

Editorial

**Slimming at all costs: Herbalife<sup>®</sup>-induced liver injury** ☆

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Complementary and alternative medicine (CAM) is experiencing an astonishing boom due to the public's increasing interest in disease prophylaxis, nutrition, and improvements to health and well-being. A substantial contribution to this development includes nutritional supplements such as vitamins, antioxidants and herbals, formula diets to reduce weight, and poorly defined preparations to “shape the body”. Most individuals who use these products should be considered “customers” rather than “patients” since they have no intention to specifically treat diseases but to improve their health in general. The majority use herbal and food supplements in self medication at considerable personal expense without prior consultation and knowledge of their doctors. A countrywide survey from the U.S. revealed a prevalence between 37.5% and 67% [1] and a steady rise [2] in the use of herbal medicine and nutritional supplements. The sales of these products are enormous; for example, an impressive \$33 billion was spent on weight-loss products alone in 1999 [3]. One may welcome this development since it actually reflects the public's increased awareness of disease prevention and health, even if real benefits from these substances for consumers are minor. However, several problems exist: (1) Reports about adverse reactions, particular liver injury, have accumulated, so, these preparations are not always as harmless as perceived [4]. (2) In most Western countries including the EU and the U.S., nutritional

supplements and herbal CAM preparations are exempt from strict licensing regulations routinely imposed on synthetic drugs or medicinal products before releasing them onto the market. CAM preparations are handled like food products for which no pre-marketing approval is required. Liability remains entirely with the company and no proof of safety, let alone efficacy, has to be provided. (3) Increasingly, customers purchase herbals and nutritional supplements from largely anonymous Internet sources without consulting a doctor or a pharmacist. (4) Composition of most products is insufficiently characterized, often unlabelled, highly variable and clear beneficial effects for the consumers do not exist. (5) Companies claim that alleged health advantages would only become visible through long-term and regular use although this is not backed up by supporting clinical evidence. Therefore, the usually high costs of these products stand in utter contrast to their unproven benefits [5,6]. (6) Often, physicians' level of knowledge about dietary supplements and herbals, their regulation and potential hazards is vague and their awareness of CAM preparations as a potential source of health damage is low [7]. (7) Products are often presented in a fashion that raises unfounded hopes and expectations which cannot be fulfilled. It has to be emphasized that online information about the products offered constitutes advertisements rather than serious scientific information; this distinction is often difficult to make for most lay customers.

Apart from the lack of evidence for a long-term clinical benefit, herbal combinations taken for weight loss have been recognized as potential causes of liver injury in several case report series demonstrating acute hepatitis following the intake of LipoKinetix [8], preparations containing ephedrin [9], and green tea extracts [10].

*Associate Editor: C.P. Day*

☆ The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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In this issue of the Journal, two case report series from Israel and Switzerland for the first time describe incidents of severe liver injury along with the intake of a panel of different Herbalife® products [11,12]. Herbalife® sells nutritional and herbal supplements for weight control, improvement of nutrition, and “well-being”, and cosmetics online or through independently operating sales agents. Among the 22 cases of liver damage following Herbalife® intake analyzed in the two reports, two patients developed fulminant hepatic failure requiring super urgent liver transplantation which saved one patient’s life while the second died due to postoperative complications. Causality between the intake of Herbalife® products and the evolution of liver injury was carefully assessed by internationally accepted causality scores [13,14]. In five patients, causality was labelled “certain” by a positive re-challenge reaction and “probable” in additional 13 patients. Other potential causes were ruled out in all patients, although one patient with positivity for HBsAg seemingly developed hepatitis B reactivation and proceeded to fulminant liver failure. Considering the patients in whom symptoms and signs of liver injury recurred following re-administration of Herbalife® products, there appears to be little doubt that these products were the cause. All internationally evaluated scoring systems regard a positive rechallenge as the strongest proof of causality [13–15]. Although entirely descriptive, the two papers are important and add another, thus far unknown, candidate to the list of products that can cause liver damage.

However, the two reports raise more questions than they answer. Although causality was tested appropriately, it remains entirely speculative what might have been the cause of liver damage in the 22 patients. The patients took between 3 and 17 different Herbalife® products which makes it extremely difficult, if not impossible, to identify the crucial compound(s). Efforts by the authors to retrieve a detailed composition analysis were apparently unsuccessful since the company refused to provide such information. In 2006, the stock market quoted Herbalife® company as having a revenue of \$ 3.1 billion; the company’s reluctance to provide detailed analyses of their products’ composition is difficult to understand considering what is at stake should news about associated dangers spread. However, due to this lack of co-operation, attempts should have been made by the investigators to analyze the ingested Herbalife® products for toxins, microbial contamination or to screen affected individuals for possible immunological reactions to the consumed material. While this was not possible in the Swiss series due to retrospective data collection, at least one of the Israeli cases was apparently followed up recently as the relapse was noticed. However, neither the batch taken by these patients nor those taken by the other patients

were subjected to a closer analysis, although all patients were contacted personally. Fulminant liver failure due to bacterial toxins was described by Mahler et al. in two cases following the ingestion of reheated pasta sauce contaminated with *Bacillus cereus* which produces a hepatotoxic toxin [16]. However, such catastrophic incidents usually do not result in larger series of unrelated cases.

Another explanation for Herbalife®-associated liver damage could be a locally restricted contamination with chemicals such as softeners, preservatives, flavour enhancers, pesticides, or heavy metals either intentionally added during the manufacturing process or contained in the unrefined raw products, i.e. herb extracts [17]. This possibility could explain the different patterns of liver injury found in the two series with predominantly cholestatic hepatitis in the Swiss patients and hepatocellular hepatitis in the Israeli subjects. Two unusual patterns of injury were observed in the Swiss series – sinusoidal obstruction syndrome and giant cell hepatitis. These two lesions are typical of intoxication with pyrrolizidine alkaloids and intake of *Plantago ovata/Emblica officinalis* (Isabgol), respectively, and it cannot be excluded that the consumed Herbalife® products contained either of these compounds. Apart from these considerations, it is well-known that a single drug/substance can produce different patterns of hepatic damage. So, should further cases of Herbalife® hepatotoxicity be detected, clinicians and researchers are urged to retrieve the batch(es) that were consumed by their patients to perform detailed screenings for microbes, their toxins, and chemicals.

It remains speculative why cases of Herbalife® hepatotoxicity were only noticed in Switzerland and Israel, although Herbalife® products are sold in at least 60 countries all over the world. Based on experiences with adverse drug reactions due to synthetic drugs, simple probability should have led to additional incidents of Herbalife®-associated hepatotoxicity. Isolated series of drug-induced liver damage are highly suggestive of either significant underreporting in other countries with a more widespread consumption, or indicate the specific distribution of “spoiled” or contaminated batches. However, as the Swiss authors rightly state, the “threat to the public health” from Herbalife® products is minor and should not be exaggerated when compared with incidence rates of adverse hepatic reactions of other over-the-counter pharmaceuticals such as non-steroidal anti-inflammatory drugs [18].

The two series emphasize the need for caution regarding poorly labelled herbal weight, loss products with questionable benefits and, considering the principle “first, do no harm”, clearly shift the risk-benefit ratio against their use.

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