

## Introduction

# Quality Assurance and Safety of Herbal Dietary Supplements

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Since the U.S. Congress passed the Dietary Supplement Health and Education Act (DSHEA) in 1994, herbal products represent the fastest growing segment of the VMH (Vitamin, Mineral supplements, and Herbal products) industry. To ensure consumer health protection, the quality and safety of raw herbal plants used for dietary supplement preparations must be determined. To date, safety issues concerning potential side-effects and toxic contamination of herbal products have not been adequately addressed, and toxicological data on the identification of genotoxic and tumorigenic ingredients in many raw herbs are also lacking. The recent pet-food poisoning problems in the United States reflect manufacturers' inability or negligence in the implementation of proper quality control measures in the manufacturing process and alert us to the importance and urgency of safety assurance for herbal dietary supplements products as well.

The eight reviews and eight research articles in this Special Issue represent a cross-section of state-of-the-art science in quality control and safety evaluation of raw herbs and herbal dietary supplements. The first review, by Academician Sinica Peigen Xiao, one of the pioneers and leaders in Chinese medicinal plant and Chinese Materia Medica, and his co-authors, provides an overview on the quality assurance of Chinese herbal medicines. The important parameters for quality assurance, including authentication and standardization of herbal products, are discussed. Quality control methods, such as the examination of taxonomic, morphological, and/or microscopic characteristics, fingerprint chromatography, and DNA molecular markers, are described and compared. On a related topic, the subsequent article by Dr. Frank Lee and co-workers addresses the immediate need of Good Agriculture Practice (GAP) for quality assurance of traditional Chinese herbs used in dietary supplements. This review points out the need to develop standardized extracts to serve as reference materials for drug discovery, product development, and quality assessment. The processes employed to prepare the extracts and the techniques used to standardize their biochemical properties are described.

In the third review, Dr. Ge Lin and co-workers discuss the most commonly used chemical markers for the quality control of medicinal herbs, particularly herbs used in traditional Chinese medicine practice. They indicate that selection of suitable chemical markers is critical to the quality control and standardization of medicinal herbs; however, this is not a straightforward issue and is susceptible to various pitfalls. The ideal chemical marker is the active principle whose clinical efficacy contributes to the therapeutic effect of the herb. The worst ones are analytical markers and phantom markers whose pharmacological actions are unknown, uncontrollable, or unpredictable.

In the fourth review Dr. J.-T. Cheng and co-workers discuss the application of bioassays in assessing the safety and/or quality control of herbal products, addressing the multiple advantages of bioassays. It is understood that there is no single method to assure absolute quality, and thus bioassays combined with other experimental data, such as plant macro and microscopic analysis, chemical profiling, and DNA fingerprinting, etc., offer the most reliable approach to ensuring the safest and most efficacious herbal products. The subsequent review by Wang *et al.* introduce the concept of pharmacovigilance planning initiated by the International Conference on Harmonization (ICH) in 2004, and the importance of evidence-based justification of medicinal products for risk prevention and minimization. The potential risks of co-medication of conventional medicine with complementary/alternative medicine are discussed.

Identification of carcinogenic components in herbal plants is timely and important but has received less attention. In this respect, aristolochic acid (AA) contained in *Aristolochiaceae* plants has received the most attention because it has been found to exert nephrotoxic, genotoxic, and carcinogenic activities in humans. Dr. Tao Chen, in his review, presents the genotoxicity of AA and discusses the possible mechanisms by which aristolochic acid induces mutation. Evidence from genotoxicity tests indicates that aristolochic acid is a clastogenic agent that breaks DNA and results in chromosome damage and chromosome mutations. The overall results indicate that aristolochic acid is a mutagenic

carcinogen. Pyrrolizidine alkaloids are a class of hepatotoxic and tumorigenic phytochemicals present in more than 6000 plants and have been detected in herbal plants and dietary supplements. In the seventh review of this Special Issue, Fu *et al.* present the analytical methods used to identify and quantify pyrrolizidine alkaloids in herbal plants and commercial samples. The human exposure to, and metabolic activation leading to hepatotoxicity and tumorigenicity of, the pyrrolizidine alkaloid-containing Chinese herbal plants are briefly addressed.

To further highlight the importance of determining whether or not an herbal dietary supplement possesses carcinogenic activity, Drs. Po-Cheun Chen and Peter Fu, in the last review article, discuss biological and toxic effects of *panax* ginseng. *Panax* ginseng and a number of herbal dietary supplements nominated by the U.S. FDA and NIH are currently undergoing National Toxicology Program (NTP) chronic toxicology and carcinogenicity studies. This illustrates the prudent actions taken by the U.S. federal agencies regarding the safety assurance of herbal dietary supplements in America. Similarly, an organized effort with international participation on the subject should be actively pursued so that the safety of commercial herbal plants and herbal dietary supplements can be ensured.

Of the eight original research articles presented in this Special Issue, the first four address methodologies to determine the quality of herbal products. Tzu-Chao Lin *et al.* present the use of Internal Transcribed Spacers as useful markers for authentication of the Chinese herb Dangshen. Chwan-Fwu Lin *et al.* establishes an HPLC method for simultaneously determining bakuchiol, psoralen, and angelicin in Fructus Psoraleae (Buguzhi, the fruits of *Psoralea corylifolia*) and its commercial concentrated products. Zhao and co-workers develop an extraction protocol to obtain reliable quantitative conversion of conjugated ferulic acid into its free forms and accurately determine the quantity by HPLC, for quality assessment. The fourth research article by Wen and co-workers, discusses an HPLC analytical method for quantitation of anthraquinone aglycones in Rhei rhizome, crude Polygoni multiflori radix, processed Polygoni multiflori radix, and Cassiae torae semen.

The last four research articles address the toxicity of herbal plants and herbal dietary supplements. Mei and Chen determine the types of mutations and mutant frequencies induced by comfrey in the lungs of transgenic Big Blue rats. Jueu-Tang Cheng and co-workers study the hepatic injury caused by chronic consumption of an alcoholic preparation of the herbal product Kinmen alcoholic medicine, a popular commercial product in Taiwan, and determine that alcohol is responsible for the liver damage. The authors propose that this finding can be used as the reference for a safe strategy for drinking alcoholic medicines in Taiwan. Dr. Frank Lee and co-workers determine that some Lingzhi products sold commercially in China and Southeast Asia are contaminated by heavy metals. The last research article, by Jen-Chih Tseng *et al.*, addresses that 7,8-dehydrorutaecarpine is a potent inhibitor of both CYP1A1 and CYP1A2 and that introduction of a methoxyl group into the molecule reduces CYP1A1 inhibition and enhances the relative inhibition selectivity to CYP1A2 or CYP1B1. These results suggest that modification of herbal plants can change their role on herb-drug interaction.

The editor sincerely thanks the authors for their efforts and submission of their manuscripts in a timely manner. We hope this issue will provide guidance to professionals in toxicology, food science, regulatory agencies, and the herbal dietary supplement industry.

#### ACKNOWLEDGEMENTS

This article is not an official U.S. Food and Drug Administration guidance or policy statement. No official support or endorsement by the U.S. Food and Drug Administration is intended or should be inferred.