Specific Comments To Authors: The authors review in depth the toxicity of pyrrolizidine alkaloids (PAs), widely used in Chines herb medicine, that may cause hepatic sinusoidal obstruction syndrome, HSOS, a progressive hepatic dysfunction that needs to be identified ab initio in order to prevent cumulative toxic effects. The etiology of the HSOS is well described and the outcomes, including MRI are convincing. Potential pathogenic mechanisms of PAs are also discussed but essentially based on protein adducts formation and decreased GSH levels. Perhaps the pharmacology associated to reduce PAs toxicity and to prevent HSOS can be developed provided the authors have clinical or experimental evidence on it. The manuscript is clear and the ideas are provided in a logical order.

Response:

Thank you so much for your positive comment. As pointed out by you, glutathione conjugation of pyrrolizidine alkaloids-derived reactive metabolites is a principal detoxification pathway in metabolism-mediated PA intoxication. In theory, the increase of GSH in hepatic sinusoidal endothelial cells will reduce the toxicity of PAs in PAs-induced HSOS patients. Oral GSH is digested by enzymes, and it does not result in the increase of GSH in hepatic sinusoidal endothelial cells. Intravenous administration of GSH might increase the level of GSH in hepatic sinusoidal endothelial cells; however, there is no evidence to support this view. Relevant studies should be performed to demonstrate the effectiveness of increased GSH levels in future.

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