Asian Journal of Plant Sciences

ISSN 1682-3974

science alert

ANSInet
an open access publisher
http://ansinet.com

Asian Journal of Plant Sciences 13 (1): 1-7, 2014
ISSN 1682-3974 / DOI: 10.3923/ajps.2014.1.7

Relevance of chemical Standardization and Innocuousness in the Process of Development of Herbal Medicines: A Review

[1]Rayn Clarenc Aarland, [2]Fernando Rivera-Cabrera, [2]Laura J. Pérez-Flores,
[2]Fernando Díaz de Léon Sánchez and [3]José Alberto Mendoza-Espinoza
[1]Laboratorio de Fisiología, Bioquímica y Biología Molecular de Plantas,
Programa de Doctorado en Biología Experimental, UAM, Iztapalapa
[2]Laboratorio de Fisiología, Biología Molecular de Plantas,
Depto. Ciencias de la Salud DCBS, UAM, Iztapalapa
[3]Cátedra Divisional Amelia Samano Bishop, Universidad Autónoma Metropolitana Iztapalapa,
Colegio de Ciencias y Humanidades, Plantel Casa Libertad,
Universidad Autónoma de la Ciudad de México, México

Abstract: Traditional medicine based on medicinal plants has survived the passing of time, coming from indigenous communities to the urban environment, where it has lost the controls established by traditional medicine techniques. The present review proposes some strategies to regulate and standardize this kind of treatments in order to make its use safe in a global market.

Key words: Traditional medicine, Standardization, Phytochemistry, Phytomedicine

INTRODUCTION

Since, the beginning of mankind, human has established a tight relationship with plants in order to fulfill its basic needs such as home, food and health. Traditional herbal medicine, conceived as a set of techniques for disease prevention and treatment, arises from this tight relationship (Koehn and Carter, 2005; Jones *et al*., 2006). These strategies for healthcare have survived the passing of time and some plants with medicinal use has been introduced in the market without any regulation and can be found in different presentations such as capsules and preparations for infusion among others. It is important to mention that the plants have been used as biological material in the allopathic medicine (Kinghorn, 2002; Cragg *et al*., 1997).

Interest in plants with therapeutic properties has increased in recent years (Breevort, 1996; Blumenthal, 1999); this can be confirmed by the increase in TV commercials offering herbal products with no medical guarantee or checking the sales of medicinal plants in local markets of Mexico City (Mercado de Sonora or Mercado de Jamaica). However, introduction of this kind of products for human consumption without the adequate quality controls may cause serious health problems. Among the most documented cases, there are interactions with prescribed medications and patients that abandon their allopathic treatment for using these herbal substances aggravating their health. Nevertheless, there are some alternatives and strategies that allow control and standardization of this kind of products to guarantee its innocuousness and its safe use as herbal drugs.

These quality controls are based on two basic aspects; control of the material processing and the good agricultural practices that guarantee innocuousness of the product and control of chemical and pharmacological characterization, a very important but less discussed topic.

In response to the described problem, the present review goes through some concepts related with the use of herbal drugs and some alternatives for its standardization.

PHYTOMEDICINES AND ITS REGULATION WORLDWIDE

A practical definition comes from the Greek root of the word "Phytomedicine", "Phyto" means plant or vegetable. Therefore, in general terms, Phytomedicines are drugs that contain as active principle exclusively plants, parts of plants, ingredients or preparations obtained from them. In general, this kind of products are the result of the accumulated experience in the practice of traditional medicine during hundreds of years (Kamboj, 2000; Yadav and Dixit, 2008).

Corresponding Author: José Alberto Mendoza-Espinoza, Cátedra Divisional Amelia Samano Bishop, Universidad Autónoma Metropolitana Iztapalapa, Colegio de Ciencias y Humanidades, Plantel Casa Libertad, Universidad Autónoma de la Ciudad de México, México

According to the definition of the World Health Organization (WHO), Phytomedicines (herbal medicines) has to contain raw or processed plant material as the active ingredient and they may also contain organic or aqueous solvents as excipients and preservatives. It is very common that the active ingredients, responsible of the therapeutic activity of these preparations has not been identified (Akerele, 1993; WHO, 1993, 1998; Calixto, 2000).

The WHO has adapted some terms related to herbal medicine and defined them. Here, some of them are described.

Herbs: Raw plant material such as leaves, flowers, fruit, seed, stems, roots, rhizomes or other plant parts which may be entire, fragmented or powdered.

Herbal material: Fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs.

Herbal preparations: They are the finished herbal products and may include ground or powdered herbal materials or extracts, tinctures and oils. They are produced by physical processes (extraction, fractionation, purification, concentration, among others). They also include preparations made by soaking or heating herbal materials in alcohol, honey or in other materials and biological processes such as fermentations (WHO, 2000).

In regards to the consumption of herbal products today, there are herbal materials from China, Europe, South America and Africa in the global market. Some of the herbal products with medicinal activity with a higher demand are ginseng (*Panax ginseng*), moringa tree (*Moringa oleifera*), valerian (*Valeriana officinalis*), chamomile (*Matricaria recutita*), sand plantain (*Plantago psyllium*), among others. However, it is important to indicate that there is a lack of control and regulation that guarantee the harmlessness of the product. This is in part due to the lack of information about the cultivation practices and the little or lacking communication between the national regulatory agencies from importing and exporting countries of these materials. For these reasons, some European countries have begun to work in the regulation of their national markets, however, there are still a number of places around the world where there is not any kind of concern for creating a separate category for Phytomedicines and therefore, these products are still commercialized as dietary supplements (Prieto, 2007).

There are currently several regulatory guidelines for herbal medicines at regional and sub-regional levels in the world, however, regulatory policies for these products varies considerably across them (Zhang, 2006).

In this sense, WHO recognized the value of traditional medicine as a source of healthcare and biodiversity in 1975, there have been financial support for research groups as well as for projects to study and support its regulated usage (WHO, 2001, 2005), monographs drafting of quality control (WHO, 1992, 1998), good agricultural practices (WHO, 2003), good manufacturing practices, regulations to assure the safety of the herbal products (WHO, 1993, 2004a) and of strategies to its correct use in the primary health care systems (WHO, 2004b; Zhang, 2006; Prieto, 2007). However, the development of international regulations to guarantee the manufacturing of Phytomedicines based on the innocuousness and chemical standardization of the finished product is still missing. This review presents some of the current regulations that could serve as the base to develop an initiative for an international regulatory system.

IMPORTANCE OF PHYTOMEDICINES HISTORY AND CURRENT PERSPECTIVES

Even though plants have long been used in traditional medicine in several countries, their regulation and standardization as Phytomedicines is relatively recent as shown in Table 1 (Choudhary and Singh, 2011).

STANDARDIZATION PROCESS FOR HERBAL MEDICINES DEVELOPMENT

Definition of standardization: Standardization is a system to make sure that every package of medicine being sold has the correct amount of the active principles that will induce its therapeutic effect (Chaudhury, 1992). In other words, this system must assure the quantity and quality of the ingredients and its therapeutic effect in each dose (Zafar *et al*., 2005). Willard (1996) adds that standardization should involve compiling complete information of the plants that have been used including kind of plant tissue (root, leaf and stem), harvesting season, developmental stage, appearance, flavor, odor, method of drying, storage conditions, manufacturing process and the chemical content (Garg *et al*., 2012). Vaidya and Devasagayam (2007) claimed that herbal medicines cannot be scientifically backed up if they have not been characterized and validated to assure reproducibility in the manufacturing process of the product.

In 1992, the WHO defined standardization and quality control as the process involved in the physicochemical evaluation of the crude drug covering aspects such as selection and handling of the crude material, safety,

Table 1: Relevant events related to the standardization of Phytomedicines such as the establishment of government policies and quality control

Years	Event
1983	The first health national policy determines that India is the richest source of herbal products and that they should be standardized
1990	Law 25/1990. The King of Spain recognizes herbal medicine and considers it in the same terms as allopathic medicine
1995	In March, a separate department currently known as AYUSH (Ayurveda, Unani, Siddha, Homeopathy) for Indian Medicine and Homeopathy systems was established in order to promote the indigenous systems
1996	The WHO recommends an agency of medicines control for regulating the quality profile and safety of herbal products
1999	The WHO presents a detailed protocol for standardization of phytomedicines that contain only one active ingredient
2002	New analytical approaches like Herboprint use three-dimensional HPLC and attempt to develop tools for activity-based standardization of herbal medicines
2003	Guidelines on good agricultural and collection practices for medicinal plants. WHO, Geneva, Switzerland
2004	WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems
2005	National policy on traditional medicine and regulation of herbal medicines. Report of a WHO global survey
2007	Guidelines for assessing quality of herbal medicines with reference to contaminants and residues. WHO, Geneva, Suiza
2009	The United States Pharmacopeia. Rockville, USA. Meeting of the United States Pharmacopeia
2011	Preliminary guidelines for the industry, dietary supplements, notifications of new dietary ingredients and related topics proposed by the Catalonian Food Safety Agency
2012	Mexican Official Standard NOM-248-SSA1-2011 for good manufacturing practices for establishments that make herbal remedies
2013	Mexican Official Standard for labeling of herbal products (NOM-072-SSA1-2012) which main objective is to guarantee its contents
2013	United Kingdom Medicines and Healthcare products Regulatory Agency announces that from April 30th, 2014, all herbal medicines will require a license to be sold

Table 2: General parameters to evaluate for standardization of herbal medicines

Parameters	Descnption
General	Geographic location
	Harvesting season
	Harvesting process
	Processing
Description identity	Macroscopic
	Microscopic
	Chemical
	Chemical fingerprint
Purity	Foreign matter
	Ash (sulfated)
	Extractable matter content
	Moisture content
Assays	Biomarkers (with known therapeutic activity)
	Other markers (with unknown therapeutic activity)
	HPLC/GC/TLC
Contaminants	Pesticides
	Heavy metals
	Aflatoxins
	Microorganisms
	Radioactivity

efficacy and stability assessment of the finished product, documentation of safety and risk based on experience, provision of product information for the consumer and product promotion. The main aspects that are taken in account are:

- **Macro and microscopic examination:** For identification of the right variety and search of adulterants
- **Foreign organic matter:** Remove matter other than the source plant to get the drug in pure form
- **Ash values:** Criteria to judge the identity and purity of the crude drug. Total ash, sulfated ash, water soluble ash and acid insoluble ash, etc
- **Moisture content:** This parameter helps to reduce errors in herbal material weight estimation. Low moisture content implies better stability of the product preventing its degradation
- **Extractive values:** Indicate the chemical constituents extractable with different solvents
- **Crude fiber:** To determine excessive woody material, criteria used to determine purity
- **Qualitative chemical evaluation:** It covers identification and characterization of the crude drug with respect to its Phytochemical constituents. It uses different analytical techniques to detect and isolate active constituents. It involves botanical identification, extraction with the suitable solvents, purification and characterization of the active constituents of pharmaceutical importance
- **Chromatographic examination:** It includes identification of the crude drug based on use of major chemical constituents as marker
- **Quantitative Chemical Evaluation:** To estimate the amount of the major class of constituents
- **Toxicity studies:** Help to determine pesticide residues, potentially toxic elements, include safety studies in animals and microbiological assays to establish the absence or presence of potentially harmful microorganisms

Yadav and Dixit (2008) arranged these points in groups to give an overview of the parameters that should be evaluated during the standardization process (Table 2). These authors also suggest that standardization should check the entire manufacturing process that can be divided in two parts; from seedling germination to harvesting and from herbal medicine manufacturing to its clinical use.

It is important to note that therapeutic activity of an herbal medicine depends on its Phytochemical constituents. Therefore, the development of authentic analytical methods for obtaining the chemical composition profile including quantitative analysis of marker bioactive

compounds and other important constituents represents one of the main challenges for scientists. Thus, standardization is a very important step for establishing a consistent biological activity and chemical profile (Patra *et al*., 2010; Kunle *et al*., 2012).

Methods of standardization: The WHO highlights the importance of the usage of qualitative and quantitative methods for samples characterization, as well as the quantification of biomarkers, chemical markers and chemical fingerprints (WHO, 1996a, b). Yadav and Dixit (2008) have previously mentioned that if the active principles are known, it is the most logical to quantify these compounds.

Methods of standardization must take in account all aspects that contribute to the quality of the herbal medicine as correct identity of the sample, sensory evaluation, pharmacognostic evaluation, volatile matter, quantitative evaluation of the main chemical compounds, Phytochemical evaluation, tests to determine the presence of xenobiotics, microbial load tests, toxicity tests and biological activity. Of these, the Phytochemical profile has special significance since it has a direct influence on the activity of the herbal medicine. The chemical fingerprint serves as a guideline for the Phytochemical profile of the medicine to guarantee there are not adulterations of the plant material, while quantification of marker compounds serve as an additional parameter for assessing the therapeutic quality of the sample (Nikam *et al*., 2012).

Phytochemical standardization comprises the generation of all possible information regarding to the chemical compounds present in the herbal medicine. Therefore, Phytochemical evaluation for standardization must include the following; preliminary tests to determine the presence of different chemical groups, quantification of the chemical groups of interest (total alkaloids, total phenolics, etc.) and establishment of chemical fingerprints profiles, multiple chemical fingerprint profiles based on markers and quantification of chemical constituents associated to the therapeutic activity (Calixto, 2000; Nikam *et al*., 2012).

Problems associated to the standardization process: The main problems that herbal drugs standardization and regulatory systems face are the lack of scientific information and effective control mechanisms. Another problem is the lack of education, training and specialization of the staff involved in producing, distributing, prescribing and following up the usage of herbal drugs (Zhang, 2006).

Another part of the problem is the complex composition of the plant tissues (stem, root or the entire plant) or plant components (secretions, exudates such as suberins, latex, etc.) that are used to manufacture the herbal drugs. On another hand, standardization based on only one presumed active component not always work. There are very few cases where therapeutic activity of an herbal drug depends on only one single compound. In general, therapeutic activity is the result of the combination of several active components and some inert accompanying substances. Even though, these substances do not directly affect the therapeutic mechanisms, it is reasonable to use the complex mixture of components of a medicinal plant since these inert components may affect bioavailability and/or excretion of the active component. Furthermore, these inert components might also stabilize the active components and/or decrease secondary effects. Other factors that may affect the quality of herbal products and therefore, also cause problems for herbal drugs standardization systems are as mentioned earlier, harvesting season and methods, drying and storage conditions as well as processing (Kunle *et al*., 2012).

Additional useful analytical methods in the standardization process: Some analytical methods useful for herbal drugs standardization are described below:

- Thin Layer Chromatography (TLC) is a simple widely used chromatographic technique that allows rapid analysis of extracts and provides qualitative and semi-quantitative information of the analyzed compounds (Ong, 2002; Liang *et al*., 2004)
- HPTLC is a widely used technique in the pharmaceutical industry for detecting adulterants in herbal products. It helps with identification of pesticides and mycotoxins (Soni and Naved, 2010)
- Preparative and analytical HPLC are techniques widely used in the pharmaceutical industry for isolating and purifying herbal compounds (Anyakora *et al*., 2008). The important parameters to be considered are resolution, sensitivity and short time of analysis (Rao and Anna, 2009)
- Liquid Chromatography-Mass Spectroscopy (LC-MS) has become an important method in several stages of drug development (Lee and Kerns, 1999). Recent advances include ionization techniques that offer advantages of high detection sensitivity and specificity (Bhutani, 2000)
- Liquid Chromatography-Nuclear Magnetic Resonance (LC-NMR) improves speed and sensitivity of detection and has been very useful in the areas of pharmacokinetics, toxicity studies and drug metabolism. The combination of the chromatographic separation technique and the NMR

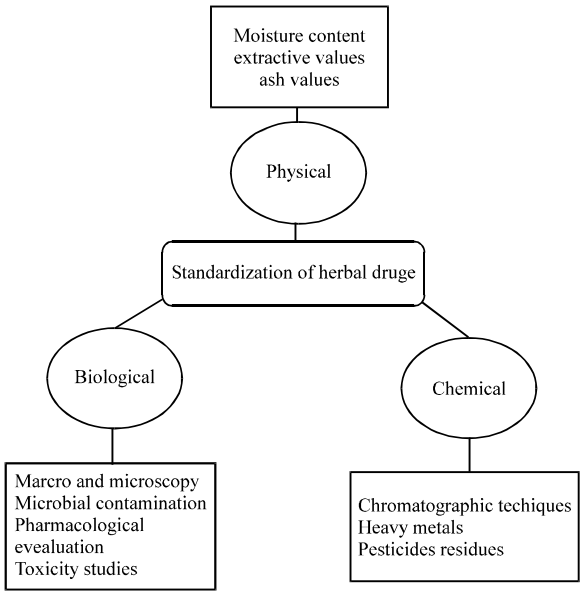

Fig. 1: Schematic representation of the steps to follow for herbal drugs standardization

spectroscopy is one of the fastest and most powerful methods for separation and structural elucidation of unknown compounds and mixtures (Patil and Rajani, 2010)

- Gas Chromatography (GC) and GC-MS are highly accepted and recommended methods for the analysis of volatile compounds due to its high sensitivity, stability and efficiency (Guo *et al*., 2006; Teo *et al*., 2008)
- DNA fingerprinting, DNA analysis has been proven as an important tool for the standardization of herbal drugs. It is a useful method for identification of indistinguishable Phytochemical compounds. This method allows identification of biological material used to prepare herbal drugs as well as the presence of adulterants of other plants. The advantage of this method is that the DNA fingerprint will be the same independently of the part of the plant being used. On the contrary, the Phytochemical content varies depending on the part of the plant, the physiology as well as the soil and climate conditions

Choudhary and Sekhon (2011) indicated the steps to follow the process of standardization of herbal drugs in Fig. 1. Figure 1 is a general representation that covers the main stages found in the literature for the standardization process.

CONTRIBUTIONS OF OUR RESEARCH GROUP

Mexico is a country with a strong practice of traditional medicine with an incalculable historic legacy. However, there are not appropriate govern policies that support herbal drugs development because the existing regulation does not guarantee its efficacy. For this reason, academic groups of public universities such Universidad Autónoma Metropolitana (UAM) and Universidad Autónoma de la Ciudad de México (UACM) are carrying out studies to achieve Phytochemical and pharmacological characterization of some plants that are used for diverse treatments (some of them listed in Table 3). Chemical and pharmacological profiles of these plants have been obtained and there is work in progress to identify the species by molecular methods.

Table 3: Plants employed for treating diabetes in Mexico

Common name using in the sonora marker, México D.F	Scientific name
Cáscara sagrada	*Rhamnus purshiana*
Chaparro amargo	*Castela erecta* ssp.
Gobernadora	*Larrea tridentata* (dc) *cav*
Guarumbo	*Cecropia obtusifolia bertol*
Guazima	*Ulmifolia lam*
Prodigiosa	*Bryophyllum pinnatum*
Nopal root	*Opuntia ficus*
Zopilote seed	*Swietenia humilis*
Tronadora	*Tecoma stans*
Wereke	*Ibervillea sonorae*

The objective of our study is to generate protocols for standardization of herbal treatments with a strong focus on material identification which, in most cases, is made using traditional protocols based on taxonomic keys established by flower and fruit characteristics. However, the majority of plant material is collected without flower, for this reason, it emerges the proposal to add identification by molecular biology tools such as amplification of conserved DNA regions by Polymerase Chain Reaction (PCR) to the protocol represented in Fig. 1 and correlate the obtained information to the described taxonomic classification. We also suggest the utilization of pharmacological models that allow assessing herbal drug activity behavior over time in order to establish expiration dates as it is done for allopathic drugs. This proposal may be applied to all herbal extracts with the idea to be part of the generation of international policies for regulation of this kind of products and as a consequence some of them may become safe treatment alternatives for some diseases and not only dietary supplements.

CONCLUSION

In order to develop reliable and high quality herbal drugs, there is a need for generation of standardization processes. Herbal drugs are made from plants, that in most cases, have many contaminants in different forms including fungi, bacteria, pesticides and even heavy metals and industrial residues. Standardization should be a uniform international process to avoid problems between countries importing and exporting these

products. WHO is actively participating in the regulation of herbal medicines but for this process to be successful, the participation and support of all countries is necessary. Traditional medicine is accepted in many parts of the world and to move forward on its regulation all specialists should participate; from people with knowledge on traditional medicine to the big pharmaceutical companies and scientific researchers. It is in this context that these two study groups from UAM and UACM are working.

ACKNOWLEDGMENTS

This study was partially financed by Universidad Autónoma Metropolitana-Iztapalapa, Universidad Autónoma de la Ciudad de México and PTC-PROMEP (José Alberto Mendoza Espinoza). We also thank CONACYT (No. 248821) for their financial support to Rayn Clarenc Aarland during his Ph.D. Studies (PNPC 001482 Experimental Biology Program). This study is part of R. Clarenc Aarland PhD dissertation.

REFERENCES

Akerele, O., 1993. Summary of WHO guidelines for the assessment of herbal medicines. HerbalGram, 28: 13-19.

Anyakora, C., I. Afolami, T. Ehianeta and F. Onwumere, 2008. HPLC analysis of nicotinamide, pyridoxine, riboflavin and thiamin in some selected food products in Nigeria. Afr. J. Pharm. Pharmacol., 2: 29-36.

Bhutani, K.K., 2000. Finger-printing of Ayurvedic drugs. Eastern Pharm., 43: 21-28.

Blumenthal, M., 1999. Harvard study estimates consumers spend $5.1 billion on herbal products? HerbalGram, 45: 68-74.

Breevort, P., 1996. The US botanical market: An overview. HerbalGram, 36: 49-57.

Calixto, J.B., 2000. Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicine (Phytotherapeutic agents). Braz. J. Med. Biol. Res., 33: 179-189.

Chaudhury, R.R., 1992. Herbal medicine for human health. Regional Publication, SEARO, No. 20, World Health Organization, Regional Office for South-East Asia, New Delhi, India, pp: 51-57.

Choudhary, N. and B.S. Sekhon, 2011. An overview of advances in the standardization of herbal drugs. J. Pharm. Educ. Res., 2: 55-70.

Cragg, G.M., D.J. Newman and K.M. Snader, 1997. Natural products in drug discovery and development. J. Nat. Prod., 60: 52-60.

Garg, V., V.J. Dhar, A. Sharma and R. Dutt, 2012. Facts about standardization of herbal medicine: A review. J. Chin. Integr. Med., 10: 1077-1083.

Guo, F.Q., L.F. Huang, S.Y. Zhou, T.M. Zhang and Y.Z. Liang, 2006. Comparison of the volatile compounds of *Atractylodes* medicinal plants by headspace solid-phase microextraction-gas chromatography-mass spectrometry. Analytica Chimica Acta, 570: 73-78.

Jones, W.P., Y.W. Chin and A.D. Kinghorn, 2006. The role of pharmacognosy in modern medicine and pharmacy. Curr. Drug Targets, 7: 247-264.

Kamboj, V.P., 2000. Herbal medicine. Curr. Sci., 78: 35-51.

Kinghorn, A.D., 2002. The role of pharmacognosy in modern medicine. Expert Opin. Pharm., 3: 77-79.

Koehn, F.E. and G.T. Carter, 2005. The evolving role of natural products in drug discovery. Nat. Rev. Drug Discov., 4: 206-220.

Kunle, O.F., H.O. Egharevba and P.O. Ahmadu, 2012. Standardization of herbal medicines: A review. Int. J. Biodivers. Conserv., 4: 101-112.

Lee, M.S. and E.H. Kerns, 1999. LC/MS applications in drug development. Mass Spectrom. Rev., 18: 187-279.

Liang, Y.Z., P. Xie and K. Chan, 2004. Quality control of herbal medicines. J. Chromatogr. B, 812: 53-70.

Nikam, P.H., J. Kareparamban, A. Jadhav and V. Kadam, 2012. Future trends in standardization of herbal drugs. J. Applied Pharm. Sci., 2: 38-44.

Ong, E.S., 2002. Chemical assay of glycyrrhizin in medicinal plants by Pressurized Liquid Extraction (PLE) with Capillary Zone Electrophoresis (CZE). J. Sep. Sci., 25: 825-831.

Patil, P.S. and S. Rajani, 2010. An advancement of analytical techniques in herbal research. J. Adv. Sci. Res., 1: 8-14.

Patra, K.C., S.K. Pareta, R.K. Harwansh and K.J. Kumar, 2010. Traditional approaches towards standardization of herbal medicines: A review. JPST, 2: 372-379.

Prieto, J., 2007. Special issue on regulation of phytomedicines. Blacpma, 4: 92-101.

Rao, U. and N. Anna, 2009. Stability-indicating HPLC method for the determination of efavirenz in bulk drug and in pharmaceutical dosage form. Afr. J. Pharm. Pharmacol., 3: 643-650.

Soni, K. and T. Naved, 2010. HPTLC: Its applications in herbal drug industry. Pharm. Rev., 4: 112-117.

Teo, C.C., S.N. Tan, J.W.H. Yong, C.S. Hewb and E.S. Ong, 2008. Evaluation of the extraction efficiency of thermally labile bioactive compounds in *Gastrodia elata* Blume by pressurized hot water extraction and microwave assisted extraction. J. Chromatogr. A, 1182: 34-40.

Vaidya, A.D.B. and T.P.A. Devasagayam, 2007. Current status of herbal drugs in India: An overview. J. Clin. Biochem. Nutr., 41: 1-11.

WHO, 1992. Quality Control Methods for Medicinal Plant Materials. World Health Organisation, Geneva, Switzerland.

WHO, 1993. Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines. World Health Organization, Geneva, Switzerland, ISBN-13: 9789290611103, Pages: 86.

WHO, 1996a. Quality Assurance of Pharmaceuticals: A Compendum of Guidelines and Related Materials, Good Manufacturing Practices and Inspection. World Health Organization (WHO), Geneva, Switzerland.

WHO, 1996b. Guidelines for the assessment of herbal medicines. WHO Technical Report Series, World Health Organization (WHO), Geneva, Switzerland.

WHO, 1998. Regulatory situation of herbal medicines: A worldwide review. World Health Organization (WHO), Geneva, Switzerland, pp: 1-43.

WHO, 2000. General guidelines for methodologies on research and evaluation on traditional medicine. WHO/EMD/ TRM/2001.1, Geneva, Switzerland, pp: 1-70

WHO, 2001. Legal status of traditional medicine and complementary/alternative medicine: A worldwide review. WHO/EDM/TRM/2001.2. Geneva, Switzerland.

WHO, 2003. [WHO guidelines on Good Agricultural and Collection Practices (GACP) for medicinal plants]. World Health Organization, Geneva. http://apps.who.int/medicinedocs/en/d/Js4928e/.

WHO, 2004a. WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems. World Health Organization, Geneva, Switzerland, ISBN-13: 9789241592215, Pages: 18.

WHO, 2004b. WHO guidelines on developing consumer information on proper use of traditional complementary and alternative medicine. World Health Organization (WHO), Geneva, Switzerland.

WHO, 2005. Summary report of the global survey on national policy on traditional medicine and regulation of herbal medicines. World Health Organization (WHO), Geneva, Switzerland.

Willard, T., 1996. Edible and Medicinal Plants of the Rocky Mountains. Wild Rose College of Natural Healing, Calgary.

Yadav, N.P. and V.K. Dixit, 2008. Recent approaches in herbal drug standardization. Int. J. Integr. Biol., 2: 195-203.

Zafar, R., R. Panwar and P.S. Bhanu, 2005. Herbal drug standardization. Indian Pharm., 4: 21-25.

Zhang, X., 2006. International regulatory cooperation on proper use of traditional medicine. Proceedings of the International Regulatory Cooperation on Regulation of Herbal Medicines, March 29, 2006, Brazil.