July 1, 2016

RE: Resubmission of Manuscript N0. 26811

Dear Drs. Garcia-Olmo, Strom, and Tarnawski,

We greatly appreciate the thorough review and comments of the editorial staff and reviewers. Attached you will find a revised copy of our manuscript entitled, **"*Dangerous Dietary Supplements: Garcinia cambogia-Associated Hepatic Failure Requiring Transplantation*."** We had revised the manuscript with the reviewer comments in mind. In addition, we have addressed the reviewers concerns in a point-by-point fashion, and all changes in the manuscript are highlighted in yellow. Thank you for your consideration.

Sincerely,

Keri E. Lunsford, MD, PhD
Transplant Surgeon and Clinician Scientist
J.C Walter Jr. Center for Transplantation and
Sherrie and Alan Conover Center for Liver Disease and Transplantation
Center for Transplantation Immunobiology
Houston Methodist Hospital and Research Institute
6670 Bertner Ave., Suite R7-416
Houston, TX, 77030
klunsford@houstonmethodist.org

Response to Reviewers Comments

Response to Reviewer #1

1. *Revise the following section by giving more information on Author's example:... "for example, weight-loss supplements containing N-nitrofenfluramine affected patients exhibiting specific phenotypes of cytochrome CYP2C19 [21]. " Revision : Lunsford et al., may discuss in a better way results of the following paper they cited in the manuscript (Reference 21) "Such as one of the patients who was poor metabolizer and two patients who were extensive metabolizers. They may use and combine this knowledge with the people who were not affected by Garcinia Cambogia. 21 Kawaguchi T, Harada M, Arimatsu H, Nagata S, Koga Y, Kuwahara R, et al. Severe hepatotoxicity associated with a N-nitrosofenfluramine-containing weight-loss supplement: report of three cases. J Gastroenterol Hepatol 2004; 19(3): 349-350 They may also use the information given in the following publication: Arinc, E.: The role of polymorphic cytochrome P450 enzymes in drug design, development and drug interactions with special emphasis on phenotyping. Journal of Molecular Catalysis B: Enzymatic, 64 (3-4), 120-122, 2010.*

Certain patients may have genetic predisposition or existing liver damage compounding hepatotoxicity. Cytochrome P450 is most commonly responsible for hepatic metabolism of drugs, and genetic polymorphisms in cytochrome P450 genes can result in toxic accumulation of certain drugs or metabolites. For example, toxicity associated with weight-loss supplements containing N-nitrofenfluramine has been associated with cytochrome CYP2C19 phenotypes [21]. Mitochondrial injury, suggesting of toxic accumulation of N-nitrofenfluramine, was associated with the poor metabolizer phenotype; while, Mitochondrial injury was not identified in extensive metabolizers of the drug. One extensive metabolizer did appear to develop hypersensitivity-associated hepatitis related to drug ingestion. Toxicity to G. cambogia may have incomplete penetrance due to a similar dependence upon genetic polymorphisms. Alternatively, injury may be more likely as a second hit in the setting of pre-existing liver damage. This expanded discussion has been added to the discussion on page 7.

Response to Reviewer #2

2. *There is no information about the amount of supplement consumed per day (exactly what means: "he imbibed high daily doses of the supplement for five months"?) and about manufacturer's recommendations. It is very important fact as there is no confirmation of a dependence between an applied dose and a toxic effect. In the literature there are various examples of with the use of relatively high doses of this supplement in human obesity when the author did not observe any health risks.*

   Due to the variations in formulations and the wide variability in manufacturer concentrations and instructions, the daily dosing for Garcinia Cambogia varies widely by each manufacturer. In addition, without independent laboratory analysis of the supplement's concentration, actual and reported concentrations of ingredients can vary significantly. For these reasons, the exact dose was excluded from the original manuscript; however, at the recommendation of the reviewer, we have included these details within the revised case report. Specifically, the patient reported taking two 80mg capsules of a 5:1 concentrate of *Garcinia cambogia* three times daily prior to meals. Each 80mg pill is equivalent to 400mg of standard *Garcinia cambogia* (a total dose of 2,400 mg daily). This information has been clarified in both the case report and in the discussion.

3. *One active ingredient in this supplement is hydroxycitric acid. The authors did not specific its content in the formulation (lack of detailed composition).*

   The formulation of *Garcinia Cambogia* taken by the patient does no specify the concentration of hydroxycitric acid. We have inquired about the concentration directly from the manufacturing company. They report that they

do not assay for the hydroxycitric acid concentration since it may be quite variable. This information has been added to the revised manuscript.

Response to Reviewer #3

4. *The authors present a very interesting and important finding in a case of Garcinia cambogia-associated hepatic failure. The story is well organized and clearly presented. The effect of Garcinia cambogia on acute or chronic liver damage should be reviewed more clearly in the discussion section.*

   We appreciate the feedback of the reviewer. The exact mechanism of hepatotoxicity induced by *Garcinia cambogia* is currently undetermined given the disagreement in the scientific community regarding its hepatotoxic potential. The majority of the mechanistic studies have been performed in rodent models and results were summarized due to the fact that they are largely inconclusive as to the exact mechanism of hepatotoxicity. We have, however, expanded upon the acute and chronic effects of *Garcinia cambogia* as suggested by the reviewer.