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Herb-Induced Liver Injury: Systematic Review and Meta-Analysis

Ballotin *et al.* HILI: Systematic Review and Meta-Analysis

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Answers to Reviewers

Reviewer 1

This systematic review identified herbal products associated with herb-induced liver injury (HILI) and described the type of lesion associated with each product with appropriate use of data sources. This paper raises awareness in the risks of medical and non-medical use of herbal products, and may benefit their applications in health care and maintenance.

We appreciate your input on our paper and we hope we can solve all of the three suggestions accordingly.

Major concerns:

1. The administration route of herbal products should be clarified or classified (if more than one route was used) in this study, e.g., by oral administration or injection, since it may greatly affect the results.

We have added the route of herbal administration in the discussion. In only 3 cases the route of administration of the herb was not oral. We added the respective references.

2. The lifestyle of patients such as smoking and alcohol can also contribute risk factors associated with liver injury. If possible, it is suggested to exclude these factors from herb-induced liver injury; otherwise, related discussion is suggested.

We have added a comment about smoking and alcohol in the discussion and other comorbidities. Alcohol use and smoking were reported by the articles in 26 and 7 patients respectively. Therefore, alcohol use and smoking correspond to a small percentage of the included cases. Lifestyle was not reported by the majority of studies, so its relationship with a worse HILI needs further investigation.

3. It's better to evaluate the correlation between age/dose/sex and HILI risks, thus the significance of this paper can be improved.

We have described the age, sex, quantity ingested and other HILI risks when available in the section about main herbs. An analysis with a direct correlation with our data is not possible, so a descriptive approach was used.

Response to Editors

We thank you for the input and the opportunity for improving our manuscript. We hope we have corrected every shortcoming accordingly, as we state below.

1. We have prepared and arranged all figures into the PowerPoint file;
2. We have added PMID and DOI in the reference list. The first page of articles without PMID or DOI was upload in supplementary material.
3. We have added the Article Highlights section in the manuscript.