Investigation of hepatotoxicity of structurally diverse pyrrolizidine alkaloids in zebrafish model

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Pyrrolizidine alkaloids (PAs) are hepatotoxic phytotoxins distributed in over 6000 plant species worldwide and pose a potential threat to human health via exposure to PA-contaminated foods and herbal medicines/supplements. PA-induced hepatotoxicity is due to metabolic activation in the liver to generate toxic metabolites, and significantly different hepatotoxic potencies have been demonstrated with structurally diverse PAs. Therefore, understanding of hepatotoxic potencies of different PAs is the prerequisite for establishing an appropriate risk assessment of PA exposure. In the present study, we used zebrafish model for evaluating hepatotoxic potency of 9 different PAs, because the zebrafish model can mimic the physiological processes, in particular the hepatic metabolism, in the body. At 6 hours after oral administration, individual PAs exhibited distinct structure-dependent hepatotoxic potencies in zebrafish, evidenced by a series of biochemical and histological detrimental changes in the liver. The assessed hepatotoxic potency order was determined to be lasiocarpine ~ retrorsine > monocrotaline > riddelliine > clivorine > heliotrine > retrorsine N-oxide ~ riddelliine N-oxide >> platyphylline. In addition, compared to the control group, varied up- or down-regulated mRNA expressions in different PA treatment groups indicated that inflammation, apoptosis, and steatosis in the liver were all involved in PA-induced hepatotoxicity. Our findings demonstrated that zebrafish is a capable model for screening the hepatotoxicity and ranking the toxic potencies of different PAs, and the results obtained would assist the establishment of a more appropriate regulation for risk assessment of PA exposure.

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