

Quality Control for Medicinal Plants

Thomas Efferth^{1*} and Henry Johannes Greten²

¹Department of Pharmaceutical Biology, Institute of Pharmacy and Biochemistry, Johannes Gutenberg University, Mainz, Germany

²Heidelberg School of traditional Chinese Medicine, Heidelberg, Germany and Biomedical Sciences Institute Abel Salazar, University of Porto, Portugal

Abstract

The scientific basis of evidence-based medicine is still poor in herbal medicine. For the integration of herbal medicine into western medicine, internationally accepted standards are necessitated, including quality control of herbal products as well as preclinical and clinical evidence of safety and efficacy. In recent years, thriving innovative technologies emerged in phytotherapy research, e.g. DNA-based technologies for the authentication of plant species, good practice guidelines for standardized experimentations. High-quality herbal materials should undergo rigorous examination by analytical techniques for chemoprofiling of medicinal herbs, as well as toxicological methods to detect contaminations. The state of the art, which is necessary for the pharmaceutical use of medicinal herbs, is documented in monographs of national and international pharmacopeias. The thriving advances in molecular biology also affect phytotherapy research, which benefits from novel technologies of systems biology. Detection of bioactivity in animal experiments is a precondition to perform clinical trials in human patients. A sound basis of evidence for the safety and efficacy of herbal medicines will foster their integration into western medicine.

Keywords: Botanical identification; Clinical trials; Herbal medicine; Phytotherapy; Systems biology

Introduction

Herbal medicine is not only easy accessible at low prices for primary health care, but also can serve as valuable reservoir for pharmacological drug development [1]. Remarkably, a majority of the world's population cannot afford the costs for western-style drugs. This is especially true for Third World countries. Hence, it does not come as a surprise that traditional medicines are far distributed on the globe [2]. On the other hand, it is estimated that there are between 30,000-70,000 medicinal plants worldwide, most of which have not been scientifically analyzed [3]. Since prehistoric times, herbal medicines are used without the rigorous rules necessary to register drugs nowadays. As a consequence, safety and efficacy of medicinal plants have been challenged by western academic medicine. Therefore, development of evidence-based traditional medicines seems to be the only option to convince skeptical western physicians.

Paradoxically, about 90% of the current western drugs are not working in about 60% of the patients using them [4], indicating that the principles of evidence-based medicine have not been vigorously applied for western medicine too. The lack of efficacy of western drugs in all patients led to the concept of personalized medicine. The vision of personalized medicine is that custom-tailored treatments may be developed for each individual patient leading to higher treatment efficacy and low adverse side effects. Personalized medicine is, however, not a new invention, but well-known feature of most, if not all traditional medicines for hundreds or thousands of years. This indicates that both systems, traditional and modern medicines have advantages and disadvantages, and that both systems may complement each other for the sake of the patients. Two major requirements for herbal medicines to be integrated in western medicine are, firstly, standardization and quality control of herbal products and secondly, proof of safety and efficacy.

Herbal recipes are frequently comprised of complex mixtures of different plant species, and even within one and the same species, the composition and amount of chemical compounds can considerably vary, depending on exogenous (e.g. climate, soil composition and altitude) and endogenous factors (e.g. genetics, epigenetics). Quality control

is therefore, of high priority to ensure herbal products' consistency and efficacy. The establishment of internationally accepted standards is certainly one of the priorities for the future of medicinal plants. Standards are necessary at three different levels: (a) Quality control of herbal products, (b) preclinical evidence of safety and efficacy, and (c) clinical evidence of safety and efficacy.

Quality Control of Herbal Products

DNA-based technologies

The correct identification of medicinal plants is essential, as wrongly identified species, subspecies or species varieties are either therapeutically less active or inactive, or may even contain poisonous ingredients [5]. The methods of classical botany for plant identification are recently supplemented by various DNA-based technologies, including RAPD, RFLP, ARMS, CAPS, AFLP, DAF, ISSR, SSR, hybridization and microarrays [6]. A recent technological development is the authentication of medicinal plants by barcode DNA. This method is based on the detection of variable sites of the rDNA internal transcribed spacer (ITS). In systematic botany, PCR-based determination of barcode DNA is used for taxonomy studies. DNA barcoding provides a powerful tool for the authentication of plants, and is exquisitely suited for quality control of medicinal plants [7-11]. Current research in this field focuses on the question, how many and which DNA fragments are necessary for the optimal discrimination of different species. The largest database on DNA barcodes of medicinal plants, with more than 1000 species listed in the Chinese Pharmacopoeia and

***Corresponding author:** Thomas Efferth, Department of Pharmaceutical Biology, Institute of Pharmacy and Biochemistry, Johannes Gutenberg University, Staudinger Weg 5, 55128 Mainz, Germany, Tel: 49-6131-3925751; Fax: 49-6131-3923752; E-mail: efferth@uni-mainz.de

Received October 08, 2011; **Accepted** October 10, 2012; **Published** October 17, 2012

Citation: Efferth T, Greten HJ (2012) Quality Control for Medicinal Plants. *Med Aromat Plants* 1:e131. doi:10.4172/2167-0412.1000e131

Copyright: © 2012 Efferth T, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

American Herbal Pharmacopoeia, represents the Medicinal Materials DNA Barcode Database (MMDBD) [12].

Good practice guidelines

Having the correctly identified plants in hand, they have to be further handled in a standardized manner [13]. For this reason, international guidelines have been developed such as Good Sourcing Practice (GSP), Good Agricultural Practice (GAP), Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), and Good Clinical Trial Practice (GCTP) [14]. In this context, an interesting project is the cultivation and breeding of Chinese herbs in Germany, which is an interdisciplinary approach covering diverse aspects from seed sourcing to medicinal application. A recent report described the outcome of the agricultural seed and field experiments, breeding program, botanical and chemical characterization of the experimental material, comparison of experimental and imported herbal material with respect to their pharmaceutical quality, transfer of production methods and plant material to specialized farmers, medicinal application and finally, information for users along the chain of distribution about the benefits of the locally produced herbal material [15].

Chemoprofiling

As already pointed out, the chemical composition of plants may vary to some extent and needs to be standardized to guarantee comparable therapeutic effects. A number of chromatographic fingerprinting analyses are known to disclose the detectable ingredients composition and concentration distribution [16,17]. Standard analytical techniques include thin-layer chromatography, high-performance liquid chromatography and capillary electrophoresis. Recently, novel technological developments became available for chemoprofiling, such as infrared spectroscopy, metabolic fingerprinting and quantitative determinations based on nuclear magnetic resonance spectra.

Toxicology

Another aspect of quality control, in addition to ensure proper composition of herbal prescriptions, is to avoid contamination with mycotoxins, pesticides, heavy metals, or other chemical toxins [18,19]. Furthermore, faked herbal prescriptions with adulteration of drugs from western medicine, e.g. with glucocorticoids, have to be banned [20,21].

Monographs and pharmacopoeias

Due to the above mentioned concerns of traditional herbal drugs, there are legal frameworks for the pharmaceutical use of herbal products. The pharmaceutically relevant knowledge of medicinal plants is collected in monographs, which are part of national or international pharmacopoeias, e.g. the International Pharmacopoeia, the European Pharmacopoeia, the American Herbal Pharmacopoeia, the German Pharmacopoeia, the Chinese Pharmacopoeia, and so on. Monographs contain definitions, analytical techniques for identity and purity and content, as well as storage regulations for all kinds of drugs (herbal, chemical, biological). Each pharmaceutically employed drug has to meet the requirements of the monograph.

Preclinical Evidence of Safety and Efficacy

In classical drug development, candidate compounds traverse a pipeline of preclinical investigations, using *in vitro* and *in vivo* test models. If the preclinical evaluation is positive, the candidate drug is further investigated in clinical phase I-IV trials, and is ultimately used in clinical everyday routine. Phytotherapy has a different

approach. Herbal medicines are used since ages, and it was only in recent years that the need to understand their mode of action and gain knowledge about their safety and efficacy came into awareness. In this sense, phytotherapeutic research may be understood as reverse pharmacology. On the other hand, research on the bioactivity of medicinal plants is a part of quality control that a certain herbal preparation is efficient and safe.

Systems biology

After the establishment of standard molecular biological techniques in the past three decades, more recently, systems biology with an array of thriving new methods came into play. Traditional medicines are often based on holistic therapeutic approaches, whereas, western medicine is reductionistic in nature. While 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 insufficiently be understood by reductionistic approaches. The advent of systems biology and “-omics” technologies has been perceived with much interest among scientists working in the field of traditional medicine, because “-omics” technologies are also holistic in the sense that they measure entire profiles of molecules in whole cells, organs or organisms [3]. Microarray hybridization and LC-MS are basic technological platforms to measure changes in the genome (genomics), transcriptome (transcriptomics), proteome (proteomics) or metabolome (metabolomics). Especially, metabolomics is of interest for herbal medicine [22,23], since plants produce a huge array of chemicals, far more than are produced by most other organisms. Bioinformatical methods such as hierarchical cluster analysis, principal component analysis and others are employed to statistically process the massive amount of data, resulting from “-omics” technologies [24]. An appealing strategy is to interconnect the data obtained from genomics, transcriptomics, proteomics and metabolomics to cellular interaction networks, which may explain the activity of complex herbal mixtures in a comprising fashion. Therefore, systems biology is appreciated as an innovative discipline to study holistic phytotherapeutic approaches. Systems biological research may also facilitate to understand synergistic interactions of herbal mixtures.

Animal experimentation

There is a plethora of investigations reporting the activity of plant extracts in *in vitro* test models. Such assays are frequently easy to perform, and used for bioactivity-guided isolation of the active phytochemicals in extracts. Sophisticated methods are sometimes also preferentially performed *in vitro*, because *in vivo* settings complicate the experimental design even more. Despite the unambiguous advantages of *in vitro* analyses, bioactivity *in vitro* does not necessarily translate into bioactivity *in vivo* [25,26]. The influence of drug metabolism in living organisms might not be appropriately reflected in cell culture models. Plant secondary metabolites may occur as prodrugs that have to be metabolized *in vivo* by the intestinal microflora or by hepatic enzymes.

Clinical Evidence of Safety and Efficacy

There is still some reluctance of western academia towards herbal medicine, which is in striking contrast to the general public, which is open-minded to phytotherapy and other forms of complementary medicine. There are several reasons that can be discussed:

- Traditional (holistic) medicines are often mixtures, which do

not fit well to the general set-up of clinical (reductionistic) trials [27,28].

- Herbal medicines are frequently sold as over-the-counter products, without official registration [29,30]. Their efficacy and safety is, therefore, doubted.

Having in mind that traditional and herbal medicines have been successfully used for thousands of years, it is not always obvious for herbalists and traditional medical doctors to perform preclinical or clinical studies, in order to proof the efficacy of herbal medicines. However, the only pragmatic way for the integration of traditional medicines into western medicine in a realistic time frame seems to perform sound clinical trials, and to convince western physicians by strong data from evidence-based herbal medicine. In recent years, an ever increasing number of clinical trials and meta-analyses focused on the efficacy of herbal medicines [31-36]. Once evidence-based traditional medicines are on the market, pharmacovigilance studies are required for monitoring the adverse effects [37].

References

1. Padalia RC (2012) Medicinal and Aromatic plants: Chemical Goldmines. *Medicinal Aromatic plants* 1: e113.
2. Hosni K (2012) Medicinal and Aromatic Plants in Developing Countries. *Medicinal Aromatic Plants* 1: e118.
3. Verpoorte R, Choi YH, Kim HK (2005) Ethnopharmacology and systems biology: a perfect holistic match. *J Ethnopharmacol* 100: 53-56.
4. (2012) What happened to personalized medicine? *Nat Biotechnol* 30:1.
5. Zhao Z, Hu Y, Liang Z, Yuen JP, Jiang Z, et al. (2006) Authentication is fundamental for standardization of Chinese medicines. *Planta Med* 72: 865-874.
6. Heubl G (2010) New aspects of DNA-based authentication of Chinese medicinal plants by molecular biological techniques. *Planta Med* 76: 1963-1974.
7. Pennisi E (2007) Taxonomy. Wanted: a barcode for plants. *Science* 318: 190-191.
8. Lin WY, Chen LR, Lin TY (2008) Rapid authentication of *Bupleurum* species using an array of immobilized sequence-specific oligonucleotide probes. *Planta Med* 74: 464-469.
9. Zhu S, Fushimi H, Komatsu K (2008) Development of a DNA microarray for authentication of ginseng drugs based on 18S rRNA gene sequence. *J Agric Food Chem* 56: 3953-3959.
10. Yao H, Song J, Liu C, Luo K, Han J, et al. (2010) Use of ITS2 region as the universal DNA barcode for plants and animals. *PLoS One* 5: e13102.
11. Cimino MT (2010) Successful isolation and PCR amplification of DNA from National Institute of Standards and Technology herbal dietary supplement standard reference material powders and extracts. *Planta Med* 76: 495-497.
12. Lou SK, Wong KL, Li M, But PP, Tsui SK, et al. (2010) An integrated web medicinal materials DNA database: MMDBD (Medicinal Materials DNA Barcode Database). *BMC Genomics* 11: 402.
13. Zhao Z, Liang Z, Chan K, Lu G, Lee EL, et al. (2010) A unique issue in the standardization of Chinese materia medica: processing. *Planta Med* 76: 1975-1986.
14. Zhang B, Peng Y, Zhang Z, Liu H, Qi Y, et al. (2010) GAP production of TCM herbs in china. *Planta Med* 76: 1948-1955.
15. Heuberger H, Bauer R, Friedl F, Heubl G, Hummelsberger J, et al. (2010) Cultivation and breeding of Chinese medicinal plants in Germany. *Planta Med* 76: 1956-1962.
16. Liang YZ, Xie PS, Chan K (2010) Perspective of chemical fingerprinting of chinese herbs. *Planta Med* 76: 1997-2003.
17. Yang H, Zhao C, Wang X, Liang Y, Zeng Y, et al. (2010) Chromatographic fingerprint investigation for quality evaluation and control of Shengui hair-growth tincture. *Planta Med* 76: 372-377.
18. Youns M, Hoheisel JD, Efferth T (2010) Toxicogenomics for the prediction of toxicity related to herbs from traditional Chinese medicine. *Planta Med* 76: 2019-2025.
19. Efferth T, Kaina B (2011) Toxicities by herbal medicines with emphasis to traditional Chinese medicine. *Curr Drug Metab* 12: 989-996.
20. Kneifel W, Czech E, Kopp B (2002) Microbial contamination of medicinal plants --a review. *Planta Med* 68: 5-15.
21. Chan K (2005) Chinese medicinal materials and their interface with Western medical concepts. *J Ethnopharmacol* 96: 1-18.
22. Shyur LF, Yang NS (2008) Metabolomics for phytomedicine research and drug development. *Curr Opin Chem Biol* 12: 66-71.
23. Saito K, Matsuda F (2010) Metabolomics for functional genomics, systems biology, and biotechnology. *Annu Rev Plant Biol* 61: 463-489.
24. Okada T, Afendi FM, Altaf-UI-Amin M, Takahashi H, Nakamura K, et al. (2010) Metabolomics of medicinal plants: the importance of multivariate analysis of analytical chemistry data. *Curr Comput Aided Drug Des* 6: 179-196.
25. Butterweck V, Nahrstedt A (2012) What is the best strategy for preclinical testing of botanicals? A critical perspective. *Planta Med* 78: 747-754.
26. Tejedor Garcia N, Garcia Bermejo L, Fernandez Martinez AB, Olmos Centenera G, Kumari R, et al. (2012) MEDLINE-based assessment of animal studies on Chinese herbal medicine. *J Ethnopharmacol* 140: 545-549.
27. Pelkonen O, Pasanen M, Lindon JC, Chan K, Zhao L, et al. (2012) Omics and its potential impact on R&D and regulation of complex herbal products. *J Ethnopharmacol* 140: 587-593.
28. Sheridan H, Krenn L, Jiang R, Sutherland I, Ignatova S, et al. (2012) The potential of metabolic fingerprinting as a tool for the modernisation of TCM preparations. *J Ethnopharmacol* 140: 482-491.
29. Eichhorn T, Greten HJ, Efferth T (2011) Self-medication with nutritional supplements and herbal over-the counter products. *Nat Products Bioprospect* 1: 62-70.
30. Efferth T, Greten HJ (2012) The European directive on traditional herbal medicinal products: friend or foe for plant-based therapies? *J Chin Integr Med* 10: 357-361.
31. Konkimalla VB, Efferth T (2008) Evidence-based Chinese medicine for cancer therapy. *J Ethnopharmacol* 116: 207-210.
32. Wang J (2010) Evidence-based medicine in China. *Lancet* 375: 532-533.
33. Hu J, Zhang J, Zhao W, Zhang Y, Zhang L, et al. (2011) Cochrane systematic reviews of Chinese herbal medicines: an overview. *PLoS One* 6: e28696.
34. Lu JZ, Zhang L, Cao XT, Yang MH, Zhao H, et al. (2012) Meta-analysis of Chinese medicines for prevention and treatment of radiation esophagitis. *J Tradit Chin Med* 32: 137-142.
35. Shi KQ, Fan YC, Liu WY, Li LF, Chen YP, et al. (2012) Traditional Chinese medicines benefit to nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Mol Biol Rep* 39: 9715-9722.
36. Cohen M (2012) Rosehip - an evidence based herbal medicine for inflammation and arthritis. *Aust Fam Physician* 41: 495-498.
37. Shaw D, Graeme L, Pierre D, Elizabeth W, Kelvin C (2012) Pharmacovigilance of herbal medicine. *J Ethnopharmacol* 140: 513-518.