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ScienceDirect
Chinese Journal of Natural Medicines 2017, **15**(1): 0049–0061
Chinese Journal of Natural Medicines

Establishment of one-step approach to detoxification of hypertoxic aconite based on the evaluation of alkaloids contents and quality

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Available online 20 Jan. 2017

[ABSTRACT] Aconite is a valuable drug and also a toxic material, which can be used only after detoxification processing. Although traditional processing methods can achieve detoxification effect as desired, there are some obvious drawbacks, including a significant loss of alkaloids and poor quality consistency. It is thus necessary to develop a new detoxification approach. In the present study, we designed a novel one-step detoxification approach by quickly drying fresh-cut aconite particles. In order to evaluate the technical advantages, the contents of mesaconitine, aconitine, hypaconitine, benzoylmesaconine, benzoylaconine, benzoylhypaconine, neoline, fuziline, songorine, and talatisamine were determined using HPLC and UHPLC/Q-TOF-MS. Multivariate analysis methods, such as Clustering analysis and Principle component analysis, were applied to determine the quality differences between samples. Our results showed that traditional processes could reduce toxicity as desired, but also led to more than 85.2% alkaloids loss. However, our novel one-step method was capable of achieving virtually the same detoxification effect, with only an approximately 30% alkaloids loss. Cluster analysis and Principal component analysis analyses suggested that Shengfupian and the novel products were significantly different from various traditional products. Acute toxicity testing showed that the novel products achieved a good detoxification effect, with its maximum tolerated dose being equivalent to 20 times of adult dosage. And cardiac effect testing also showed that the activity of the novel products was stronger than that of traditional products. Moreover, particles specification greatly improved the quality consistency of the novel products, which was immensely superior to the traditional products. These results would help guide the rational optimization of aconite processing technologies, providing better drugs for clinical treatment.

[KEY WORDS] Aconite; Detoxication methods; Quantitative determination; Cardiac effect; Quality consistency.

[CLC Number] R917 **[Document code]** A **[Article ID]** 2095-6975(2017)01-0049-13

Introduction

Aconite, also called “Fuzi” in Chinese, is derived from the processed lateral root of *Aconitum carmichaelii* Debx. As one of the most important emergency drug, it has been widely used in East Asia for 2 000 years [1]. Aconite is extremely wonderful for its cardiac effects and cardiac toxicity [2]. On one hand, there are significant cardiotonic effects for acute and chronic heart failure either used alone or in combination with other drugs [3-5]. On the other hand, cases of poisoning related to taking aconite herbs or their preparations are reported every year, and many of them are thought to be associated with herb quality [6-7]. For the safety of clinical applications, the use of aconite only after careful processing has become a classic creed in traditional Chinese medicine.

Since ancient times, more than seventy kinds of detoxification methods have been developed [8]. However, those traditional methods are typically carried out with complex processes, including burning, grilling, baking, boiling, soaking, and steaming, which result in a significant loss of alkaloids [9]. Some Chinese scholars have found that more than 70%

[Received on] 15- Feb.-2016
[Research funding] This work was supported by National Nature Science Fundation of China (Nos. 81274026 and81403115).
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These authors have no conflict of interest to declare.

of the total alkaloids are lost during immersion in brine [10-11], and only about 10% alkaloids are saved in processed products. There is no doubt that the efficacy is greatly reduced. Due to the differences in experience and random factors in processing, processed products have poor quality consistency. For instance, the RSD% of diester diterpenoid alkaloids (DDAs) and monoester diterpenoid alkaloids (MDAs) in different batches of Heishunpian are 66.3% and 88.9%, respectively, according to Chen's results [12]. Furthermore, traditional processes increase the risk of introduction of hazardous substances to the final prodcuts. For instance, immersion in brine is a traditional preservation method for aconite. The material of brine is a mixture of industrial grade calcium chloride, magnesium chloride, and a certain amount of heavy metals [13]. Such substances may be introduced into aconite products and cause potential safety concern. Therefore, it is necessary to develop a new detoxification approach to overcome these drawbacks.

Currently, the toxic substances and detoxification mechanisms of aconite are well known. The key of detoxification processing is that poisonous DDAs are decomposed into the less toxic MDAs under heating conditions, and the toxicity is decreased to 1/50–1/200 of its original level [14-16]. In addition, it should be noted that loss of alkaloids is closely associated with long-time immersion and repeated washing, while quality consistency is related to the controllability of the processing flow. The simpler and more controllable the processing technology, the more stable the product quality. These observations provide a basis for developing innovative detoxification processing methods.

Based on the above analysis, we first designed a novel one-step detoxification approach for aconite in the present study. Meanwhile, crude aconite and another five kinds of products were collected as references. Fig. 1 shows the detoxification processing steps and appearance of several processed products. During the research, the contents of mesaconitine (MA), aconitine (AC), hypaconitine (HA) were determined to characterize the toxicity, while the total of benzoylmesaconine (BMA), benzoylaconine (BAC), benzoylhypaconine (BHA), neoline, fuziline, songorine, and talatisamine were determined to represent the efficacy. To further study the composition variations in detoxification processing, quantitative results were further analyzed by Cluster analysis (CA) and Principal component analysis (PCA). Moreover, the acute toxicity and cardiac effects of some representative detoxification products were compared. It is hoped that our results will help guide the rational optimization of aconite processing technologies, providing better drugs for clinical treatment.

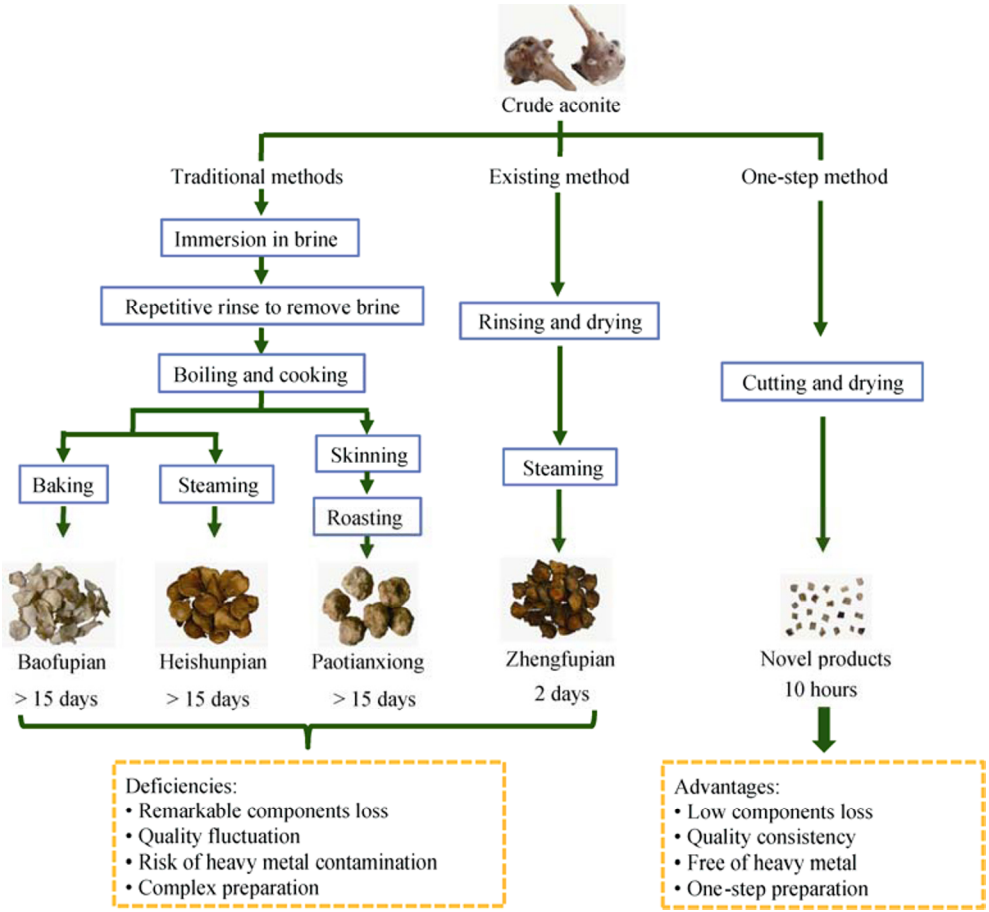

Fig. 1 Detoxification processing and appearance of several processed products