

Differentiation and Analysis of Nephrotoxicity Between *Caulis Clematidis Armandii* (Chuan Mu Tong) and *Aristolochia Manshuriensis* (Guan Mu Tong)

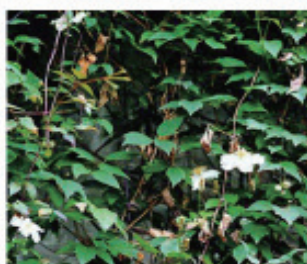
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Highlights

This paper analyzed and verified nephrotoxicity of *Aristolochia manshuriensis* (Guan Mu Tong) and *Caulis Clematidis Armandii* (Chuan Mu Tong) from the species, composition and efficacy.



***Caulis Clematidis Armandii*
(Chuan Mu Tong)**

***Aristolochia manshuriensis*
(Guan Mu Tong)**

Abstract

Mutong is a kind of medicine for promoting water circulation and drenching. There are many kinds of *Aristolochia manshuriensis* (Guan Mu Tong), which are commonly used in clinic, such as Mutong, *Caulis Clematidis Armandii* (Chuan Mu Tong) and Mutong. After the event of "Longdan Xiegan pill", the doctor made Chuanmu general taboo, or replaced it with other drugs, or did not dare to use it for a long time, which affected the clinical effect. This paper discusses the toxicity of Mutong.

Keywords: *Aristolochia manshuriensis*, Guan Mu Tong, *Caulis Clematidis Armandii*, Chuan Mu Tong

Abbreviations:

AA, Aristolochic acid; AL, Aristolochic lactam-I.

Competing interests:

The authors report no conflicts of interest in this work.

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Introduction

As early as 1964 [1], it was reported that there was serious nephrotoxicity of *Aristolochia manshuriensis* (Guan Mu Tong), but it did not cause widespread clinical attention. Until the Belgian scholar Vanherweghem et al., reported 9 cases of rapidly progressive interstitial fibrosis nephritis related to aristolochic acid (AA), the main component of aristolochic acid, in 1993, the concept of "Chinese herbal nephropathy" was put forward.

Because aristolochic acid is contained in *Aristolochia manshuriensis* (Guan Mu Tong), there is a risk of renal toxicity, so it has been stopped. As another variety of Mutong, *Caulis Clematidis Armandii* (Chuan Mu Tong) is often confused with each other in clinical practice. Many doctors and patients have a big misunderstanding about the safety of Mutong. They think that all Mutong can cause serious renal damage. This paper analyzed and verified nephrotoxicity of *Aristolochia manshuriensis* (Guan Mu Tong) and *Caulis Clematidis Armandii* (Chuan Mu Tong) from the species, composition and efficacy.

Plant species

Aristolochia manshuriensis (Guan Mu Tong) is the dry cane of *Aristolochiae* in Northeast China, which contains aristolochic acid and has certain nephrotoxicity; however, *Caulis Clematidis Armandii* (Chuan Mu Tong) is the dry rattan of *Akebia* or *Hydrangea* [3], which is different from *Aristolochia manshuriensis* (Guan Mu Tong) in genus.

Ingredients and pharmacological actions

According to modern pharmacological research, *Aristolochia manshuriensis* (Guan Mu Tong) are mainly contained aristolochic acid, aristolochic acid amine, Magnolia alkaloid, β - sitosterol, allantoin and other ingredients; Aristolochic acid is the main component [4]. For a long time, Chinese herbal medicines containing aristolochic acid have been widely used in the treatment of various diseases of digestive system, urinary system, respiratory system and cardiovascular system [5-6]. Aristolochic acid belongs to nitrophenanthric acid, which mainly contains aristolochic acid-I (AA-I) and aristolochic acid-II (AA-II). Aristolochic acid I and II are mainly metabolized as aristolochic lactam-I (AL-I) and aristolochic lactam-II (AL-II) in vivo. Because AA-I has high content in aristolochic acid and has direct renal toxicity, it

is generally considered that AA-I may be the main toxic component leading to renal damage [7]. The mechanism of aristolochic acid induced nephrotoxicity includes necrosis and apoptosis of renal tubular epithelial cells [8-10], tubular epithelial myofibroblast transformation, renal ischemia and hypoxia, AA-DNA adduct formation [11-12]. Some researchers think that the aggregation of aristolochic acids is also one of the mechanisms of nephrotoxicity [13]. At present, the nephrotoxicity of *Aristolochia manshuriensis* (Guan Mu Tong) has been confirmed by clinical research [14-18], animal experiment [19-21] and epidemiology. Its toxicity can be divided into two types: acute injury type and chronic injury type, which are mainly damage to renal tubules and between kidneys, can cause acute renal tubular injury (ADT), acute renal tubular necrosis, chronic tubulointerstitial nephritis (CIN), etc. Most of the clinical manifestations were acute renal failure (ARF) or chronic renal insufficiency. In addition to nephrotoxicity, some patients often have urinary system tumors after entering the stage of chronic renal failure, mainly located in the pelvis ureter and bladder [22]. Aristolochic acid can be accumulated in human body after long-term administration of aristolochic drugs, and there is a "dose toxicity" dependence on kidney damage [23].

The main component of *Caulis Clematidis Armandii* (Chuan Mu Tong) is oleanolic acid and other saponins, which does not contain aristolochic acid A [24] with nephrotoxicity. On the contrary, oleanolic acid has no obvious toxic effect, but also has the effect of protecting liver, reducing enzyme, reducing lipid and anticancer [25].

Efficiency

Aristolochia manshuriensis (Guan Mu Tong) is mainly used to treat such symptoms as heat drenching, upset heat in the heart, red and astringent urination, abnormal leucorrhea, amenorrhea, sore in the mouth and tongue, dampness and heat arthralgia, and postpartum milk obstruction. There is no related description of therapeutic effect on nephropathy [26]. After aristolochic acid induced nephrotoxicity was found, *Aristolochia manshuriensis* (Guan Mu Tong) was disqualified as the raw material of traditional Chinese medicine, and was excluded from the Chinese Pharmacopoeia.

Caulis Clematidis Armandii (Chuan Mu Tong) is bitter and cold, which is used to treat drenching syndrome, edema, upset urine red, sore mouth and tongue, less menstrual closure and milk, dampness and heat arthralgia, etc. It has the effect of treating acute

nephropathy.

Research on the dosage

The clinical and pathological characteristics of the nephrotoxicity cases caused by *Aristolochia manshuriensis* (Guan Mu Tong) are different. The short-term overdose of *Aristolochia manshuriensis* (Guan Mu Tong) is shown as acute nephrotoxicity, while the long-term low dose of *Aristolochia manshuriensis* (Guan Mu Tong) is shown as chronic nephrotoxicity [27]. Aristolochic acid has accumulation effect and strong carcinogenicity [28]. There are strict restrictions on the general quantity of aristolochic acid. According to research [29], the limit standard of aristolochic acid in decoction pieces is 0.00115%.

According to the pharmacopoeia in 2000 and the textbook of traditional Chinese medicine in Colleges and universities of China, the safe dosage of *Caulis Clematidis Armandii* (Chuan Mu Tong) is 3-6g [30] [31]. However, if it is taken in a short period (1-10 days) or a large amount (25-200g / day), acute renal damage may occur; Long term (66-1036 days), low dose (1g / day) administration resulted in chronic renal damage [32]. *Caulis Clematidis Armandii* (Chuan Mu Tong) has no toxicity in pharmacological research and animal test [33]. At present, there is no relevant report on renal damage caused by this drug in domestic and foreign literature.

Textual research on the materia medica of Mutong

Mutong was first recorded in Shennong's materia medica. It is named Tongcao and ranks among the best. But there is no specific shape description of the wood. In the Tang Dynasty of China, the new materia medica written by Su Jing described the characteristics of the stem, leaf and seed of Mutong. Su Jing's Mutong conform to the basic characteristics of the wooden Tongke. Therefore, Tongcao before Tang Dynasty is a kind of akebiaceae. The description of Mutong in compendium of Materia Medica in Ming Dynasty is the same as that of Materia Medica in Tang Dynasty and Song Dynasty, and there are attached figures. It is proved that Mutong belongs to the family Mutong [34]. Before the Qing Dynasty, all the recorded wood links were wood links of the family of wood links. Nowadays, the common *Aristolochia manshuriensis* (Guan Mu Tong), *Caulis Clematidis Armandii* (Chuan Mu Tong) and Mutong recorded in ancient books have the same name of Mutong, but they are actually different plants. Chinese Pharmacopoeia

(1963 edition) also includes *Aristolochiae's Passiflora*, *Ranunculaceae's Caulis Clematidis Armandii* (Chuan Mu Tong) and *Passiflora*.

Summary

Mutong is a commonly used Chinese herbal medicine. Because *Caulis Clematidis Armandii* (Chuan Mu Tong), *Aristolochia manshuriensis* (Guan Mu Tong) and Mutong of Mutong family are called Mutong for short, there has been confusion in clinical application for a long time. *Aristolochia manshuriensis* (Guan Mu Tong) and *Caulis Clematidis Armandii* (Chuan Mu Tong) have different origins, active ingredients, pharmacological effects and functions. *Caulis Clematidis Armandii* (Chuan Mu Tong) has no nephrotoxicity and high safety. This also reminds us that we should strengthen the identification study of drugs with the same name and near name, and implement the application of drugs according to the efficacy of syndrome differentiation, which can not be confused with each other, so as to reduce the occurrence of adverse reactions and improve the safety of drug use.

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