Toxicology 475 (2022) 153228

Contents lists available at ScienceDirect

Toxicology

journal homepage: www.elsevier.com/locate/toxicol

Oral subacute nephrotoxicity of aristololactam I in rats

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ARTICLE INFO

Handling Editor: Mathieu Vinken

Keywords:
Aristolactam I
Subacute nephrotoxicity
Intragastric administration
Renal inflammation
Aristolochic acid I

ABSTRACT

Aristolactams (ALs) have been recognized as one kind of metabolites of aristolochic acids (AAs), the nephrotoxic components of Aristolochiaceae plants, and are more widely distributed than AAs in herbal medicines. This study evaluated the oral subacute nephrotoxicity of aristolactam I (AL I), a representative compound of ALs. AL I was intragastrically administered to rats at 20 $mg \cdot kg^{-1} \cdot d^{-1}$ for 10 or 20 days, with aristolochic acid I (AA I) used as positive control at the same dose. After 10-day treatment, AL I led to a significant increase in early renal injury-related indices in urine and obvious histopathological lesions in kidneys, including degeneration of tubular epithelial cells, inflammatory cell infiltration and fibrosis. The lesions induced by AL I were significantly aggravated after 20-day exposure. However, AL I induced less histopathological damage in kidneys than AA I in both 10- and 20-day groups. Our results indicated that oral AL I caused nephrotoxicity by inducing oxidative stress, inflammation, and overactivation of the complement system as AA I did. Three detected apoptosis-associated indicators were not affected by AL I but remarkably increased by AA I. In summary, oral AL I induced evident renal damage in rats after only 10 days of treatment, and the damage was aggravated after 20 days. However, AL I was obviously less nephrotoxic than AA I via oral gavage.

1. Introduction

Aristolochic acids (AAs) are one kind of the acknowledged toxic constituents of herbal medicines. The renal disease "aristolochic acid nephropathy" (AAN) was induced by oral intake of herbal medicines containing AAs (Arlt et al., 2002). The toxicity of AAs has attracted widespread attention since the 1990 s (Gao et al., 2017). Whether administered orally or intravenously, AAs caused severe kidney damage in rats and mice mainly directed at the renal tubules, especially proximal tubules, resulting in cell necrosis or apoptosis, tubular atrophy, lymphocytic infiltration, and significant stromal cell fibrosis (Mengs, 1987). Current studies have demonstrated *in vivo* that, AAs are metabolized into aristolactams (ALs) after oral and intraperitoneal intake (Bárta et al., 2021; Krumbiegel et al., 1987).

Aristolactam I (AL I) is the main metabolite of aristolochic acid I (AA I) and a representative compound of ALs. *In vitro* experiments showed that AL I was more toxic to renal tubular epithelial cells than AA I and caused cell fibrosis (Li et al., 2004; Zhang et al., 2021). The cytotoxic potency of AL I and AA I was involved with the induction of apoptosis in a Caspase 3-dependent pathway (Li et al., 2010). In addition, Li pointed out that the *in vivo* renal toxicity of AL I was not weaker than AA I after intraperitoneal injection (Li et al., 2016). In Li's study, the increased content of β2-microglobulin (β2-MG) in urine occurred both in the AL I- and AA I-treated rats. However, according to another study, AL I caused no nephrotoxicity in mice after daily intraperitoneal administration for 2 weeks (Sato et al., 2004). In addition, no relevant reports on the intragastric administration of ALs were noted.

While AAs have been found only in the Aristolochiaceae family, ALs and their analogs are more widely distributed in nature (Zhang et al., 2016). Besides Aristolochiaceae plants, various ALs have also been continuously separated from herbs of Piperaceae, Annonaceae, and Saururaceae, etc. (Marques et al., 2011; Probstle and Bauer, 1992; Zhong et al., 2021).

Herbal medicines containing ALs have traditionally been used orally. Some of them are edible herbs and even widely used as vegetables in some regions, e.g., *Houttuynia cordata* (Kim et al., 2001). Nonetheless, the oral toxicity of ALs has not been explored, and the safety of herbal medicines containing ALs needs more attention. To explore the oral nephrotoxicity of AL I, a subacute experiment in rats was performed with intragastric administration of AL I for 10 or 20 days, using AA I as

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https://doi.org/10.1016/j.tox.2022.153228
Received 11 April 2022; Received in revised form 17 May 2022; Accepted 6 June 2022
Available online 8 June 2022