10

Quality Control for the Safety of Natural Products

Tadele Mekuriya Yadesa[1,2], Patrick Engeu Ogwang[1,2], and Casim Umba Tolo[2,3]

[1] *Department of Pharmacy, Faculty of Medicine Mbarara University of Science and Technology, Mbarara, Uganda*
[2] *Pharmbiotechnology and Traditional Medicine Center (PHARMBIOTRAC), Mbarara University of Science and Technology, Mbarara, Uganda*
[3] *Department of Biology, Faculty of Science Mbarara University of Science and Technology, Mbarara, Uganda*

CONTENTS

Poisonous Plants and Phytochemicals in Drug Discovery, First Edition.
Edited by Andrew G. Mtewa, Chukwuebuka Egbuna, and G.M. Narasimha Rao.

10.1 Introduction

The World Health Organization (WHO) has defined a medicinal plant as any plant in which one or more of its parts consists of substances that are used for the synthesis of beneficial drugs [1]. These plants need to be studied to better comprehend their characteristics, safety, and efficacy [2]. They comprise biologically active chemicals, including saponins, tannins, essential oil flavonoids, and alkaloids, among others [3], which all serve remedial purposes. It is estimated that 30 000–70 000 medicinal plants exist worldwide, most of which have not been systematically investigated [4]. Generally, herbal products are safer than conventional medications. While monitoring thousands of people who used ginkgo, St. John's wort, and kava in Europe, a study revealed that mild adverse effects were encountered in fewer than 3% of users [5]. Controlled studies of other common European herbal medicines, such as *Echinacea*, horse chestnut, saw palmetto, and valerian, have shown rare and mild side effects, generally similar to those seen in placebo groups [6–9]. The relative scarcity of severe adverse effects from herbal medicinal products most likely reflects a combination of factors that set them apart from conventional drugs, including weaker and less potent pharmacological activity, less consistent usage, and a poorly established mechanism for distinguishing and reporting adverse outcomes.

Accurate authentication of natural products including those from medicinal plants is crucial, as mistakenly identified species or varieties are either remedially less effective or not active at all, or may even contain poisonous ingredients [10]. The methods of classical botany for plant identification have latterly been accompanied by numerous DNA-based technologies, including random amplification of polymorphic DNA, restriction fragment length polymorphism, the amplification–refractory mutation system, cleaved amplified polymorphic region, amplified fragment length polymorphism, DNA amplification fingerprinting, inter-sample sequence repeat, simple sequence repeat, hybridization, and microarrays [11]. Apart from correct identification of plants, establishing their safety is another topic of interest. Although herbal products are often promoted to the public as "natural" and totally "safe" alternatives to conventional medicines, many are possibly toxic [12].

In 1993, the US Food and Drug Administration (FDA) proposed that those herbal medicines and other nutritional supplements that were not already well controlled as drugs should undergo stringent marketing regulations. Strong opposition by consumer groups and the supplement industry led to a concession passed by Congress in 1994, called the Dietary Supplement Health and Education Act (DSHEA), which classified herbal medicines (along with vitamins, minerals, amino acids, enzymes, etc.) as "dietary supplements." Moreover, herbal medicines and other dietary supplements do not have to be approved by the FDA prior to marketing [13]. In European countries, however, herbal medicines are more strictly regulated. In Germany, where most of the Western world's scientific

botanical research is conducted, herbal medicines are well regulated and available as over-the-counter and prescription drugs [14].

10.2 Quality Assurance of Herbal Products

Quality control and standardization of herbal medicines is carried out by means of several steps. However, the source and quality of raw materials contribute a key role in assuring the quality and stability of herbal medicinal products. Other factors related to growth conditions, collection method, and processing technique of the medicinal plants – such as the use of fresh plants; temperature; light exposure; water availability; nutrients; period and time of collection; method of collecting, drying, packing, storage, and transportation of the raw material; age and part of the plant collected, etc. – can significantly affect the quality and, consequently, the healing value of herbal medicines.

Some plant ingredients are heat labile; therefore, the plants containing these ingredients have to be dried at low temperatures. Moreover, other active chemicals may be destroyed by enzymatic processes that continue for some time after plant collection. This could explain why the composition of medicinal products from plants is quite variable. Thus, proper quality control and standardization of raw material and herbal preparations themselves should be carried out stringently. In addition, other issues such as the method of extraction and contamination with heavy metals, microorganisms, pesticides, etc. can interfere with the safety, quality, and efficacy of these products. Current technological advances in the purification, isolation, and structural elucidation of naturally occurring substances has enabled appropriate methods to be established for the analysis of the quality of herbal preparations as well as the process of standardization. This, in turn, affects the possible homogeneity and consistency of the plant extract and ultimately the herbal medicinal product. Among others, thin layer chromatography, gas chromatography, high-performance liquid chromatography, mass spectrometry, infrared spectrometry, ultraviolet/visible spectrometry, etc., used alone or in combination, can be effectively used to standardize and control the quality of both the raw material and the finished herbal medicine [15].

As herbs are increasingly packaged and promoted to compete with pharmaceutical drugs, consumers and healthcare providers are anticipating medicinal products that meet equivalent quality standards. In contrast to pure pharmaceutical preparations, most herbal medicinal products have few generic equivalents. Herbal products from different manufacturers vary considerably because it is virtually impossible to control all the variables that affect a plant's chemical composition. Natural conditions, such as sunlight and rainfall, as well as manufacturing procedures, such as selecting, drying, purifying, extracting, and storing herbs, can result in high inconsistencies in product quality and in the concentration of plant chemicals across products. This problem is not just imagined. In one analysis, the

concentration of the active agent in St. John's wort varied sevenfold among different products [16]. In another study, an active ingredient in different products of garlic tablets fluctuated more than 40-fold [17]. The concentration of important ingredients among 10 varieties of ginseng products fluctuated 10-fold in an analysis commissioned by *Consumer Reports*, and other analyses of ginseng products identified preparations that contained no ginseng at all [18, 19]. Accordingly, these products contrast substantially with standard aspirin tablets, which are mandated by law and are certified to contain 95–105% of labeled amounts of acetylsalicylic acid and which must undergo a series of purification tests. Similarly, regarding the safety of these products, concern over the lack of manufacturing standards and quality control has already been demonstrated by several reports of contaminated herbal products causing serious adverse effects, such as digitalis toxicity and lead poisoning [20, 21]. When original reports of a variety of herbal medicine poisonings were carefully scrutinized, many cases were found to be due to substitution or contamination of the declared ingredients [22]. Contamination with environmental pollutants (such as microorganisms, pesticides, and toxic metals), deliberate adulteration (with non-steroidal anti-inflammatory drugs [NSAIDs] or benzodiazepines), and misidentification or mislabeling of herbal products have all been described [22–24]. Such cases are likely tremendously underreported, since only serious adverse outcomes are usually investigated.

10.3 Methods of Quality Control for Herbal Products

10.3.1 DNA-Based Technologies

Barcode DNA is among the recent technological developments for the authentication of medicinal plants. This method is based on the detection of variable sites of the rDNA internal transcribed spacer. In systematic botany, polymerase chain reaction-based determination of barcode DNA is commonly employed for taxonomy studies. DNA barcoding provides a suitable tool for the authentication of plants and is well suited to quality control of medicinal plants [25, 26]. Current investigations in this field place emphasis on how many and which DNA fragments are required for the best discernment of different species. The largest database of DNA barcodes of medicinal plants, with more than 1000 species enumerated in the *American Herbal Pharmacopoeia* and the *Chinese Pharmacopoeia*, is the Medicinal Materials DNA Barcode Database (MMDBD) [27].

10.3.2 Good Practice Guidelines

Having been collected and correctly identified, medicinal plants must be subsequently handled in a standardized manner [28]. To this effect, prominent guidelines have been devised, including good sourcing practice, good agricultural

practice, good laboratory practice, good manufacturing practice, and good clinical trials practice [29].

10.3.3 Chemoprofiling

As stated above, the chemical composition of medicinal plants may substantially vary and must be standardized to effect comparable therapeutic effects. Several chromatographic fingerprinting analyses are known to identify ingredients and their concentration distribution [30, 31]. Standard analytical technologies available to this effect include thin layer chromatography, high-performance liquid chromatography, and capillary electrophoresis. Recently, new technological developments have become available for chemoprofiling, including metabolic fingerprinting, infrared spectroscopy, and quantitative determinations based on nuclear magnetic resonance spectroscopy.

10.3.4 Toxicology

Another facet of quality control, besides confirming the proper composition of herbal prescriptions, is to exclude possible contamination with pesticides, mycotoxins, heavy metals, or other chemical toxins or microbial toxins [32, 33]. Moreover, herbal medicinal products adulterated with conventional drugs (glucocorticoids and NSAIDs) must be prevented from reaching consumers.

10.3.5 Monographs and Pharmacopeias

Because of the aforementioned concerns about some traditional herbal products, there is a need for sound legal frameworks for the pharmaceutical use of herbal products. Pharmaceutically relevant knowledge of medicinal plants is systematically gathered and documented in monographs, which mostly form part of national or international pharmacopeias. Examples of these include the *International Pharmacopoeia*, the *European Pharmacopoeia*, the *American Herbal Pharmacopoeia*, the *German Pharmacopoeia*, and the *Chinese Pharmacopoeia*. Monographs contain technical definitions, analytical techniques for the identification of content and purity testing, as well as logistical and warehousing regulations for all kinds of drugs (herbal, chemical, and biological). Each pharmaceutically used drug has to meet the requirements of the monograph [34].

10.3.6 Preclinical Evidence of Safety and Efficacy

Traditionally, candidate compounds pass through a pipeline of preclinical investigations, using in vitro and in vivo test models. If the preclinical evaluation is promising, the candidate drug advances to clinical trial phases I–IV before it can

be recommended for clinical use. Phytotherapy has a different approach. Herbal medicines have been used for centuries, and it was only in recent years that inquiry and expectations about their mode of action, safety, and efficacy became a concern. In this sense, phytotherapeutic research may be understood as reverse pharmacology. On the other hand, research on the overall or partial bioactivity of medicinal plants or their parts is a part of quality control of herbal preparations that certifies whether they are effective and safe [34].

10.3.7 Systems Biology

Although classical pharmacological approaches are able to explain some of the mechanisms of medicinal plants (e.g. receptor–ligand interactions), the chemical composition of herbal mixtures is extremely complex and can only be understood incompletely by reductionistic approaches. The advent of systems biology and "-omics" technologies have been received with much curiosity among scientists in the areas of traditional medicine, because "-omics" technologies are all encompassing as they assess entire profiles of molecules at various levels of life such as in whole cells, organs, or organisms [4]. Liquid chromatography/mass spectrometry and microarray hybridization are basic technologies that are used to detect changes in the genomic makeup (genomics), proteome (proteomics), transcriptome (transcriptomics), or metabolome (metabolomics). Metabolomics is especially of interest in herbal medicine [35, 36] since plants synthesize abundant varieties of chemicals, much more numerous than those produced by most other organisms. Therefore, systems biology is appreciated as an innovative discipline to investigate holistic phytotherapeutic approaches. Systems biological research may also enable the determination of synergistic interactions of herbal mixtures.

10.3.8 Animal Experimentation

There are many investigations documenting the activity of plant extracts in in vitro test models. Such assays are normally easy to perform and are used for bioactivity-guided isolation of the active phytochemicals in extracts. Sophisticated methods can also be easily carried out in vitro, as in vivo conditions complicate experimental designs even more. Despite their crucial roles, in vitro bioactivity results do not necessarily translate into bioactivity in vivo [37, 38]. In vitro studies more often fail to appreciate the possible enzymatic activation of prodrug components and the role of presystemic metabolism of some chemicals in the body.

10.3.9 Clinical Evidence of Safety and Efficacy

In contrast to the general public, who widely use the products, Western academies are still reluctant to investigate herbal medicines. The major reasons for this include the complexity of the composition of the products and the fact that they

are usually sold over the counter. Their efficacy and safety are, therefore, doubted. On the other hand, given that traditional and herbal medicines have been successfully used for thousands of years, it is not always obvious to herbalists and traditional medical doctors that preclinical or clinical studies should be conducted in order to prove the efficacy of herbal medicines. However, the only practical way to integrate traditional medicines into conventional ones in a realistic time frame requires clinical trials to be conducted and to convince physicians with strong evidence-based data from herbal medicines. In recent years, an ever-increasing number of clinical trials, reports, and meta-analyses have focused on the efficacy of herbal medicines [39, 40]. Once evidence-based traditional medicines are on the market, appropriate pharmacovigilance studies are required to monitor any adverse effects [41].

10.4 WHO Guidelines for Quality Standardization of Herbal Formulations

Quality control and standardization parameters for herbal products are based on the following basic parameters: plant preparation; quality control of crude drug material and finished products; stability and shelf life assessments; safety assessment; documentation of safety based on toxicological studies or experience; and assessment of efficacy by biological activity evaluations and ethnomedical information. The following sections discuss some of these parameters.

10.4.1 Quality Control of Crude Material

There are a few challenges as far as standardization of a herbal product is concerned, such as deliberate adulteration of plant material, controversial identity of various plants, and problems with storage and transportation, and they need to be considered and seriously addressed in every practice [42]. One of the obstacles in the recognition of herbal products worldwide is the lack of standard quality control profiles. Most of the herbal formulations, particularly the classical formulations of traditional medicine, are polyherbal. A formulation may be found to contain 10–20 or, at times, 50–75 ingredients [43].

10.4.2 Identity of Plant Material

Authenticity, purity, and assay are important aspects of standardization and quality control. Authenticity refers to the state that proves the material is genuine and corresponds to the correct identification and profile. Quality control of botanicals starts with plant identification. According to the WHO general guidelines for methodologies on the research and evaluation of traditional medicines, the first step in assuring the safety, quality, and efficacy of traditional medicines is correct identification. If appropriate taxonomical names are not used, misidentification is

likely to occur. For example, two or more different plants often have the same name in Ayurveda. The challenges in medicinal plant authentication include limited knowledge about the medicinal plants produced by different traders or suppliers, the collection process by untrained people, and non-homogeneity of plant material because of unsystematic collection from wild sources and widely and differently controlled geographical locations [43, 44]. Thus, chemical analysis serves as the best method for identification, standardization, and detection of contamination.

10.4.3 Safety Assessment and Documentation

Adulteration of botanical preparations is another important issue that not only relates to the therapeutic efficacy of the product but also raises safety concerns. Because of overexploitation, habitat loss, and deforestation, many medicinal plants have been listed as endangered or rare species. The unavailability of the genuine drug, in turn, can result in the adulteration of plant materials by substitution with inferior commercial varieties, artificially manufactured substances, and cheaper plant materials or by another vegetative part [45]. Several reports have disclosed that herbal products quite often contain hidden pharmaceuticals and heavy metals. Agrochemicals used while growing the plants might also contaminate the crude plant material. Moreover, the mechanisms of action, stability, pharmacokinetics, compatibility, and drug–drug interactions of numerous herbs are still unknown. At the same time, an increasing number of reports about fatal adverse effects of herbal preparations demand the need for more stringent regulation and registration of herbal medicines and the establishment of proper safety monitoring [43, 46].

10.5 Concept of Validation in Herbal Products

In order to control the quality of herbal products effectively, an amalgamation of newer techniques is required. The FDA defines validation loosely as establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics. This has applied to manufacturers of synthetic conventional drugs for many years now, but it is not yet quite consistently or methodically studied and applied in the manufacturing of herbal products. All international regulations such as the Medicines Control Council (South Africa), FDA (USA), Therapeutic Goods Administration (Australia), and Medicines and Healthcare products Regulatory Agency (UK), show that it is possible to apply validation to pharmaceutical manufacturing, but only a few of the regulators together with WHO apply the validation concept to manufacturing of herbal drugs. Even WHO places very little emphasis on validation. Generally, one can

describe this model in a straightforward way as starting from the input and ending with the output. However, in the case of validation one must go in the reverse direction. The first step should be to identify and define what quality of the product is required [43].

Such a model is applicable for herbal drugs but there are some limitations, such as certification. Certification of herbal product manufacturers is a demanding procedure, but it is still possible. Problems with the standardization of the strength of the active moiety imply the requirement for validation. There are many parameters that must be considered when certifying the manufacturer:

- type of herbs
- environmental conditions
- time of collection.
- variation in composition, etc.

10.6 Challenges Related to Quality Control and Monitoring the Safety of Herbal Products

It is very obvious that research protocols as well as the requirements and standards needed for the evaluation of the efficacy and safety of herbal medicines are much more complex than those required for conventional synthetic drugs [47, 48]. A single herbal formulation may comprise hundreds of natural constituents, and a mixed herbal medicinal product may contain several times that number. Such a high number of components may be impossible to isolate and study singly from the formulations [47].

WHO continues to encourage the establishment of good manufacturing practices to ensure good quality and safety for herbal products [49, 50].

Adverse events arising from the use of herbal medicinal products are ascribed to many factors, such as the use of the wrong species of plant; adulteration of herbal products with other, undeclared medicines or with toxic or hazardous substances; overdosage; misuse of herbal medicines by either healthcare providers or consumers; and drug–drug interactions with other medicines. Although the assessment of the safety of herbal medicines has become an important issue, the analysis of adverse events related to the use of these products is much more complex than in the case of modern medicinal products [47, 48]. The evaluation of safety is even further complicated by factors such as the geographical origin of the plant material, different processing techniques, the route of administration, and uncertain compatibility with other medicines [51]. In addition, the lack of knowledge and/or poor emphasis of most manufacturers regarding the significance of taxonomic botany and the documentation of herbal medicines poses tremendous difficulties for the identification and collection of medicinal plants [52].

References

1 World Health Assembly. (1977). *Resolution WHA30.49: Promotion and Development of Training and Research in Traditional Medicine*. Geneva, Switzerland: World Health Organization.

2 Nascimento, G.F., Locatelli, J., Freitas, P.C., and Silvia, G.L. (2000). Antibacterial activity of plant extracts and phytochemicals on antibiotic resistant bacteria. *Braz. J. Microbiol.* 31 (247): 256.

3 Sofowora, A. (1996). *Medicinal Plants and Traditional Medicines in Africa*. Ibadan, Nigeria: Spectrum Books 112 pp.

4 Verpoorte, R., Choi, Y.H., and Kim, H.K. (2005). Ethnopharmacology and systems biology: a perfect holistic match. *J. Ethnopharmacol.* 100: 53–56.

5 Schulz, V., Hubner, W.-D., and Ploch, M. (1997). Clinical trials with phytopsychopharmacological agents. *Phytomedicine* 4: 379–387.

6 Chavez, M.L. and Chavez, P.I. (1998). Echinacea. *Hosp. Pharm.* 33: 180–188.

7 Pittler, M.H. and Ernst, E. (1998). Horse-chestnut seed extract for chronic venous insufficiency: a criteria-based systematic review. *Arch. Dermatol.* 134: 1356–1360.

8 Wilt, T.J., Ishani, A., Stark, G. et al. (1998). Saw palmetto extracts for treatment of benign prostatic hyperplasia: a systematic review. *JAMA* 280: 1604–1609.

9 Bos, R., Woerdenbag, H.J., De Smet, P.A.G.M., and Scheffer, J.J.C. (1997). Valeriana species. In: *Adverse Effects of Herbal Drugs*, vol. 3 (ed. P.A.G.M. De Smet), 165–180. Berlin: Springer.

10 Zhao, Z., Hu, Y., Liang, Z. et al. (2006). Authentication is fundamental for standardization of Chinese medicines. *Planta Med.* 72: 865–874.

11 Heubl, G. (2010). New aspects of DNA-based authentication of Chinese medicinal plants by molecular biological techniques. *Planta Med.* 76: 1963–1974.

12 Fennell, C.W., Lindsey, K.L., McGaw, L.J. et al. (2004). Assessing African medicinal plants for efficacy and safety: pharmacological screening and toxicology. *J. Ethnopharmacol.* 94: 205–217.

13 Dietary Supplement Health and Education Act of 1994 (1994). US Public Law 103-417, S. 784.

14 Blumenthal, M. (1998). *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines*. Austin (TX): American Botanical Council.

15 Calixto, J.B. (2000). Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents). *Braz. J. Med. Biol. Res.* 33: 179–189. The medicinal use.

16 Monmaney, T. (1998). Labels' potency claims often inaccurate, analysis finds. *Los Angeles Times* (31 August). https://www.latimes.com/archives/la-xpm-1998-aug-31-mn-18279-story.html (accessed 11 October 2019).

17 Schardt, D. and Schmidt, S. (1995). Garlic: clove at first sight? *Nutri. Action Health Lett.* 22 (July/Aug): 3–5.

18 Consumer Reports. (1995). Herbal roulette. *Consumer Reports* 60 (November):698–705.

19 Cui, J., Garle, M., Eneroth, P., and Bjorkhem, I. (1994). What do commercial ginseng preparations contain? [letter]. *Lancet* 344: 134.

20 Slifman, N.R., Obermeyer, W.R., Aloi, B.K. et al. (1998). Contamination of botanical dietary supplements by Digitalis lanata. *N. Engl. J. Med.* 339: 806–811.

21 Beigel, Y., Ostfeld, I., and Schoenfeld, N. (1998). A leading question. *N. Engl. J. Med.* 339: 827–830.

22 De Smet, P.A.G.M. (1992). Toxicological outlook on the quality assurance of herbal remedies. In: *Adverse Effects of Herbal Drugs*, vol. 1 (ed. P.A.G.M. De Smet), 1–72. Berlin: Springer.

23 Ko, R.J. (1998). Adulterants in Asian patent medicines [letter]. *N. Engl. J. Med.* 339: 847.

24 Huxtable, R.J. (1990). The harmful potential of herbal and other plant products. *Drug Saf.* 5 (Suppl 1): 126–136.

25 Pennisi, E. (2007). Taxonomy. Wanted: a barcode for plants. *Science* 318: 190–191.

26 Yao, H., Song, J., Liu, C. et al. (2010). Use of ITS2 region as the universal DNA barcode for plants and animals. *PLoS One* 5: e13102.

27 Lou, S.K., Wong, K.L., Li, M. et al. (2010). An integrated web medicinal materials DNA database: MMDBD (medicinal materials DNA barcode database). *BMC Genomics* 11: 402.

28 Zhao, Z., Liang, Z., Chan, K. et al. (2010). A unique issue in the standardization of Chinese materia medica: processing. *Planta Med.* 76: 1975–1986.

29 Zhang, B., Peng, Y., Zhang, Z. et al. (2010). GAP production of TCM herbs in China. *Planta Med.* 76: 1948–1955.

30 Liang, Y.Z., Xie, P.S., and Chan, K. (2010). Perspective of chemical fingerprinting of Chinese herbs. *Planta Med.* 76: 1997–2003.

31 Yang, H., Zhao, C., Wang, X. et al. (2010). Chromatographic fingerprint investigation for quality evaluation and control of Shengui hairgrowth tincture. *Planta Med.* 76: 372–377.

32 Youns, M., Hoheisel, J.D., and Efferth, T. (2010). Toxicogenomics for the prediction of toxicity related to herbs from traditional Chinese medicine. *Planta Med.* 76: 2019–2025.

33 Efferth, T. and Kaina, B. (2011). Toxicities by herbal medicines with emphasis to traditional Chinese medicine. *Curr. Drug Metab.* 12: 989–996.

34 Efferth, T. and Greten, H.J. (2012). Quality control for medicinal plants. *Med. Aromat. Plants* 1: 7.

35 Shyur, L.F. and Yang, N.S. (2008). Metabolomics for phytomedicine research and drug development. *Curr. Opin. Chem. Biol.* 12: 66–71.

36 Saito, K. and Matsuda, F. (2010). Metabolomics for functional genomics, systems biology, and biotechnology. *Annu. Rev. Plant Biol.* 61: 463–489.

37 Butterweck, V. and Nahrstedt, A. (2012). What is the best strategy for preclinical testing of botanicals? A critical perspective. *Planta Med.* 78: 747–754.

38 Tejedor Garcia, N., Garcia Bermejo, L., Fernandez Martinez, A.B. et al. (2012). MEDLINE-based assessment of animal studies on Chinese herbal medicine. *J. Ethnopharmacol.* 140: 545–549.

39 Wang, J. (2010). Evidence-based medicine in China. *Lancet* 375: 532–533.

40 Hu, J., Zhang, J., Zhao, W. et al. (2011). Cochrane systematic reviews of Chinese herbal medicines: an overview. *PLoS One* 6: e28696.

41 Shaw, D., Graeme, L., Pierre, D. et al. (2012). Pharmacovigilance of herbal medicine. *J. Ethnopharmacol.* 140: 513–518.

42 Thatte, U. (2003). Challenges in clinical research on herbs. *Indian J. Nat. Prod.* 19 (1): 35–36.

43 Vaibhav, M., Shinde, K.D., Potdar, M., and Mahadik, K.R. (2009). Application of quality control principles to herbal drugs. *Int. J. Phytomed.* 1: 4–8.

44 Raina, M.K. (2003). Quality control of herbal and herbomineral formulations. *Indian J. Nat. Prod.* 19 (1): 11–15.

45 Mukherjee, P.K. (2002). *Quality Control of Herbal Drugs: An Approach to Evaluation of Botanicals*, 1e, 113–119. India: Business horizons.

46 Robert, B.S., Stefanos, N.K., Janet, P. et al. (2004). Heavy metal content of Ayurvedic herbal medicine products. *J. Am. Med. Assoc.* 292 (23): 2868–2873.

47 WHO (2005). *National Policy on Traditional Medicine and Regulation of Herbal Medicines. Report of a World Health Organization Global Survey*. Geneva, Switzerland: WHO.

48 Zhou, J., Ouedraogo, M., Qu, F., and Duez, P. (2013). Potential genotoxicity of traditional Chinese medicinal plants and phytochemicals: an overview. *Phytother. Res.* https://doi.org/10.1002/ptr.4942.

49 WHO (2004). *WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems*. Geneva, Switzerland: World Health Organization.

50 WHO (2003). *WHO Guidelines on Good Agricultural and Collection Practices (GACP) for Medicinal Plants*. Geneva, Switzerland: World Health Organization.

51 Zhang, L., Yan, J., Liu, X. et al. (2012). Pharmacovigilance practice and risk control of traditional Chinese medicine drugs in China: current status and future perspective. *J. Ethnopharmacol.* 140: 519–525. https://doi.org/10.1016/j.jep.2012.01.058.

52 Farah, M.H., Edwards, I.R., Lindquist, M. et al. (2000). International monitoring of adverse health effects associated with herbal medicines. *Pharmacoepidemiol. Drug Saf.* 9: 105–112. https://doi.org/10.1002/(SICI)1099-1557(200003/04)9:2<105: AID-PDS486>3.0.CO;2-2.