Acta Pharmaceutica Sinica B 2015;5(1):38–46

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Acta Pharmaceutica Sinica B

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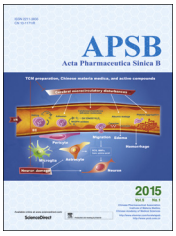

REVIEW

Safety issues and new rapid detection methods in traditional Chinese medicinal materials

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Received 21 October 2014; received in revised form 25 November 2014; accepted 12 December 2014

KEY WORDS

Traditional Chinese medicine;
Safety issue;
Rapid detection;
Mycotoxins;
Pesticide residues;
Authentication;
2D DNA barcodes;
Traceability

Abstract The safety of traditional Chinese medicine (TCM) is a major strategic issue that involves human health. With the continuous improvement in disease prevention and treatment, the export of TCM and its related products has increased dramatically in China. However, the frequent safety issues of Chinese medicine have become the 'bottleneck' impeding the modernization of TCM. It was proved that mycotoxins seriously affect TCM safety; the pesticide residues of TCM are a key problem in TCM international trade; adulterants have also been detected, which is related to market circulation. These three factors have greatly affected TCM safety. In this study, fast, highly effective, economically-feasible and accurate detection methods concerning TCM safety issues were reviewed, especially on the authenticity, mycotoxins and pesticide residues of medicinal materials.

Abbreviations: AA, aristolochic acid; Afs, aflatoxins; DON, deoxynivalenol; GICA, gold immunochromatographic assay; LOD, limit of detection; OTA, ochratoxin A; PAs, pyrrolizidine alkaloids; SNP, single nucleotide polymorphism; SSCP, single-strand conformation polymorphism; ZEN, zearalenone

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Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

http://dx.doi.org/10.1016/j.apsb.2014.12.005

1. Safety issues of traditional Chinese medicine (TCM)

1.1. Safety issues of adulterants and toxic TCM in the market

Various TCM materials are confusing because of historical and geographical reasons and this confusion brings enormous danger to the TCM safety. Potent toxic substances, including aconite, aristolochic acid, anticholinergic, podophyllin, grayanotoxin, pyrrolizidine alkaloids, matrine, gelsemine, teucvin and strychnine[1–4], were easily misidentified, erroneously substituted with other herbs or intentionally adulterated for greater benefit. Traditional identification methods recognize materials by the morphological characteristics of TCM; such methods mainly depend on the expertise of the person who identifies. Once misidentified, the TCM can cause serious toxicity problems[5–8]. The problem is, however, that we are facing the lack of the experts in TCM identification. At present, the most commonly used detection platforms are based on analytical laboratory instruments. These approaches fail to meet the purpose of rapid on-site analysis in the quarantine clearance of quarantine-related departments.

1.2. Mycotoxin-related safety problems of TCM materials

Medicinal plants are the main raw materials in TCM production. These plants may be infected by fungi and mycotoxins during their growth in fields or in the process of harvest and storage, thereby increasing the odds of significant health problems induced by TCM (*e.g.*, teratogenesis, immunotoxicity or even cancer)[9]. Currently, 500 different mycotoxins have been recognized, among which the most common and of particular interest are aflatoxins (AFs), ochratoxins, fumonisins and deoxynivalenol (DON). Medicinal plants, such as platycladi seed and raw malt, are often infected by AFs[10]. The positive rate of AFs present in *Nelumbo nucifera* (Gaertn.) is up to 70%, in which the content of 30% AF B1 samples and the total content of 25% AF samples both exceeds the standard limits of 5 μg/kg and 10 μg/kg, respectively[11]. Moldy licorice samples are infected by both AFs and ochratoxin A (OTA), and their infection levels are relatively high[12,13]. In OTA investigations of 57 medicinal material samples distributed in six regions in China, the results showed that the positive rate of molded samples by storage is 74%, and that of un-molded samples is only 8%. The OTA content of partial samples exceeded the standard limit set by the European Union, implying serious undetected toxicity for clinical drug use[14]. Furthermore, Semen Coicis listed in the 'Medicine Food Homology' could be easily infected by zearalenone (ZEN) besides DON, and Baohe pills made from the powder of Semen Coicis are also easily infected by DON[15,16]. In recent years, foreign scholars reported that 5% OTA in licorice root was transferred into boiling tea, and 1% OTA was transferred into impregnated tea[17–19]. The above results demonstrate the urgent need for the monitoring of mycotoxin residues during TCM production.

1.3. Pesticide-related safety problems of TCM materials

More than 12,000 pesticides exist throughout the world. The pesticides mainly found in TCM materials include organochlorine, organophosphorus, pyrethroid and carbamate pesticides[20,21]. Although organochlorine pesticides have been banned for many years, their residues may still exist in TCM because of their stable nature. Moreover, these residues are uneasy to decompose and can be stored in water, soil or biological organisms for a long time. Long-term use of TCM may lead to exposure to pesticide residues beyond safety limits, resulting in bioaccumulation and poisoning. Some cause-and-effect relationships of pesticides (*e.g.*, arsenide and organochlorine) have been clearly established. Epidemiological investigations showed that the risk of cancer is increasing in rural areas, including leukemia, malignant brain tumor, testicular cancer, multiple myeloma and lymphoma. Washing methods can be used to remove residual water-soluble pesticides from the plants successfully. However, to remove most fat-soluble pesticides, which possess high biological attachment coefficient, strong penetrability, and can easily enter plant, washing is much ineffective.

In view of the above, the establishment of accurate, rapid and simple methods for safety monitoring of TCM materials is urgently needed.

2. New rapid detection methods of the safety monitoring of TCM materials

2.1. Rapid detection of authenticity

2.1.1. DNA barcode

DNA barcode was proposed for the first time by Canadian zoologist Paul Hebert in 2003[22]. It is a new molecular diagnostic technology that identifies species using a recognized standard short sequence in the genome. Gregory[23] believed that global DNA barcode innovation research would become a "big science" program after the human genome project. Miller[24] explained and popularized DNA barcoding in "the Renaissance of DNA barcode and taxonomy". DNA barcode has become a global research highlight and direction for biological taxonomy in both academic journals and lay media. DNA barcoding technology has superceded the limitations imposed by traditional morphological identification methods. By establishing a TCM identification database, the digitalized DNA barcode moves TCM identification methods from morphological identification to molecular identification[25].

Based on standardized DNA barcodes and universal primers, the DNA barcode method is universal. By comparing sequences among species, identification can be easily processed without the taxonomic knowledge of a specialist. DNA barcoding is not restricted by morphological characteristics and physiological conditions. Researchers can accurately determine the information of a species by analyzing DNA sequences. Chen et al.[26] first developed ITS2 as a DNA barcoder of medicinal plants, established a plant barcode identification system that was mainly based on ITS2, and used *psbA-trnH* as a complementary barcode. This system has high identification efficiency in Rosaceae, Asteraceae, and many other families or genera[27–33]. Chen et al.[34] also developed an animal barcode identification system, which was mainly based on CO1, and used ITS2 as acomplementary barcode. Chen et al. completed the construction of a standardized DNA barcode database of TCM materials and identification website (http://www.tcmbarcode.cn/en/). With this platform, rapid identifi cation of original plants, pills, powder, tissues, or cells can be realized. The TCM barcode database will become permanent data that can be improved by adding new research sequences from taxonomists. Based on the database of the TCM barcode, Chen et al. designed the DNA barcode identification software for many companies to meet their requirements of rapid detection. Chen's research[35,36] proposed a new perspective for potential universal barcode sequence identification of all land plants, stimulating wide