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Re: Severe Liver Injury Due to Herbal and Dietary Supplements and the Role of Liver Transplantation (World J Gastroenterology Manuscript NO: 50861)

Dear Sir/Madam,

We are submitting our revised manuscript on *Severe Liver Injury Due to Herbal and Dietary Supplements and the Role of Liver Transplantation*.

We have addressed the reviewers' comments as indicated below:

Reviewer #1: The review of severe liver injury (LI) due to herbal and dietary supplements (HDS) & the role of liver transplantation is timely and interesting. The description of LI caused by HDS in the respective countries is also interesting, but some analyses may be needed to review the LI due to HDS. The UP-TO-DATE well documents about LI due to HDS, but does not precisely about liver transplantation for the LI due to HDS.

Thank you for your thoughtful comments.

Reviewer #2: Drugs and dietary supplements induced liver injury has increasingly become a major clinical problem worldwide. This work by Priya Grewal et al reviewed the geographic variability of herbal and dietary supplements (HDS) - related DILI in major areas in the world. This review is instructive which includes issues in interpretation and comparison of global data, liver transplantation (LT) in this population, and emphasizes the need for physicians to be aware of the possibility of HDS use in patients with unexplained acute liver injury. This review was well organized and written. The authors are suggested to discuss the situation

in patients with underlying liver disease, such as NAFLD and chronic viral infection, since that these patients are more sensitive to HDS-related DILI, particularly in China and other far east regions.

Thank you for your thoughtful comments.

There is virtually no adequate data on acute liver injury from HDS occurring in patients with underlying liver disease. Based on the reviewer's suggestion, we have added a paragraph based on data from a single case series that suggested that acute injury in this setting can lead to worse outcomes. (Association between the concurrence of pre-existing chronic liver disease and worse prognosis in patients with an herb- *Polygonum multiflorum* thunb. induced liver injury: a case-control study from a specialised liver disease center in China. Jing J, et al. BMJ Open 2019;9(1):e023567. doi: 10.1136/bmjopen-2018-023567.PMID:30782709

Reviewer #3: The article discusses on an interesting topic as is the liver complications associated to HDS use. There are no much systematic analyses providing statistically reliable data, but the compilation of the information available with a critical discussion is relevant and highlights the potential risks of an increasing consumption of HDS without any strict regulation as in the case of therapeutic drugs. I would recommend to include incidence figures from the different studies in table 1 and also a new table with the products for which any adverse effects have been documented, indicating the type of complication.

Thank you for your thoughtful comments. Since the actual number of HDS users in any given country is not known the incidence figures are not reported in the literature. Thus, published prevalence figures have been displayed in the table. In response to the second suggestion, the adverse effects being evaluated were severe liver injury and liver failure leading to liver transplantation. Hence, the adverse effect was the same, mainly severe hepatocellular injury across all types of HDS used in different countries.

Reviewer #4: Comments to the Author: Thank you for allowing me to review the manuscript: "Severe Liver Injury Due to Herbal and Dietary Supplements and the Role of Liver Transplantation". I enjoyed this review. This review is well written and comprehensive about this topic. Thank you. I have one suggestion. #1 I think more tables or figures can help readers to easily understand this review. I would recommend providing a table containing characteristics of DILI from HDS in each country. Minor In the introduction, "complimentary" mistype? →complementary.

Thank you for your thoughtful comments. The spelling mistake has been corrected. Table of characteristics of DILI from HDS in each country (table 2) has been added.

Reviewer #5: The manuscript is quite well written and is a very important topic because more and more people choose alternative ways to healthcare

pharmaceutical choices. However, the Oxyelite Pro has not been completely perused. More information on the sequelae for the law are necessary. The SLIMQUICK product needs more details about the composition of the product. Finally, the French experience (France data on DILI) is missing and all three data need to be implemented to the best of my knowledge. In 2019, it is not possible to write-up such a review and missing data from the Presse Medical. There is plenty of translating services. Merci!

Thank you for your thoughtful comments. We have added a section on HDS DILI in France with additional references and more information on SLIMQUICK and OxyElite Pro.

Sincerely,

Jawad Ahmad

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