

Botanicals: Quality and regulatory issues

Dnyaneshwar Warude and Bhushan Patwardhan*

Interdisciplinary School of Health Sciences, University of Pune, Pune 411 007

Received 29 December 2003; rev recd 16 September 2004; accepted 09 November 2004

Practice of complementary therapies has grown globally. Use of indigenous drugs from plant origin forms a major part of such therapies. Increased demand of medicinal plants and related products is an opportunity sector for Indian trade and commerce. Widespread and growing use of botanicals has created public health challenges globally in terms of quality, safety and efficacy. Regulatory authorities of different countries have contributed in developing guiding principles addressing issues related to these aspects of botanical medicine. This review discusses various regulatory issues related to quality of botanicals.

Keywords: Botanicals, regulatory issues, quality, safety, efficacy, Indigenous drugs

Introduction

Practice of Complementary and Alternative Medicine (CAM)/ Traditional Medicine(TM) has grown globally. Almost half of the population of many industrialized countries regularly uses some form of CAM¹. Use of indigenous drugs from plant origin forms a major part of such therapies. The world market for botanical medicines including drug products and raw materials has been estimated to have an annual growth rate between 5-15 per cent. Total global botanical drug market is estimated as US\$62 billion and is expected to grow to the tune of US\$ 5 trillion by 2050². In the USA alone, use of botanicals has been increased by 380 per cent between 1990 and 1997. In 2001, USA spent US\$17.8 billion on dietary supplements, of which US\$4.2 billion for botanical remedies. China's herbal drug production is worth US\$48 billion and export worth US\$3.6 billion and the projected growth is estimated as US\$ 400 billion by 2010³. Within the European Union, botanical medicines represent an important share of the pharmaceutical market, with annual sales of US\$7 billion⁴. In India, the value of medicinal plant related trade is about US\$ 10 billion per annum and this industry is growing at the rate of 7-15 per cent annually with exports of US\$1.1 billion per year⁵. Although, Ayurveda, the Indian system of medicine is

one of the most ancient, yet living traditions, faces a typical western bias⁶. Global trend leading to increased demand of medicinal plants for pharmaceuticals, phytochemicals, nutraceuticals, cosmetics and other products is an opportunity sector for Indian trade and commerce. Widespread and growing use of botanicals has created public health challenges globally in terms of quality, safety and efficacy^{7,8}. Scientifically validated and technologically standardized botanical medicines will play an important role in future advancement in healthcare. The development of parameters for standardization and quality control of botanicals is a challenging task. Various regulatory authorities, research organizations and botanical drug manufacturers have contributed in developing guiding principles addressing issues related to quality, safety and efficacy⁹. This review discusses various regulatory issues related to quality of the botanicals.

Definitions and Description

Terms like phytomedicines, herbs, herbal materials, botanicals and botanical drugs are used to define medicines from plant origin. Phytomedicines are preparations consisting of complex mixture of one or more plant materials¹⁰. Herbs include botanical materials such as leaves, flowers, fruit, seed, stems, wood, bark, roots, rhizomes or other plant parts. Herbal materials include, in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders.

* Author for correspondence
Telefax: 020-25690174
E-mail: bhushan@unipune.ernet.in

of herbs¹¹. In some countries, these materials may be processed by various local procedures, such as steaming, roasting or fermentation. Botanicals encompass herbal materials algae, macroscopic fungi and/or their combinations. Botanical drugs are the botanicals intended for use as drugs with therapeutic claim¹². Herbal preparations are the basis for finished botanical products and may include comminuted or powdered materials, or extracts, tinctures and volatile and fatty oils of herbal materials. Such preparations are produced by distillation, extraction, fractionation, purification, concentration or other physical or biological processes. Sometimes, Ayurvedic medicines are confused with herbals. In Indian Drugs and Cosmetics Act, 1940, Ayurvedic medicines are considered as classical preparations intended for internal or external use for or in the diagnosis, treatment, mitigation or prevention of diseases or disorder in human beings or animals and manufactured exclusively in accordance with formulae described in authentic books of Ayurveda¹³.

Regulatory Status in Different Countries

The regulatory situation for botanical preparations varies from country to country. In some developed countries, phytomedicines are well established, whereas in others they are regarded as foods, and therapeutic claims are not allowed. Though developing countries have large number of traditionally used botanical medicines and tremendous folk knowledge about them, very few steps have been taken to establish these medicines as part of drug legislation.

India

Recognizing the global demand, Government of India has released Good Manufacturing Practices (GMPs) for the pharmacies manufacturing Ayurvedic, Siddha and Unani medicines to improve the quality and standard of drugs¹⁴. The new rules came into force from June 2000 as an amendment to the Drugs and Cosmetics Act, 1940. These rules give details regarding essential infrastructure, personnel and quality control requirements for herbal drug manufacturing. Implementation of GMP requirements is mandatory to the industry. Qualifying units can get the GMP certificate immediately. Exemption has been given to the registered practitioners and teaching institutions that prepare medicines for their patients. Department of Indian Systems of Medicine and Homeopathy (ISM&H) is trying to frame safety and

efficacy regulations for licensing new patent and proprietary botanical medicines¹⁵. Indian Pharmacopoeia¹⁶ (1996) covers few Ayurvedic medicines. Monographs have been given for some ayurvedic drugs like clove, guggul, opium, mentha, senna. The Ayurvedic Pharmacopoeia of India gives monographs for 258 different Ayurvedic drugs. The standards mentioned are quite inadequate to build quality of the botanical materials¹⁷. Indian Drug Manufacturers Association (IDMA) has published Indian Herbal Pharmacopoeia¹⁸ (2002) with 52 monographs of widely used medicinal plants found in India. The latest available scientific data has been incorporated in these monographs.

China

China has modernized its traditional medicine profession with government-sponsored good agricultural policies (GAPs) and GMPs. In GAPs, stress has been given on selection of the correct germplasm with high content of stable active components. Cultivation practices offer standard operating procedures (SOPs) for use of fertilizers, irrigation system, disease management and insects and pest prevention. GAPs also provide standards for noxious and harmful contaminants in plants like heavy metals, pesticide residues, microbes etc. Selection of correct germplasm using modern DNA fingerprinting and chemoprofiling techniques is also on priority¹⁹. China has shown active interest and reinforced more than 100 research units and enterprises to join and build more than 600 standard planting bases for the herbs having great demand. This involves major aspects like identification of areas suitable for farming of the herbs free from pollutants, having low level of organic and inorganic fertilizers and pesticides etc. It has become mandatory that all manufactures of traditional Chinese medicine must comply with guidelines laid down by China's State Drug Administration (SDA) by 2004 and farms producing raw ingredients must comply with SDA-imposed standards by 2007. As a result, 1,470 companies have registered for GMPs while 570 failed to meet the standards²⁰. Pharmacopoeia of the people's republic of China²¹ (2000) contains 992 monographs of Chinese crude drugs and traditional Chinese patent medicines, in which 76 new admissions and 248 monographs are revised.

United States

In the United States, Dietary Supplement and Health Education Act (DSHEA), 1994 classifies

botanical medicines as dietary supplements along with vitamins, minerals, amino acids, enzymes and other health products.²² Under DHSEA, botanicals can be labeled and advertised as having certain healthful or nutritional properties as long as no “therapeutic claims” are made. Those botanicals making “therapeutic claim” can be approved as drugs by United States’ Food and Drug Administration (USFDA). FDA has published specific guideline for industries manufacturing such botanical drug products. This guidance explains when a botanical drug may be marketed under an over-the-counter (OTC) drug and when FDA approval of a new drug application is required for marketing. It provides guidance for submitting investigational new drug applications for botanical drug products, including those botanicals currently lawfully marketed as foods and dietary supplements in the United States. It also discusses several areas, in which, because of unique nature of botanicals, FDA finds it appropriate to apply regulatory policies that differ from those applied to synthetic, semi synthetic, or otherwise highly purified or chemically modified drugs (including antibiotics)¹².

European Union (EU)

In EU, botanicals are more strictly regulated. The European Agency of Evaluation of Medicinal Products (EMA) provides general guidelines for setting uniform set of specifications for the botanical preparations manufactured and sold in Europe²³. These guidelines for assessing quality of botanicals provide specifications for tests, procedures, and acceptance criteria used to assure the quality of botanical preparations at release and during its shelf life. The norms consider the marketing approval of botanical products (including fixed combinations). Specific guidelines also address the assessment of safety and efficacy. The strategy is to follow the concept of evidence based medicine. Botanicals that have been used for at least 30 y, with a minimum of 15 y in EU are eligible for registration as traditional medicinal products in EU. Preclinical and clinical studies are proposed if a completely new indication is requested for the botanical product that has been already marketed for a different use. However, if the product has well-established medicinal use with recognizable efficacy and acceptable level of safety, these studies are exempted. Further, due to complex composition of botanical preparations, pharmacokinetics studies are not suggested unless there are safety concerns²⁴.

Canada

Health Canada is one of the most influential agencies affecting herb and spice production, processing and manufacturing. Facilities where herbal products are manufactured are encouraged to conform to GMPs in Canada. Main stress is given on the parameters like premises, sanitation, equipment, personnel and raw material testing. In addition, federal, provincial, and municipal food regulations also apply. Consequently, these regulations require the upgrade of existing facilities. Documentation and records of quality assurance laboratory analyses need to be done. Botanicals are classified as either a food or drug by Health Canada. If the product falls into the category of a drug, the Drugs Directorate of Health Canada becomes involved. As like USA, when medical claim or pharmacological effect or both are made for a botanical medicine, it needs to have a FDA drug approval. There is no distinction between a natural product, and a synthetic product manufactured in a facility. Some manufacturers of herbal products have been able to avoid much of the regulatory cost associated with medicinal herbs by not classifying them as drugs and making no medicinal claims. The Health Canada Food Inspection Program is responsible for regulatory issues concerning foods. However, if the product to be marketed is classified as a drug, such as fever few (used to help prevent recurring migraine headaches), then a Drug Identification Number (DIN) is required. Government approval of a health claim requires proof of a causal relationship; careful scientific evaluation and unambiguous conclusions between a nutrient, drug or other compounds and a disease condition. The process used by the pharmaceutical industry in making a health claim includes a detailed biochemical investigation, and rigorous efficacy and toxicity testing²⁵.

Australia

Complementary medicines, including botanical medicines in Australia are regulated under therapeutic goods legislation²⁶. For managing the risk associated with therapeutic goods, it undergoes processes of licensing of manufacturers, pre-market assessment of products and post-market regulatory activity. Based on risk, Australia has developed two approaches for regulation of these therapeutic goods. Listed medicines are considered to be of lower risk than Registered medicines. Most, but not all, complementary medicines are Listed medicines,

which are individually assessed by the Therapeutic Goods Administration for compliance with legislation. They are not evaluated before release. They may only be formulated from ingredients that have undergone pre-market evaluation for safety and quality and are considered at low risk. Listed complementary medicines may only carry indications and claims for the symptomatic relief of non-serious conditions, health maintenance, health enhancement and risk reduction. Registered medicines are individually evaluated for safety, quality and efficacy before they are released onto the market. An important feature of risk management in Australia is that early market access for low risk complementary medicines is supported by appropriate post-market regulatory activity.

WHO on Botanicals

World Health Organization (WHO) has tried to establish internationally recognizable regulatory guidelines to define basic criteria for the evaluation of quality, safety and efficacy of botanical medicines. WHO assists national regulatory authorities, scientific organizations and manufacturers to undertake an assessment of the documentation/submissions /dossiers in respect of such products. Guidelines for assessing the quality of botanical materials mainly emphasize the need to ensure the quality of medicinal plant products by using modern techniques and applying suitable standards. A series of tests for assessing the quality of medicinal plant materials have been described. Botanical characterization using macroscopic and microscopic methods has been recommended. For physical evaluation, parameters like ash value, extractable matter, volatile matter etc. have been suggested. Pharmacological evaluation has been recommended for certain norms like bitterness value and hemolytic activity. Detection of pesticidal residue, arsenic and heavy metal content, microbial load and radioactive contaminants has been suggested for safety of the botanical materials²⁷.

In 1997, WHO developed draft guidelines for methodology on research and evaluation of traditional medicine (TM)¹¹. It mainly focuses on current major debates on safety and efficacy of traditional medicine. It also tries to provide answer for some of the challenging questions concerning evidence base of the traditional knowledge of medicine. These guidelines present some national regulations for the evaluation of botanical medicine, and also recommend new approaches for carrying out clinical research. Specific

objectives of these guidelines are to harmonize the use of certain accepted and important terms in TM, summarize key issues for developing methodologies for research and evaluation of TM, improve the quality and value of research in TM, and to provide appropriate evaluation methods to facilitate the development of regulation and registration in TM.

Under the overall context of quality of botanical medicines, WHO developed the Guidelines on Good Agricultural and Collection Practices (GACP) for medicinal plants. GACP provides general technical guidance on obtaining medicinal plant materials of good quality for the sustainable production of herbal products classified as medicines²⁸. The main objectives of these guidelines are to guide the formulation of national and/or regional GACP guidelines and GACP monographs for medicinal plants and related standard operating procedures and to encourage and support the sustainable cultivation and collection of medicinal plants of good quality.

WHO also has published monographs for selected medicinal plants. It will provide models to assist member states in developing their own monographs or formularies for these and other herbal medicines and facilitate information exchange among Member States. However, these are not pharmacopoeial monographs, rather they are comprehensive scientific references for drug regulatory authorities, physicians, traditional health practitioners, pharmacists, manufacturers, research scientists and the general public.

Quality Aspects

Purity and quality of botanicals is a critical determinant of safety²⁹. The first stage in assuring quality, safety and efficacy of botanical medicines is identification and selection of the correct plant species. The information required for an authentic botanical includes the currently accepted Latin binomial name and synonyms, vernacular names, the parts of the plant used for each preparation and detailed instructions for agricultural production and collection conditions according to each country's good agricultural practices. Regulatory authorities for control of raw material have suggested various methods. Most of the guidelines suggest macroscopic and microscopic evaluation and chemical profiling of the botanicals^{12, 23, 27}. Characterization using sensory parameters like color, odor, taste and surface characteristics are studied in macroscopic evaluation.

Size and shape of the plant part used is also taken into consideration³⁰. However, since these characteristics are judged subjectively and substitutes and adulterants may closely resemble the genuine material, it is often necessary to substantiate the findings by microscopy and/or physicochemical analysis²⁷. An examination by microscopy alone cannot always provide complete identification, though when used in association with other analytical methods it can frequently supply supporting evidence³¹.

Chemoprofiling using HPLC, HPTLC and GC have wide applicability in quality control of herbal medicine. Multi-component botanical formulations can be standardized by using these sophisticated techniques. A polyherbal formulation (Artrex) designed for the treatment of arthritis contains four botanicals. The formulation has been standardized using HPLC and HPTLC fingerprinting profile with known markers. This formulation has been granted a US patent³². Spectroscopic analysis has also been suggested by certain pharmacopoeias for analysis of botanicals. European Pharmacopoeia gives assay of quinine-type alkaloids and cinchonine-type alkaloids in cinchona bark using UV spectroscopy; and United States Pharmacopoeia (USP) includes an UV absorption test for the absence of foreign oils in oils of lemon and orange. UV spectroscopic analysis has been used for quantitative and qualitative detection of marker compounds from the herbal material. Infrared spectroscopy; NMR and Mass Spectroscopy have been used for structure elucidation of marker or active components from plants³³.

By nature, botanicals may be highly variable in their chemical composition. The variability in the flavours, aroma, physical characteristics of wine and coffee from year to year and region to region provide a good analogy. There are numerous factors that may affect the ultimate chemical profile of a botanical and the content of a specific marker, including intrinsic factors such as genetics and extrinsic factors such as growing, harvesting, drying and storage conditions. In order to ensure efficacy, selection of the correct chemotype of the plant is necessary. Even when there are known chemotypes of a plant species, selection of the right chemotype to which all clinical effects are attributed is difficult. *Withania somnifera* is reported to have three chemotypes depending upon the presence of class of closely related steroidal lactones like withanolides, withaferin A etc³⁴. The content of withanolides, withaferin A and other biologically

active compounds may vary depending upon the environment, genotype, time of collection of plant material etc. Hence, selection of the right chemotype having therapeutic efficacy is required.

The use of chromatographic techniques and marker compounds to standardize botanical preparations has its own limitations. Analysis of secondary metabolites is restricted to those plants that produce a suitable range of metabolites which can be easily analyzed and which can distinguish between varieties. Also, the metabolites being used as markers should ideally be neutral to environmental effects and management practices³⁵. Establishing the presence of a marker compound in a herb is not sufficient to determine desired quality, since the marker compound may not necessarily be responsible for the biological activity that is attributed to the whole herb³⁶. In view of these limitations of the currently used methods there is a need for new approaches that can complement or serve as an alternative for the existing methods. Some of the newly emerging techniques for ensuring quality are HerboprintTM³⁷ capillary electrophoresis and DNA analysis. Herboprint evaluates Ayurvedic medicines on the basis of HPLC fingerprint. The capillary electrophoresis is based upon the simple phenomenon of electrophoresis, which is the movement of electrically charged particles or molecules in a conductive liquid medium under the influence of electric field³⁸. Some publications have presented persuasive evidence that capillary electrophoresis may provide a superior alternative to HPLC in some cases, by facilitating the reliable discrimination of the species³⁹.

Similarly, DNA methods for species characterization and adulteration detection have been published^{40,41, 42}. DNA-based molecular markers have acted as versatile tools in plant genome analysis and are specifically important in differentiating different plant species and their varieties. Various techniques like Random Amplified Polymorphic DNA (RAPD), Amplified Fragment Length Polymorphism (AFLP), Restricted Fragment Length Polymorphism (RFLP) and Inter-Simple Sequence Repeat (ISSR) have been successfully used for DNA analysis. Further, these techniques have been successfully applied for characterization of semi-processed and processed herbal drug materials. Being environmentally stable and specific, DNA markers could gain wide popularity in quality control and standardization of medicinal plant materials⁴³.

Quality control of polyherbal formulations is a critical task. The formulation may contain combination of two to maximum up to 50 ingredients. The plant material can be in the form of extracts or powdered crude drugs or a combination of both. In addition to this, herbo-mineral formulation contains minerals along with the botanical materials. This makes standardization of polyherbal formulations difficult. The quality of the finished formulation will depend upon quality of raw material, uniformity of manufacturing processes and standard operating procedures and testing procedures. Proper control over these will ultimately result in quality botanical medicine⁴⁴. In India, there are about 9000 licensed firms manufacturing TMs with or without proper standardization of the botanicals⁴⁵. As there is lack of standard norms for quality production of botanical medicines, the Indian manufacturers generally follow WHO standards. India needs to design its own parameters and standard sets of guidelines for quality control of Ayurvedic medicines. Some of the polyherbal formulations have undergone detailed experimental and clinical studies. A hepatoprotective Liv.52 improves ethanol metabolism in rat model⁴⁶ and prevents lipid peroxidation in CCl₄ induced liver damage⁴⁷. Mentat augments acquisition and retention of learning in experimental studies⁴⁸. Such evidence-based studies will build faith in multi component herbal formulations globally.

Toxic Contaminants

Over the past decade, several adverse effects of botanical medicines due to chemical composition of botanicals or extraneous matters present in/on the plant material have been reported. This has raised many questions regarding safety of the botanicals. Botanical medicines may be associated with contaminants like microorganisms, excessive or banned pesticides, heavy metals, chemical toxins, and radioactive substances etc.

Microbial Contamination

Medicinal plants are associated with a broad variety of microbial contaminants, mainly bacteria (bacterial endospores) and fungi (fungal spores). Also broad diversity of bacterial, fungal cells and viruses can be found either in or on the plant material. Among microorganisms, occurrence of pathogens particularly limits the use of these plants⁴⁹. Microbial contamination can render plant material toxic either by transforming the benign chemicals in the plant into

harmful substances, or through the microbes' production of toxic compounds. For example, the moulding of sweet clover (*Melilotus officinalis*) causes a chemical transformation of clover's constituents; the resultant compounds can cause hemorrhaging. The potentially toxic effects of bacterial and fungal endotoxins such as *Escherichia coli* endotoxin and aflatoxin from *Aspergillus* sp. are well known. Commonly found pathogenic bacteria on botanicals include *E. coli*, *Salmonella typhi*, *Pseudomonas aeruginosa* and *Styphalococcus aureus*.

Mycotoxins are toxic metabolites produced by certain fungi that can infect and proliferate on various medicinal plants in the field and/or during storage. Mycotoxins may exhibit various toxicological manifestations; some are teratogenic, mutagenic and/or carcinogenic and are associated with various diseases⁵⁰. The different mycotoxins of relevance to human health are aflatoxins, ochratoxins, zearalenone, fumonisins, and trichothecenes.

Studies have been conducted to determine the types of fungi and their toxins contaminating medicinal plants, processed and non-processed foods and other materials of plant origin⁵¹. The fungal species commonly encountered are *Fusarium*, *Aspergillus*, *Penicillium*, *Mucor*, *Rhizopus*, *Absidia*, *Alternaria*, *Cladosporium* and *Trichoderma*⁵²⁻⁵⁶. *Aspergillus*, *Penicillium*, *Rhizopus*, *Mucor*, *Cladosporium* and *Aureobasidium* spp. can be found quite often in association with botanicals⁵⁷, but mycotoxin producers were only present at the level of 2 per cent. On the contrary⁵⁸, considerable risk levels of aflatoxins in several botanical medicinal samples of different taxa have been detected.

Risk assessment of the microbial load of medicinal plants has become an important subject in the establishment of Modern Hazard Analysis and Critical Control Point (HACCP) schemes. Various guidelines such as WHO, British Herbal Pharmacopoeia (BHP), Indian Herbal Pharmacopoeia, European Pharmacopoeia have issued special guidance for assessing microbial contaminations of both raw as well as processed botanicals. All these guidelines provide specific limits for the contaminants (Table1). These limits give due consideration to the level of treatment given to the processing material. WHO Quality Control Methods for Medicinal Plant Materials mentions that the presence of aflatoxins can be hazardous to health if absorbed even in very small amounts. The document provides the procedure for

Table 1— Permissible limits of microbial contaminants

Microbial Analysis	WHO			BHP	
	Crude	Pretreated	Other for internal use	Pretreated with boiling water	Other herbs
Form of botanicals					
Total viable aerobic count	—	10 ⁷ /g	10 ⁵ /g	10 ⁷ /g	10 ⁵ /g
Total fungal count	10 ⁵ /g	10 ⁴ /g	10 ³ /g	10 ⁵ /g	10 ⁴ /g
Total Enterobacteriaceae	—	10 ⁴ /g	10 ³ /g	—	10 ³ /g
<i>E. coli</i>	10 ⁴ /g	10 ² /g	10/g	10 ² /g	Nil
<i>Salmonella typhi</i>	—	Nil	Nil	—	Nil

qualitative determination of aflatoxins B1, B2, G1 and G2 by TLC. It also gives the procedure for total viable count for bacteria and fungi, qualitative and quantitative determination of *Enterobacteriaceae* and certain other Gram-negative bacteria, qualitative tests for determination of specific organisms such as *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Salmonella* species. The Indian Herbal Pharmacopoeia (2002) recommends the WHO limits for microbial contamination. Very few published reports are available on nature and content of microbial load in Indian medicinal plants. There is need to generate own guidelines for limits and indicator organisms.

Microbial contamination of botanicals is influenced by environmental factors such as temperature, humidity, extent of rainfall during the pre-harvesting, harvesting, and post-harvesting periods, handling practices and storage conditions of crude and processed medicinal plant materials. This reflects the importance of indicator organisms and framing of limits for microbial contamination based on the existing environmental conditions in the country. Further, the microbial risk inherent to botanical may vary with regard to the different stages of the production line and processing factors largely determine the microbial quality of the final product. The application of hot water extraction (herbal infusion, herbal tea) usually compensates for microbiological contamination, since it can be expected that boiling water markedly reduces the viable counts by several log units and also inactivates possible pathogens. However, those drugs, which are subjected to cold-water extraction (herbal maceration), may host a considerable amount of microbes, and the extraction procedure carried out at ambient temperature usually enables microbial multiplication. In principle, most quality aspects of botanical drugs can be compared with those considered in food microbiology, since spices, herbs, tea, vegetables, cereals may exhibit similar

microbiological tendencies. However, unlike foods, botanicals contain specific compounds of particular pharmaceutical and medical relevance with dose-dependent properties, and are not consumed for a nutritive or relishing function. Moreover, the consumers of medicinal plants are people who undergo some form of therapeutic treatment. Therefore, toxicological factors and higher risk levels and hazard classes have to be considered³⁹. USFDA strategies to minimize mycotoxins in the food supply include establishing guidelines (e.g., action levels, guidance levels), monitoring the food supply, through formal compliance programs (domestic and import) and taking regulatory action against product that exceeds action levels, where action levels have been established³⁶.

Pesticide Residues

Medicinal plant materials are liable to contain pesticide residues, which accumulate from agricultural practices such as spraying, soil treatment, and administration of fumigants during storage. Although, the use of pesticides in the agricultural sector has greatly reduced the presence of insects, fungi, and moulds in the plants, prolonged or excessive usage of pesticides ultimately intoxicate the entire plant material causing several health hazards. WHO, therefore, recommends that every country producing medicinal plant materials (naturally grown or cultivated) should have at least one control laboratory capable of performing the determination of pesticides in accordance with the procedure specified in Quality Control Methods for Medicinal Plant Materials. The guidelines suggests intake of pesticide residue from medicinal plant materials should be less than 1 per cent of total intake from all sources, including food and drinking water.

Chromatography (mostly column and gas) has been recommended as the principal method for the determination of pesticide residues. In chromatography, the separations may not always be complete,

pesticides may decompose or metabolize, and many of the metabolic products may be unknown. As a result of limitations of the analytical techniques and incomplete knowledge of pesticide interaction with the environment, it is not possible to apply an integrated set of methods that will be satisfactory in all situations. WHO suggests that plant materials of unknown history should be tested for groups of compounds rather than individual pesticides and in case where the pesticide to which the plant material is exposed is known or can be identified by suitable means, an established method for determination of that particular pesticide should be employed. The European pharmacopoeia defines limits for plant drugs with respect to 34 specific pesticides under Part 1, V.4.6 Pesticide Residues (1995) and offers methods of analysis under Part 1, VIII.17 Tests for Pesticides (1995). Limits applying to other pesticides not specified in the V.4.6 text, and whose presence is suspected for any reason, are in accordance with European Community Directives 76/895 and 90/642. In UK legislation the latter limits are given in The Pesticides (Maximum residue Levels in Crops, Food and Feeding Stuff) Regulations 1994 (SI 1994 No. 1985). USP also provides limits for 34 different types of pesticide residues including organochlorides and organophosphorus⁵⁹.

The appropriate frequency of testing for pesticide residues in plant drugs should be determined on the basis of historical data for particular materials and the level of knowledge on their sources and pesticide treatments (if any)⁶⁰.

Heavy Metals

Heavy metals cause toxic effects. They include mainly lead, arsenic, cadmium and mercury, besides chromium, iron, copper, zinc, nickel, and tungsten. Some are essential nutrients in trace amounts (e.g. copper, iron, zinc) and some of which have relatively low toxicity (e.g. nickel, chromium)⁶¹. The British Pharmacopoeia uses the term 'Potentially Toxic Elements' rather than 'heavy metals'. Contamination of medicinal plant materials with arsenic and heavy metals can be attributed to many causes including environmental pollution and traces of pesticides.

Many herbal products contain undisclosed heavy metals⁶²⁻⁶⁴. WHO has proposed the maximum amounts of lead (10mg/kg) and cadmium (0.3mg/kg) based on Allowed Dietary Intake values. The methods for determining the content of arsenic, lead and cadmium have been given in WHO Quality Control

Methods for Medicinal Plant Materials. Testing for heavy metals and other potentially toxic elements by traditional methods can be problematic. Atomic absorption spectrophotometry is a more precise technique, enabling individual elements to be assayed. Considerable technical expertise and experience is required to obtain reproducible results. With regard to medicinal plants, the toxic elements which may be present in sufficient quantity to cause concern vary from plant to plant as their physiological uptake of these elements varies; amounts present also depend on the location, quality of soil or aerial pollution. A general screen on plant materials will give a guide as to what specific elements in which plants may be of concern. There have been sporadic reports of heavy metal toxicity following traditional medicine use, however, in most of the cases such toxicity is result of incorrect manufacturing process for which traditional systems are held responsible. Such incidences highlight urgent need to address quality control related issues of herbo-mineral preparations.

Radioactive Contamination

A certain amount of exposure to ionizing radiation cannot be avoided since there are many sources, including radionuclides occurring naturally in the ground and in atmosphere. Dangerous contamination may be the consequence of a nuclear accident⁶⁵. Amount of exposure to radiation depends on the intake of radionuclides and other variables such as age, metabolic kinetics, and the weight of the individual (also known as the dose conversion factor). Even at maximum observed levels of radioactive contamination with the more dangerous radionuclides, significant risk is associated only with consumption quantities of over 20 kg of plant material per year so that a risk to health is most unlikely to be encountered given the amount of medicinal plant materials that would need to be ingested. Additionally, the level of contamination might be reduced during the manufacturing process. Therefore, no limits for radioactive contamination are proposed²⁷.

Conclusions

Botanical medicine has become a topic of increasing global importance, with both medicinal and economical implications. The numerous reports of adverse effects and widespread sale of adulterated products and misleading health claims of these products demands proper regulations on botanical medicine⁶⁶. Quality of botanicals must be improved

greatly if botanical medicines are to assume a respected place in the contemporary health care system. Pharmacoepidemiological studies can be used as a tool for assessment of safety and efficacy of traditional systems like Ayurveda⁶⁷. Various regulatory authorities and industry are trying to address this issue of quality worldwide. In India, Council of Scientific & Industrial Research (CSIR), Central Council for Research in Ayurveda Siddha and Unani, (CCRAS), Indian Systems of Medicine and Homeopathy (ISM&H) and Indian Council of Medical Research (ICMR) are actively involved in validation of Ayurvedic and botanical medicines. Although, considerable progress has been made in characterizing botanical medicine there is need for global harmonization of the botanical quality and health claims. International Conference on Harmonization (ICH) has tried to harmonize technical requirements for registration of pharmaceuticals for human use by setting specific guidelines⁶⁸ These guidelines may be applicable to uplift quality of botanicals globally.

References

- 1 WHO policy perspectives on medicine, traditional medicine-growing needs and potential (World Health Organization, Geneva) May 2002.
- 2 Report of the inter regional workshop on intellectual property rights in the context of traditional medicine, Bangkok, Thailand, 2000.
- 3 Zhen G W & Jun R, Current status and future directions of traditional Chinese medicine, *Trends Pharmacol Sci*, **23** (2002) 347.
- 4 Bodekar G & Kronenberg F, A public health agenda for complimentary, alternative and traditional (indigenous) medicine, *Am J Publ Health*, **92** (2002) 1582-1591.
- 5 Singh J, Singh A K & Khanuja S P S, Medicinal Plants: India's opportunity, *Pharma Bio World*, **1** (2003) 59-66.
- 6 Patwardhan B, Chopra A & Vaidya A D B, Herbal remedies and the bias against Ayurveda, *Curr Sci*, **84** (2003) 1165-1166.
- 7 Straus S E, Herbal Medicines - What's in the bottle? *N Engl J Med*, **347** (2002) 1997-1998.
- 8 Drew A K and Myers S P, Safety issues in herbal medicine: Implications for the health professions, *Med J Aust*, **166** (1997) 538-541.
- 9 Bhutani K K, Strategies for R& D in natural products for the new millennium, *JPAS*, **2** (2000) 91-98.
- 10 Calixto J B, Efficacy, safety, quality control marketing and regulatory guidelines for herbal medicines (Phytotherapeutic agents), *Brazilian J of Med Biol Res*, **33** (2000) 179-189.
- 11 WHO, *General guidelines for methodologies on research and evaluation of traditional medicine*, (World Health Organization, Geneva) 2000, pp 1-73.
- 12 USFDA, *Draft guidance for Industry on Botanical drug products*, (U. S. Department of Health and Human services, Food and Drug Administration and Center of Drug Evaluation and Research) 2000, pp 1-22.
- 13 Indian Drugs and Cosmetics Act, 1940 and Rules 1945, in *Drugs and Cosmetics* (Akalan Publications, Delhi) Chapt I, 3.
- 14 *GMP for Indian systems of medicine and homeopathy*, (Department of Indian Systems of Medicine & Homeopathy) 2000 1-12.
- 15 *National policies on Indian systems of medicine and homeopathy*, (Department of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy) 2002, pp 1-18.
- 16 *Indian Pharmacopoeia*, Vol. I & II (Controller of publication, New Delhi) 1996.
- 17 Raina M K, Quality control of herbal and herbo-mineral formulations, *Ind J Nat Prods*, **19** (2003) 11-15.
- 18 *Indian Herbal pharmacopoeia*, (Indian drug manufacturers' association, Mumbai), 2002, pp 1-521.
- 19 Wo J, Thinking about the situation of research on GAP in China, *Proc First Joint Workshop on Quality Control and Standardization of Traditional Medicine- Indo- China experience* (January8-10, 2004) 16.
- 20 Starling S, China's new quality control, *Functional Foods and Nutraceuticals*, **3** (2003) 18.
- 21 *The Pharmacopoeia of People's Republic of China*, (Pharmacopoeial Commission of the ministry of Public Health, China) 2000.
- 22 Talalay P, The importance of using scientific principles in the development of medicinal agents from plants, *Acad Med*, **76** (2001) 238-247.
- 23 *EMA Guidance on herbal products*, (The European Agency for the Evaluation of Medicinal Products, London) 2001, pp 1-10.
- 24 Benzi G & Ceci A, Herbal medicines in European regulation, *Pharmacol Res*, **35** (1997) 355-362.
- 25 Ramsey C, A cure worth than the illness, *Public Policy Sources*, **55** (2002) 1-62.
- 26 Briggs D R, The regulation of herbal medicines in Australia, *Toxicology*, **181-182** (2002) 565-570.
- 27 WHO *Quality Control Guidelines for Medicinal plant materials*, (World Health Organization, Geneva) 1998, pp 1-111.
- 28 WHO *Guidelines on good agricultural and cultivation practices (GACP) for medicinal plants*, (World Health Organization, Geneva) 2003, pp 1-124.
- 29 Peter AG M & De Smet, Herbal remedies, *New Engl J Med*, **347** (2002) 2046-2056.
- 30 Kokate C K, Gokhale S B & Purohit A P, *Pharmacognosy*, 11th ed (Nirali Prakashan, Pune) 1999, pp 17-45.
- 31 Wallis T E, *Textbook of Pharmacognosy* 5th ed (CBS publication, New Delhi) 2002, pp 78-571.
- 32 Patwardhan B, A method of treating musculoskeletal disease and a novel composition there of, *US Pat* 5,494,668, (1996).
- 33 Evans W C, *Trease and Evans Pharmacognosy* 15th ed (W. B. Saunders), 2002, pp 102.
- 34 Laxmikumaran M S, Singh A, Negi M S & Srivastava P S, Assessment of genetic diversity of medicinal plants: Case study on *Withania somnifera*, Presented in Int Workshop on Biotechnol Interven for Dry land Agriculture: Opportunities and Constraints, 2002.

- 35 Joshi K, Chavan P, Warude D and Patwardhan B, Molecular markers in herbal drug technology, *Curr Sci*, **87** (2004) 159-165.
- 36 Nrayana D B A, Baba B & Katiyar C K, Herbal remedies: Through GMP/HACCCP techniques, *Eastern Pharmacist*, **9** (1997) 21-27.
- 37 Vijaya Kumar D & Raghavan K V, *Novel Chromatographic fingerprinting method for standardization of single medicines and formulations*, WO 0246739-EP2 0000991 991-263397CSIR G01N30-88 (Indian Institute of Chemical Technology, Hyderabad) 2002.
- 38 Frazier R A, *Capillary electrophoresis for food analysis-Method development* (The Royal Society of Chemistry, UK) 2000, pp 1-20.
- 39 *An exploration of current issues in botanical quality: A discussion paper*, (Natural Health Products Directorate, Canada) 2002, pp 1-32.
- 40 Wolf H T, Zundorf I, Winckler T, Bauer R & Dingermann T, Characterization of Echinacea and detection of possible adulterants by RAPD analysis, *Planta Med*, **65** (1999) 773-774.
- 41 Cheng K T, Tsay H S, Chen C F & Chou T W, Determination of components in a Chinese preparation "Yu-Ping-Feng San" by RAPD analysis, *Planta Med*, **64** (1998) 563-565.
- 42 Shaw P C & But P P, Adulteration of Panax species and their adulterants by random-primed polymerase reaction, *Planta Med*, **61** (1995) 649-642.
- 43 Lalita S K, DNA markers in plant improvement: An overview, *Biotech Adv*, **17** (1999) 143-182.
- 44 Raina M K, Quality control of herbal and herbo-mineral formulations, *Ind J Nat Prods*, **19** (2003) 11-15.
- 45 Dubey N K, Rajeshkumar & Tripathi P, Global Promotion of herbal medicine: India's opportunity, *Curr Sci*, **86** (2004) 37-41.
- 46 Chavan B L, Mohan A R, Kulkarni R D & Mitra S K, Bioassay for evaluation of hepatoprotective effect of Liv. 52, a polyherbal formulation on ethanol metabolism in chronic exposed rat, *Ind J Pharmacol*, **26** (1994) 117.
- 47 Kataria M & Singh L N, Hepatoprotective effect of Liv. 52 and kumariasava on CCl₄ induced hepatic damage in rats, *Ind J Exp Biol*, **35** (1997) 665.
- 48 Handa S S & Bhargava V V, Effect of BR-16A (mentat) on cognitive deficits in aluminum treated and aged rats, *Ind J Pharmacol*, **29** (1997) 258.
- 49 Wolfgang K, Erich C & Brigitte K, Microbial Contamination of Medicinal Plants-A Review, *Planta Med*, **68** (2002) 5-15.
- 50 Molecular biology and natural toxins. *Food and Drug Administration Compliance Program Guidance Manual*, 7307.001, Ch.7, p. 74-77.
- 51 Cirillo T, Ritieni A, Galvano F & Amodio C R, Natural occurrence of deoxynivalenol and fumonisins B1 and B2 in Italian marketed foodstuffs, *Food Addit Contam*, **20** (2003) 566-571.
- 52 Halt M, Moulds and mycotoxins in herb tea and medicinal plants, *J Epidemiol*, **14**(3) (1998) 269-274.
- 53 Abeywickrama K & Bean G A, Cytotoxicity of Fusarium species mycotoxins and culture filtrates of Fusarium species isolated from the medicinal plant Tribulus terrestris to mammalian cells, *Mycopathologia*, **120**(3) (1992) 189-193.
- 54 Aziz H N, Youssef Y A, El-Fouly M Z & Moussa L A, Contamination of some common medicinal plant samples and spices by fungi and their mycotoxins, *Bot Bull Acad Sin*, **39**(4) (1998) 278-285.
- 55 Blunden. G, Roch O G, Rogers D J, Coker R D, Bradburn N & John A E, Mycotoxins in food, *Med Lab Sci*, **48**(4) (1991) 271-282.
- 56 Vrabcheva T M, Mycotoxins in spices, *Vopr Pitan*, **69**(6) 2000 40-43.
- 57 Hitokoto H, Fungal contamination and mycotoxin detection of powdered herbal drugs, *Appl Environ Micro*, **36** (1978) 252-256.
- 58 Kumar S, Occurrence of aflatoxin in some liver curative herbal medicines, *Letters in Applied Micro*, **17** (1993) 112-114.
- 59 *The United States Pharmacopoeia and National Formulary* (USP24& NF19), (The United States Pharmacopoeial Convention Inc.) 2000, 1888-1889.
- 60 *British Herbal Pharmacopoeia*, (British Herbal Medicine Association, London) 1996 1-16.
- 61 Borkowski B, Contamination of plants by heavy metals, *Farm Pol*, **50**(15) (1994) 697-710.
- 62 Ernst E, Heavy metals in traditional Indian remedies, *Eur J Clin Pharmacol*, **57** (2002) 891-896.
- 63 Ko R J, Adulterants in Asian patent medicines, *N Engl J Med*, **339** (12) (1998) 847.
- 64 Au A M, Screening methods for drugs and heavy metals in Chinese patent medicines, *Bull Environ Contam Toxicol*, **65** (2000) 112-119.
- 65 Chan K, Some aspects of toxic contaminants in herbal medicine, *Chemosphere*, **52** (2003) 1361-1371.
- 66 Marcus D M and Grollman A P, Botanical Medicines- The Need for new regulations, *New Engl J Med*, **347**(25) (2002) 2073-2076.
- 67 Vaidya R A, Vaidya A D B, Patwardhan B Tillu G & Rao Y, Ayurvedic pharmacoepidemiology: A proposed new discipline, *JAPI*, **51** (2003) 528.
- 68 Harmonization of quality requirements for the registration of medicines, *The Pharmaceutical journal*, (Meetings and Conferences, Royal Pharmaceutical Society, London), (July 2001) 1-2