

July 21, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 19645-review.doc).

Title: Herbal medicine-related hepatotoxicity

Author: Evangelos Stournaras, Konstantinos Tziomalos

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 19645

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers. All changes are shown in red in the revised paper.

Reviewer 01560058

In this manuscript, the author pointed to the importance of being vigilant for the possible occurrence of herbal medicine-related liver injury. This is a well-written review on this field.

We thank this Reviewer for stating "This is a well-written review on this field".

Reviewer 03262381

Dear Editor, A very good review article about herbal medicine associated hepatotoxicity, a good written English and novelty at scientific content.

We thank this Reviewer for her/his positive comments.

Reviewer 00722050

Stournaras and Tziomalos wrote the narrative review of herbal medicine-related hepatotoxicity. It is indeed a narrative and not a systematic review. It does not seem to add anything new to the field. What I suggest is to re-analyze the data that the authors collected and connect them with their country or European situation, which seems to be different from the Asian and North-America setting. Once the data are collected, the authors may carry out a meta-analysis and give enormous power to their hypotheses. There is quite a difference between hypothesis and theory and, of course, conclusions. In addition, or alternatively, the authors may differentiate between childhood and adulthood and GSH systems, for instance. Please review most recent systematic reviews on this topic.

We thank this Reviewer for her/his constructive criticism. We must clarify that our paper is an invited editorial and not a review. In addition, well-performed studies in the field are few and most data originate from case reports. Therefore, a meta-analysis is difficult to perform and might have limited value, in face of the low-quality evidence on the topic. However, we reviewed again the recent literature and we added a recently published study from the United States (Gastroenterology 2015; 148: 1353-1361) and an earlier large study from Spain (Gastroenterology 2005; 129: 512-521). We added in the text "In another recent retrospective cohort study using data from a Northern California health care system between 2004 and 2014, 18.8% of cases of acute liver failure were caused by over-the-counter herbal supplements. In Europe, an earlier study performed between 1994 and 2004 in Spain reported that 9% of 461 cases of DILI were caused by medicinal herbs."

Reviewer 00181532

In this mini review, the authors review the current knowledge of liver injuries caused by herbal supplements. The manuscript is well written and I have a few minor comments.

We thank this Reviewer for stating “The manuscript is well written”.

page 3, second last line: suggest changing ‘USA’ to ‘United States’ to be consistent.

We made this change.

page 4, line 6: The authors wrote ‘...they are responsible...’. Do they mean ‘not responsible’?

No, “they are responsible” is correct.

page 6, line 4: suggest using Drug Induced Liver injury Network for consistency reason (this is the only place using DILI Network in the manuscript).

We made this change.

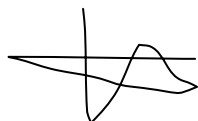
page 6, line 20: diptheroids should be diterpenoids. Please change the word in reference 22 as well.

We made this change.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Hepatology*.

Sincerely yours,



Konstantinos TZIOMALOS, MD, PhD

First Propedeutic Department of Internal Medicine

Medical School, Aristotle University of Thessaloniki, AHEPA Hospital

Thessaloniki, 1 Stilponos Kyriakidi street

54636-Greece

Fax: +30-2310994773

E-mail: ktziomalos@yahoo.com