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Review

A review of traditional and current methods used to potentially reduce toxicity of Aconitum roots in Traditional Chinese Medicine

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ABSTRACT

Context: Aconitum species are well-known for their medicinal value and high lethal toxicity in many Asian countries, notably China, India and Japan. The tubers are only used after processing in Traditional Chinese Medicine (TCM). They can be used safely and effectively with the methods of decoction, rational compatibility, and correct processing based on traditional experiences and new technologies. However, high toxicological risks still remain due to improper preparation and usage in China and other countries. Therefore, there is a need to clarify the methods of processing and compatibility to ensure their effectiveness and minimize the potential risks.

Object: The aim of this paper is to provide a review of traditional and current methods used to potentially reduce toxicity of Aconitum roots in TCM.

Materials and methods: The use of Aconitum has been investigated and the methods of processing and compatibility throughout history, including recent research, have been reviewed.

Results and conclusions: Using of the methods of rational preparation, reasonable compatibility, and proper processing based on traditional experiences and new technologies, can enable Aconitum to be used safely and effectively.

1. Introduction

In TCM, toxic herbs refers to certain types of drug which have known toxic or side effects but where the efficacy is recognized within the TCM system (Wang et al., 2009). They cause toxic reactions or serious side effects when they are used improperly or over-dosed; and can even endanger lives (Dickens et al., 1994). However, in general, toxic herbs have a potent pharmacological activity. Therefore, their therapeutic range and curative effect cannot be replaced by conventional Traditional Chinese Medicine (TCM). Consequently, for thousands of years, throughout the development of TCM, toxic herbs have always played an important role (Xia, 2011). In the *Shennong Bencao Jing*, the earliest book of Chinese materia medica, the drugs were classified into three grades from toxic to nontoxic. For example, Aconitum is listed under the inferior category in the *Shennong Bencao Jing* because of its high toxicity. It is clear that historically the Chinese physicians had a deep understanding of potential risks of certain TCM preparations and recognized that strict control of dosage, reasonable compatibility, attenuated processing and correct decocting methods were needed to reduce or eliminate harmful effects (Bai, 2010). Processing and compatibility are characteristics of TCM that play an important role in ensuring the safe use of potentially toxic herbs (Cao et al., 2014).

Processing refers to the necessary procedure before using or producing Chinese pharmaceutical preparations (Xiao et al., 2016). The processing of TCM is determined by the source of the Chinese herbal medicine (D.K. Zhang et al., 2015). Chinese herbal medicine is derived from natural sources and may therefore contain poisonous substances which can affect safety and effectiveness (Abbott, 2005). TCM preparation must be processed to ensure the ideal balance of safety and effectiveness (especially safety). The theory of processing was clearly represented in *Yixue Yuanliu Lun(1757 , written by Xu Dachun, a Well-known Therapeutist in Qing Dynasty)* is: “Herbs with a lot of pharmacological activity are both beneficial and harmful. When processed in an appropriate way, its advantages are retained and its toxicity is reduced.” Complex processing of Chinese herbal medicine

Abbreviations: TCM, Traditional Chinese Medicine; DDA, diester diterpene alkaloid; MDA, monoester diterpene alkaloid; NDA, non-esterified diterpene alkaloid; AC, aconitine; MA, mesaconitine; HA, hypaconitine; BAC, benzoylaconine; BMA, benzoylmesaconine; BHA, benzoylhypaconine; GL, diammonium glycyrrhizinate; RG, Radix Glycyrrhizae; ZR, Zingiberis Rhizoma; CF, Chebulae Fructus; RPA, Radix Paeoniae Alba; LC/ESI/MS^n, liquid chromatography-electrospray ionization multi-stage mass spectrometry; PF, paeoniflorin; LD_{50}, median lethal dose; C_{max}, maximum plasma concentration; AUC_{0-t}, the concentration–time curve; CP 2015, Chinese Pharmacopoeia 2015

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has the ability to enhance the effects and reduce the toxicity or side effects. One of the main purposes of TCM processing is to detoxify the preparations (Yang et al., 2013).

After thousands of years, through clinical application, and continuous improvements, many processing methods for toxic herbs have been explored in order to detoxify a poison (Bai et al., 2009). Agkistrodon (*Agkistrodon acutus* (Güenther)) is toxic because its head contains a poisonous gland, removing the head is needed for safe use in clinical practice. Croton (*Croton tiglium* L.) is poisonous , in clinical practice Croton cream is commonly used after being processed by steam heating and defatting (Zeng et al., 2012). Steaming causes poisonous protein denaturation of the toxic constituents and the defatting by pressing reduces the content of toxic oil ensuring the toxic components are controlled within a safe dose range (Zhang et al., 1992) . Crude Pinelliae Rhizoma (*Pinellia ternata (Thunb.) Breit.*) contains a poisonous needle that consists of a toxic protein and calcium oxalate crystal; a mechanical stimulation is caused by the needle crystal and a chemical stimulus is induced by the toxic protein; this occurs simultaneously in the body (Yu et al., 2015a, 2015b). Pinelliae Rhizoma praeparatum, a processed product of Pinelliae Rhizoma, which is processed by: decocting together with Radix Glycyrrhizae (RG, made from the root of *Glycyrrhiza uralensis Fisch.*, *Glycyrrhiza inflata Bat.*and *Glycyrrhiza glabra* L.)and then soaking with lime water (F. Zhang et al., 2008; L. Zhang et al., 2008). Modern research shows that soaking with lime water can eliminate the side effects by destroying the poisonous needle crystal structure and denaturing the toxic protein (Wu et al., 2012) . Unprocessed Strychni Semen (*Strychnos nux-vomica* L.) is for external application only because of its high toxicity. When it is processed by sand-scorching, there is no decrease in pharmacological effects, however, the toxicity is greatly reduced due to strychnine and brucine transforming to corresponding special-shaped structures and nitrogen oxide by isomerization (Jia et al., 2009) ; after being sand-scorched, the hard texture becomes loose texture and makes active ingredients easily dissolve (Ying et al., 2013). There are numerous similar examples of toxic herbs being detoxified by processing. Over time and with further research an understanding has been gained of how processing reduces the toxicity of potent herbs. Processing toxic herbs in order to reduce their toxicity and side effects is an important step to ensure the safe usage of toxic herbs (Feng and Min, 2014).

Compatibility of Chinese materia medica is a characteristic and advantage in TCM prescriptions (Zhen et al., 2015). The compatibility of drugs causes there to be some interactions between the drugs. The original performance changes, resulting in different effects. Through reasonable compatibility, TCM not only can enhance the curative effect, but also reduce or eliminate drug toxicity (Guo et al., 2012). The compatibility of toxic herbs with other herbs can reduce the toxicity in clinic, this was acknowledged by generations of physicians and gradually formed the theory of compatibility in TCM. The Prescription Principles: sovereign, minister, assistant and guiding, were early recorded in the Huangdi Neijing (*a classic book of traditional Chinese medicine, written during the period of 475 BCE to 26 CE*), of which the assistant and guiding medicine refers to the herbs used to detoxify the toxic herbs and alleviate the drastic effects. “The toxic effects of herbal medicine should be detoxified, methods of mutual restraint and mutual suppression are achievable”, recorded in *Shennong Bencao Jing*. That was the main theoretical basis of compatibility in TCM reducing toxicity, meaning that using a drug can reduce or eliminate the toxicity or side effects of another drug. In TCM, many examples of compatibility used to guard against toxicity were recorded in *Shanghan Zabing Lun*, written by Zhang Zhongjing (*a famous therapeutist, honoured as a medical sage in China*) in the Han Dynasty. For example, Zingiberis Rhizoma (ZR, made from the root of *Zingiber offcinale Rosc.*) was combined with Fuzi (*Radix Aconiti Lateralis Preparata*) in *Sini Soup*. Modern studies looking at aspects of chemical composition change, pharmacodynamics, and pharmacokinetics have revealed that not only can the combination with ZR enhance cardiac effects but it can also detoxify Fuzi (Peng et al., 2013). Another example, Pinelliae Rhizoma mostly combined with ginger in prescriptions; its main purpose lies with the ginger being able to reduce its toxicity (Wu et al., 1998b). Zhao et al. have reported that ginger juice can inhibit the inflammatory reaction caused by the needle crystal of calcium oxalate in crude Pinelliae Rhizoma (Zhao et al., 2013; Wu et al., 1998a). Through reasonable compatibility, the reduction of toxicity in toxic herbs is achievable, which is an important part in the theory of traditional Chinese medicine. Combinations, such as Fuzi and RG, Chuanwu, and Radix Paeoniae Alba (RPA, made from the root of *Paeonia lactiflora Pall.*), were widely used in clinic by doctors in past dynasties (Wang et al., 2012).

Aconitum, as a representative of toxic herbs, is widely used in clinical practice in China. Aconitum was first recorded in the book *Shennong Bencao Jing*, which dates to a period around 200 BCE to 200 CE, more than 2000 years ago (Li et al., 2013). The treatment effect of Aconitum is reported to be very significant, especially in rescue critical illnesses, and chronic, stubborn diseases, showing a unique curative effect. It has been widely used in clinic since ancient times. Modern medical research shows that Aconitum has anti-inflammatory, analgesic, and anti-tumor effects (Wada et al., 2007; Zeng et al., 2010; Solyanik et al., 2004; Li et al., 2013). There are about 50 herbal formulas containing Aconitum, recorded in the Chinese Pharmacopoeia 2015 (CP 2015), such as “Fuzi Lizhong Wan”, “Xiao Huoluo Dan”, “Jingui Shenqi Wan”, “Xiaojin Wan”, and “Fengshi Gutong Jiaonang”. Moreover, Fuzi has always been regarded as the most important medicine in history to restore Yang. There is a large number of formulas containing Fuzi as a main ingredient, such as ‘Sini Tang’(formulation that revives the Yang for resuscitation, for cold limbs and cold sweat), ‘Wutou Tang’ (formulation for rheumatic arthritis) and ‘Zhenwu Tang’ (formulation for warming Yang to promote diuresis, for dysuria, heavy limbs or edema) etc. Unprocessed Aconitum contains aconitine type alkaloids with high toxicity, so it is hazardous in clinical use (Vietnam, 1990). If Aconitum is not processed or where the processing is not sufficient, taking it may be poisonous and severe cases may lead to death (Chan et al., 1993; Csupor et al., 2009). From 1995–2013, there were eight reports of aconite poisoning after consumption of these herbal soups and meals, including two reports of large clusters of cases (n = 19–45) and two reports of cases (n = 15–156) managed by two hospitals over a period of 4.5–5 years (Chan et al., 2014). The main toxic and effective components of the crude Aconitum are two kinds of terpenoid alkaloids. As a result of its toxic components, Aconitum has a narrow therapeutic window (He and Yan, 2012) and frequent reports of incidents caused by unsafe usage highlight the risks (Chan et al., 2014; Ma and Zhang, 2006; Guo, 2014). Processing and reasonable compatibility can reduce the toxicity and achieve the purpose of treatment, which guarantees safe usage and effectiveness when using aconitine in clinic. This paper discusses how traditional Chinese medicine can achieve a safer and effective application of Aconitum through validated processing methods and rational compatibility.

2. Summary of Aconitum

2.1. Botany

Aconitum belongs to the Ranunculaceae, which includes over 300 species distributed in the temperate regions of the northern hemisphere. Among them are 211 species in China, most are found in Sichuan, Yunnan, and Tibet (Committee for the flora of China of Chinese Academy of Sciences, 2004; Luo et al., 2005). And 76 species of Aconitum have been used as herbal medicine or ethnomedicine. In CP 2015, only two species have been recorded. One is *Aconitum kusnezoffii Reichb.*, named “Caowu” (草乌) (Fig. 1C) in Chinese,