ABSTRACT

Aristolochic acids (AA) are the major alkaloid of Aristolochia species. Carcinogenic and nephrotoxic plant alkaloid aristolochic acid I (AAI), the major toxic component of AA, causes the development of Aristolochic acid nephropathy (AAN). It is a unique type of rapidly progressive renal fibrosis which leads to a total renal failure. AAI also causes a similar type of kidney fibrosis with malignant transformation of the urothelium, Balkan endemic nephropathy (BEN). One of the common features of AAN and BEN is that not all individuals exposed to AA suffer from nephropathy and tumor development. One possible explanation for these different responses could be individual differences in the activities of the enzymes catalyzing the biotransformation of AAI. Thus, the identification of enzymes principally involved in the metabolism of AAI, and detailed knowledge of their catalytic specificities is of a major importace.

Aristolochic acid I is oxidized by demethylation to form AAIa. This metabolic pathway is known as detoxication. AAI metabolite AAIa was separated from AAI by HPLC.

Therefore, the present study has been designed to evaluate the cytochrome P450 (CYP)-mediated oxidative detoxification of AAI in rat and human liver. The efficiency of human recombinant CYPs to oxidize AAI was also tested. To find out which cytochromes P450 are involved in AAI oxidation, we also investigated the modulation of this reaction by specific inducers and selective inhibitors of these enzymes.

The most effective in oxidation of AAI, from those used for testing, were human liver microsomal system. Of the tested human recombinant CYP enzymes, CYP1A1 and 1A2 were the most efficient in AAI oxidation. Based on these studies, we attribute the major role of CYP1A1 and 1A2 in AAI detoxication to AAIa