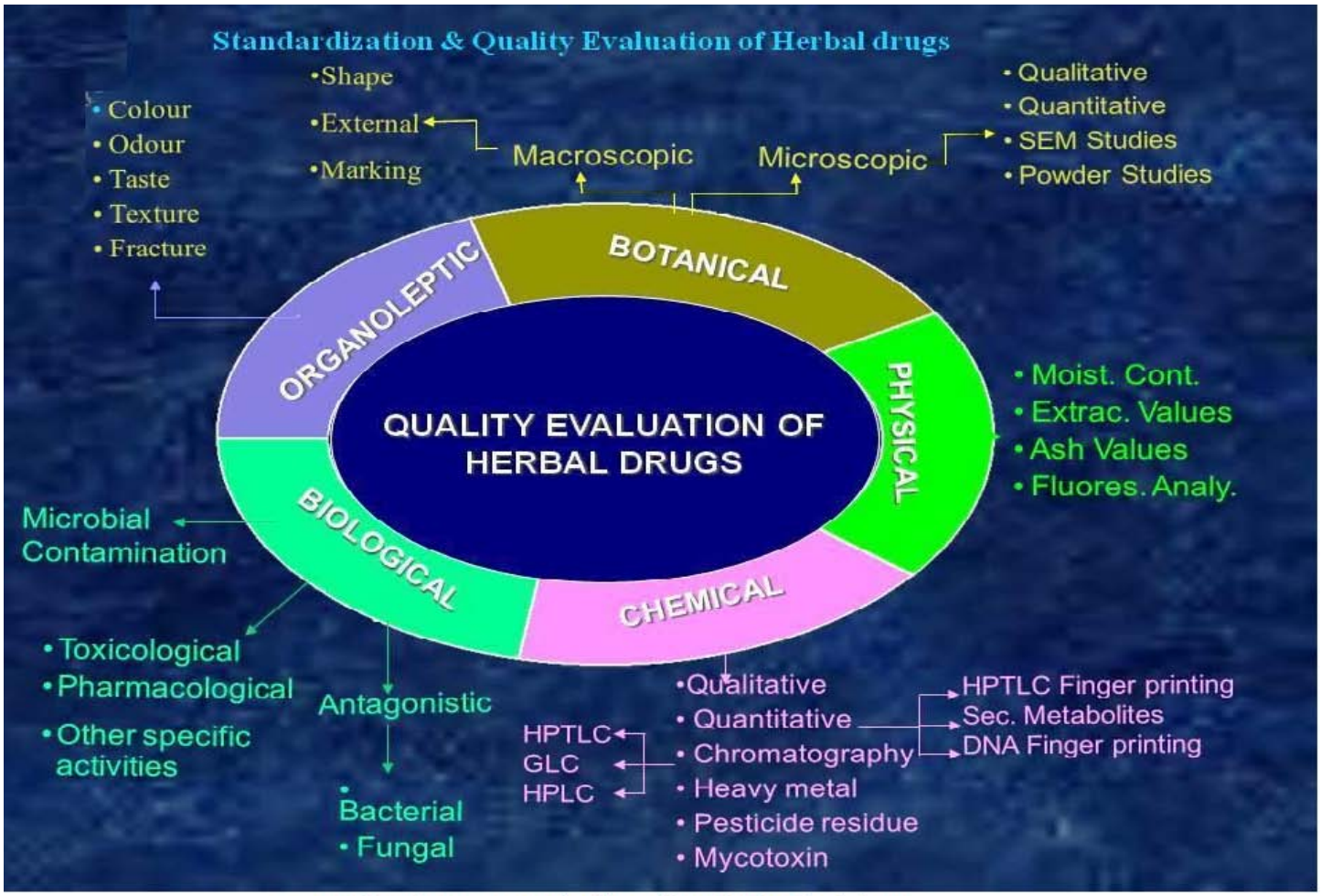
As per API[10]:

1. taphylococcus aureus/g. - Absent
2. Salmonella sp./g. - Absent
3. Pseudomonas aeruginosa/g - Absent
4. Escherichia coli - Absent
5. Total microbial plate count (TPC) - 10^5/g*
6. Total Yeast & Mould - 10^3/g
(*For topical use, the limit shall be 10^7/g)

Microbial growths 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. Some of the metals assessed for radioactivity are Cs-134, Cs-137, Ru-103, I-131, Sr-90 etc. Not only the assessment of microbial overload is necessary, rather assessment of bacterial toxins in also of prime importance. Aflatoxin is an endotoxin product of the microbial strain *Aspergillus flavus*. Herb contaminated by this toxin is severely fatal on internal administration. Therefore, its levels are also to be checked. The presence of aflatoxins can be determined by chromatographic methods using standard aflatoxins B_1, B_2, G_1, G_2 mixtures.

CONCLUSION:

With the tremendous increase in the global use of medicinal plants, several concerns regarding the efficacy and safety of the herbal medicines have also been raised. Hence it has become necessary to standardize the efficacy and safety measures so as to ensure supply of medicinal plant materials with good quality. The botanical definition, including genus, species and authority, should be given to ensure correct identification of a plant. A definition and description of the part of the plant from which the medicine is made (e.g. leaf, flower, root) should be provided, together with an indication of whether fresh, dried or traditionally processed material is used. The active and characteristic constituents should be specified and, if possible, content limits should be defined. Foreign matter, impurities and microbial content should be defined or limited. Voucher specimens, representing each lot of plant material processed, should be authenticated by a qualified botanist and should be stored for at least a 10-year period. A lot number should be assigned and this should appear on the product label[11]. Quality control ensures that the plant material is not contaminated with microbes, pesticides, heavy metals or other toxic agents[12] and that the final product is of consistent high standard.



An Overview of Parameters Involved in Quality Evaluation of Herbal Drugs
(Courtesy: ppt. of Dr. Pushpagandhan)

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