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Revisiting acute liver injury associated with herbalife products

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Abstract

In the November 27, 2010 issue of the *World Journal of Hepatology (WJH)*, three case reports were published which involved patients who had consumed various dietary supplements and conventional foods generally marketed as weight loss products. The reference to Herbalife products as contaminated and generally comparable to all dietary supplements or weight loss products is not scientifically supported. The authors provided an insufficient amount of information regarding patient histories, concomitant medications and other compounds, dechallenge results, and product specifications and usage. This information is necessary to fully assess the association of Herbalife products in the *WJH* case reports. Therefore, the article does not objectively support a causal relationship between the reported cases of liver injury and Herbalife products or ingredients.

Key words: Herbalife; Liver; Hepatotoxicity; Weight loss products; Dietary supplements

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TO THE EDITOR

In the November 27, 2010 issue of the *World Journal of Hepatology* (*WJH*), three case reports were published which involved patients who had consumed various dietary supplements and conventional foods generally marketed as weight loss products. Case 1 involved a patient who did not consume Herbalife products, while Cases 2 and 3 each reportedly consumed various Herbalife products. Herbalife fundamentally disagrees with the conclusions made by the authors with regard to any cause and effect relationship related to the intake of Herbalife products. First, Herbalife is not a single product and no unique suspect product or ingredient has been implicated in this paper amongst the reported cases. In addition, the authors arbitrarily compared cases involving the use of a single product (Hydroxycut) with patients who consumed a group of totally unrelated products produced by the company Herbalife. To bundle a brand of products such as Herbalife with another company that sells different products simply because they are all dietary supplements is not valid. Finally, there are specific considerations, in regard to the two patients who consumed Herbalife products, that would render many of the observations and conclusions discussed by the authors as speculative and unsubstantiated. The specific and factual points supporting these views are further detailed below.

Case 2 describes a 37-year-old female who developed symptoms of abdominal pain, mild nausea, and painless

jaundice 1 mo prior to presenting at the hospital[1]. Several pertinent negatives were disclosed by the authors, including autoimmune markers and viral serology. According to the authors, the patient did not report any pre-existing medical conditions for which the onset had preceded the use of Herbalife products. However, the pathology assessment concluded that this patient's biopsy result was consistent with chronic liver disease, in which case Herbalife products were thought to have had an additive effect. This opinion contradicts repeated statements by the authors that acute liver injury in each case report was due to the use of herbal weight loss products. In addition, the etiology of the pre-existing condition was not identified by the authors, and there was no discussion regarding the role of the condition in the acute onset of her symptoms. Furthermore, the dosage and frequency at which this patient consumed Herbalife products is unknown. Finally, the inconsistency of the objective findings with the patient's reported medical history would suggest that further investigation is warranted. This should include a review of the patient's pre-existing condition, potential use of medications prescribed for her condition, other compounds she may have been consuming, and the status of her health prior to the reported incident. In the absence of the aforementioned data, the exclusion of possible differential diagnoses is not well-supported.

Case 3 describes a 53-year-old female who developed symptoms of painless jaundice and pruritus 3 wk prior to presenting at the hospital[1]. This patient denied family history of liver disease, but no discussion was provided regarding her own medical history, other than the fact that she reportedly denied the use of alcohol and did not engage in "illicit substance abuse". The authors further stated that the patient had not been prescribed any new medications, which implies that she may have been taking other agents concomitantly. However, information regarding the use of concomitant medications, or the conditions for which she may have been receiving treatment, was not disclosed. Such information is critical and should have been obtained through follow-up review of the patient's previous medical records. Without this information, it is unknown whether concomitant medication(s) were withdrawn and/or accounted for during the dechallenge process. The patient's use of Herbalife products was also not specified by product names and it is unknown whether the dosage and frequency of consumption was adherent to recommendations indicated on the product label(s). In addition to the absence of the aforementioned pertinent patient data, there are various refutable facts that remain in regard to the comments and conclusions made by the authors.

In their *WJH* article, the authors concluded that it was difficult to isolate a single ingredient or mechanism associated with acute liver injury for either patient consuming Herbalife products[1]. In an effort to discuss potential causative agents for the reported conditions in these patients, the authors extraneously reference previously published case reports involving Herbalife products, including those of two consumers who reportedly developed hepatotoxicity following exposure to *Bacillus subtilis* (*B. subtilis*)[2].

In review of this reference, it has been noted that there were various critical deficiencies in the scientific methodology used to isolate *B. subtilis* in the Herbalife samples reported to have been contaminated. For example, a dose dependent increase in LDH leakage in HepG2 cells was observed in the experimental assay, but investigators did not present any control data for their experiments, nor did they present any data that suggested this assay is a valid proxy for liver injury in healthy individuals "*in vivo*". Neither patient reported symptoms consistent with classical *B. subtilis* food poisoning and they did not report testing the product for the detection of cerulide or any of the reported heat-stable toxins associated with certain strains of *B. subtilis*. Furthermore, the investigators did not enumerate the levels of *B. subtilis* in the products tested or report testing relevant specimens from the patients for these organisms or their toxins. This was a crucial step missing in the reported investigation as all previous documented reports find that high levels of the organism must be consumed to cause illness. Herbalife products, consumed by the patients described in the *WJH* article, to date show no evidence of *B. subtilis* contamination. *B. subtilis* infections are relatively rare and seldom contracted through food sources. This bacterium is actually ubiquitous in nature and generally recognized as safe with a history of safe use in food, and is considered to be safe for the production of enzymes or ingredients for use in food[3]. There have been reported cases of *B. subtilis*-related gastroenteritis and other complications, usually involving immuno-compromised patients or those with other underlying chronic illnesses, which did not appear to be the case for any of the patients presented in the *WJH* article. Therefore, it is highly unlikely that *B. subtilis* could be the cause or have contributed to the severe hepatotoxicity of patients in either the referenced article or the two patients discussed in the *WJH* article.

The *WJH* authors also suggest intentional or incidental contamination of Herbalife ingredients and identify various potential sources, including unrefined raw herbal extracts, heavy metals, pesticides, and additives[1]. However, some of the additives mentioned as potential contaminants by the authors (e.g., flavoring, colors, and preservatives) are commonly used and well-documented industry-wide as safe for consumption in conventional foods, as well as dietary supplements,. In addition, authors also reference an article from 2002 that reviews possible contamination sources inherent to herbal remedies marketed without proper quality control measures in place[5]. Herbalife is not specifically implicated in the referenced article, yet the authors imply that Herbalife product contamination and lack of quality control contributed to the liver injury. The authors' assumption is wrong and does not take into consideration that the United States FDA requires dietary supplement manufacturers to use current Good Manufacturing Practices (cGMPs) in the produc-

tion of dietary supplements[4]. The goal of these regulations is to "ensure that a dietary supplement contains what the manufacturer intends" and meets specifications to ensure the dietary supplement contains the correct ingredient, purity, strength and composition intended. Herbalife has rigorous processes in place concerning quality control, including extensive safety reviews based on existing literature for product ingredients, testing to confirm that labeled ingredients are present in finished goods, and to assure all tested ingredients meet product specifications on an ongoing basis. In addition to complying with cGMP regulations, Herbalife acts in accordance with other generally recognized industry standards or requirements by sourcing and testing raw materials to further ensure that the final product complies with specifications for identity, purity, potency and contaminants.

The authors also try to implicate the *Camellia sinensis* (*C. sinensis*) used in Herbalife's tea drink products by citing case reports of liver injury in association with ethanolic extracts of *C. sinensis*, which contain a concentrated fraction of EGCG[1]. The most important safety consideration for green tea is the extraction method. The historical data supporting the safety of green tea is based on the consumption of an aqueous extract over thousands of years, specifically, the typical three cups per day that are commonly consumed in Asian countries. Aqueous extracts of green tea are quite different from solvent extractions, which are commonly used to concentrate select fractions of green tea, such as EGCG or caffeine. Again, the *WJH* authors have not considered the clinical significance of potential differences in raw material processing amongst manufacturers, controls for contamination and identification of raw materials, and the implication of these differences when reviewing published case reports of liver injury. In addition, the authors state that Herbalife has refused to provide detailed analyses of ingredients and formulations, although no attempt was made by these authors to contact Herbalife to obtain further information regarding Herbalife products or ingredients. Herbalife has, to date, remained compliant with all formal regulatory requests and requirements for product information.

The authors state that significant liver injury induced by herbal supplements is a rare event[1]. This statement is true as approximately 20 to 50 percent of all cases presenting as hepatotoxicity are cryptogenic leading to the incidental association of liver disease with a group of products in the absence of specific evidence[5]. While this disease is the most common cause of drug withdrawal during post-marketing surveillance, it is an uncommon cause of liver disease. The background incidence of hepatotoxicity in populations is clearly comparable to the reported incidence of immunoallergic and individualistic reactions to allergens in foods, supplements, or the environment. For example, in a study of 71 000 North Americans in 1992, the background rate of idiopathic or cryptogenic liver disease was 24 cases per 100 000 individuals compared to 14 per 100 000 attributed to cases of hepatitis B, 25 per 100 000 due to alcoholism, and 7 per 100 000 to other viral illnesses[6]. While the spectrum of liver diseases may well have changed since 1992 when this survey was done, idiopathic liver disease remains a significant percentage of all cases. Therefore, it is particularly important in making such associations to have incontrovertible evidence such as is often available for prescription drugs where, under controlled conditions, a cause-effect relationship can be established.

Finally, the authors also state that existing case reports of dietary supplement-induced hepatotoxicity include patients with pre-existing liver disease and that weight loss supplements could worsen such conditions in these patients. However, this effect could occur from many different substances, including over-the-counter and prescription medications, as these patients may be "pre-sensitized" due to an underlying hepatic condition.

In conclusion, the reference to Herbalife products as contaminated and generally comparable to all dietary supplements or weight loss products is not scientifically supported. Further information regarding patient histories, concomitant medications and other compounds, dechallenge results, and product specifications and usage is indicated to assess fully the association of Herbalife products in the *WJH* case reports. Therefore, the article does not objectively support a causal relationship between the reported cases of liver injury and Herbalife products or ingredients.

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