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Severe hepatotoxicity following ingestion of Herbalife® nutritional supplements contaminated with *Bacillus subtilis*☆

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***Background/Aims*: Nutritional supplements are widely used. Recently, liver injury after consumption of Herbalife® preparations was reported but the underlying pathogenesis remained cryptic.**

***Methods*: Two patients presented with cholestatic hepatitis and pruritus, and cirrhosis, respectively. Viral, alcoholic, metabolic, autoimmune, neoplastic, vascular liver diseases and synthetic drugs as the precipitating causes of liver injury were excluded. However, both patients reported long-term consumption of Herbalife® products. All Herbalife® products were tested for contamination with drugs, pesticides, heavy metals, and softeners, and examined for microbial contamination according to standard laboratory procedures. Bacteria isolated from the samples were identified as *Bacillus subtilis* by sequencing the 16S rRNA and *gyrB* genes.**

***Results*: Causality between consumption of Herbalife® products and disease according to CIOMS was scored "probable" in both cases. Histology showed cholestatic and lobular/portal hepatitis with cirrhosis in one patient, and biliary fibrosis with ductopenia in the other. No contamination with chemicals or heavy metals was detected, and immunological testing showed no drug hypersensitivity. However, samples of Herbalife® products ingested by both patients showed growth of *Bacillus subtilis* of which culture supernatants showed dose- and time-dependent hepatotoxicity.**

***Conclusions*: Two novel incidents of severe hepatic injury following intake of Herbalife® products contaminated with *Bacillus subtilis* emphasize its potential hepatotoxicity.**

***Keywords*: Drug-induced hepatitis; Food supplement; Herbal medicine; Herbalife; Weight reduction; Hepatotoxicity**

1. Introduction

Widespread use of nutritional supplements containing vitamins, antioxidants, trace elements, proteins, amino acids and herbal components has been recorded both in the US [1] and Europe [2,3]. Consumers turn to such products for presumed benefits regarding enhanced physical performance during sports activities, disease prophylaxis, improvement of nutritional status, and, particularly, weight reduction [2–4]. Consequently, dietary weight loss products have become a multi-billion market [5], and although not recommended for losing weight by nutrition expert panels [6,7], their long-term use without medical consultation is frequent [8]. Strong evidence supporting health advantages from these weight loss remedies is lacking and the significant costs

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of these products contrast sharply with their unproven benefits [9,10]. Even more worrisome are recent reports about adverse effects, particular liver injury, following the intake of LipoKinetix [11], preparations containing ephedrin [12], and green tea extracts [13,14] resulting in acute and chronic liver injury.

Recently, three case series from Israel, Switzerland and Spain analyzed incidents of severe liver injury after the intake of several Herbalife® products [15–17]. Among a total of twenty-six cases of liver damage following Herbalife® intake, two patients developed fulminant hepatic failure requiring liver transplantation after which one patient survived while the second died. Causality of consumption of Herbalife® products and disease was considered "certain" in six patients due to a positive re-challenge reaction, and "probable" in 16 further patients applying the CIOMS and WHO score [18,19]. However, causality scores serve as tentative diagnostic tools to compensate for lacking specific markers and are not a substitute for a clarification of hepatotoxic mechanisms; in relation to Herbalife® this remains cryptic.

Here, we describe two novel incidents of severe hepatic injury subsequent to intake of Herbalife® products contaminated with *Bacillus subtilis* of which bacterial supernatant revealed a dose-dependent direct hepatotoxicity in HepG2 cells.

2. Patients

2.1. Patient 1

A 78-year old man was referred to the Institute's out-patient clinic by his general practitioner presenting with nausea, painless jaundice, light stools, dark brown urine lasting 4 weeks, weight loss of 2.5 kg, and elevated serum levels of aspartate-aminotransferase (AST) of 2100 U/L (normal range 10–41), alanine-aminotransferase (ALT) 2339 U/L (5-41), alkaline phosphatase (AP) 168U/L (36–108), and gamma-glutamyl-transpeptidase (γ-GT) 111U/L (<60). Apart from moderate pruritus during the last week prior to admission the patient had no other skin-related symptoms. His medical history revealed arterial hypertension for several years, implantation of a hip endoprosthesis, appendectomy and cholecystectomy for cholecystolithiasis, but was otherwise uneventful regarding liver illnesses. He reported alcohol consumption between 60 and 80 g/week and denied the use of illicit drugs. Laboratory tests showed elevated serum bilirubin 611 μmol/L (3–26), decreased albumin 28 g/L (30–52), and prolonged INR 1.7. His blood cell count showed normal red and white blood cells without eosinophilia, and normal platelets. Serology and viral markers were all negative. Carbohydrate-deficient transferrin (CDT), serum iron, ferritin, transferrin saturation, ceruloplasmin and alpha-fetoprotein were normal. However, autoantibodies were elevated with anti-nuclear antibodies (ANA) at 1:1280 and anti-smooth muscle antibodies (SMA) at 1:320, but liver-kidney microsomal antibodies type 1 (LKM-1), anti-mitochondrial antibodies (AMA), p-ANCA, soluble liver antigen antibodies (SLA) and immunoglubulin subclasses G, M and A were normal. Computed tomography (CT) revealed moderate ascites, splenomegaly, and a cystic lesion located in the pancreatic head without obstructive features on either the pancreatic or the bile duct. Two follow-up CT scans revealed a stable lesion diagnosed as a cystic adenoma. Prescribed medication consisted of irbesartan/hydrochlorothiazide (300 mg/12.5 mg) and carvedilol (25 mg) for hypertension, occasional omeprazole 20 mg for reflux symptoms, and zolpidem

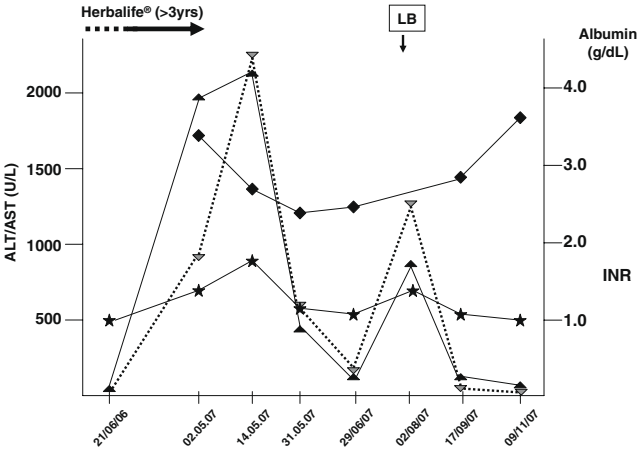

Fig. 1. Major liver laboratory results of case 1 show a biphasic course. Along with elevation of transaminases, coagulopathy and hypalbuminemia reflecting impaired hepatic synthetic function is evident. Liver biopsy (LB) was performed during the secound bout of hepatitis. (▲, AST; ▽, ALT; ♦, albumin; ★, INR).

10 mg as a sleeping aid all of which were started more than 12 months previously. Upon direct questioning the patient admitted to the consumption of a Herbalife® product (Herbalife® F1 Shake Strawberry and Cappuccino) in the previous 3 years recommended by his daughter, a Herbalife® sales person. The Herbalife® Shake was stopped whereas all other drugs were continued and was followed by an immediate improvement of liver enzyme levels and synthetic function without specific treatment. However, 8 weeks later the patient presented again with elevated serum liver enzyme activities and impaired liver function with coagulopathy and hypalbuminemia (Fig. 1). Treatment with corticosteroids at 40 mg daily and ursodeoxycholic acid at 15 mg/kg body weight was initiated resulting in a rapid normalization of abnormal liver laboratory including coagulation parameters and albumin. Both drugs were stopped 3 months after normalization of liver laboratory with no relapse after 10 months of follow-up. At the second bout of hepatitis the patient underwent transjugular liver biopsy and histology showed mixed lobular and portal/periportal hepatitis, no eosinophilia or plasma cells, marked cholestasis and partial cirrhotic transformation compatible with toxic liver injury (Fig. 2A and B). According to CIOMS, causality in this patient is "probable" due to temporal relationship, response to dechallenge, exclusion of other causes, and, although not part of the CIOMS criteria, compatible liver histology.

2.2. Patient 2

A 50-year old, female Herbalife® sales person presented with weakness, painless jaundice and fluctuating lower abdominal pain of 4 weeks' duration. She reported similar symptoms intermittently for several years, but lately, pruritus had evolved the week before presentation. Her past medical history revealed a cholecystectomy in 1978 for cholelithiasis and vaginal hysterectomy for myoma of the uterus. She denied any regular medication, alcohol consumption, drug abuse, and had stopped smoking the previous year. She had moderate jaundice, several spider angiomata on her shoulder, and her liver was tender on palpation. Clinically, there was no ascites and the spleen was not enlarged. Laboratory investigations revealed ALT levels of 128U/L, AST 153U/L, AP 597U/L, γ-GT 810U/L, bilirubin 83 μmol/L, bile acids 51 μmol/L (upper limit of normal [ULN] <20), normocytic anemia with hemoglobin of 99 g/L, elevated total cholesterol of 6.77 mmol/L (ULN, <5.00), but normal INR and serum albumin. Anti-HAV IgG were positive but other viral markers including anti-HBc, HBsAg, and anti-HCV were negative, as were ceruloplasmin, ferritin, and CDT. ANA were found slightly elevated at 1:160, but AMA-M2, SMA, SLA, p/c-ANCA tested negative and immunoglobulins G and M were normal. The patient took no prescribed medication, but repeated interrogation revealed that she had consumed

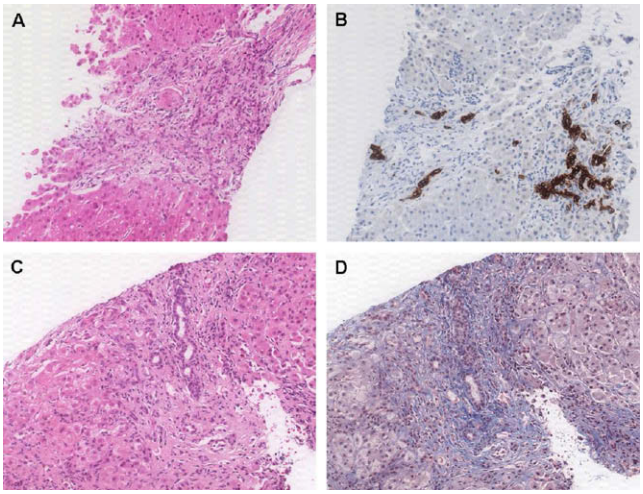

Fig. 2. (A) H&E staining of the liver biopsy of case 1 reveals a ductular reaction with increased cellularity of granulocytes and mononuclear cells, in part focused on genuine bile ducts. Moreover, collagen is increased with occurence of porto-portal septa. (B) Immuno-histochemical staining with cytokeratin 19 highlights the ductular reaction in the portal tract. (C) H&E staining of case 2 demonstrates a lobular and portal inflammation with cholestatsis and (D) an increase of collagen in the portal tracts and beginning septal demarcation.

several Herbalife® products including RoseOx tablets, Complexe Multivitaminé tablets, Thermojetics granules, Tang Kuei Plus tablets, Vitamin C tablets, Personalized Protein Powder Mix Formula 3, and Herbalifeline omega 3 fatty acid capsules daily for more than one year.

Non-invasive transient elastography determined a liver stiffness of 19.2 kPa indicative of advanced fibrosis which was subsequently confirmed by a liver biopsy showing extensive bile duct lesions, periductular fibrosis, ductopenia, ductular proliferation with granulocytic ductulitis/periductulitis, and partially complete fibrotic septa compatible with drug-induced biliary injury (Fig. 2C and D). The patient was strongly advised to stop all supplements and prescribed ursodeoxycholic acid at 15 mg/kg body weight. After 6 months without consumption of Herbalife® products clinical symptoms resided and a normalization of AST/ALT levels and marked reduction of cholestasis markers was recorded (Fig. 3).

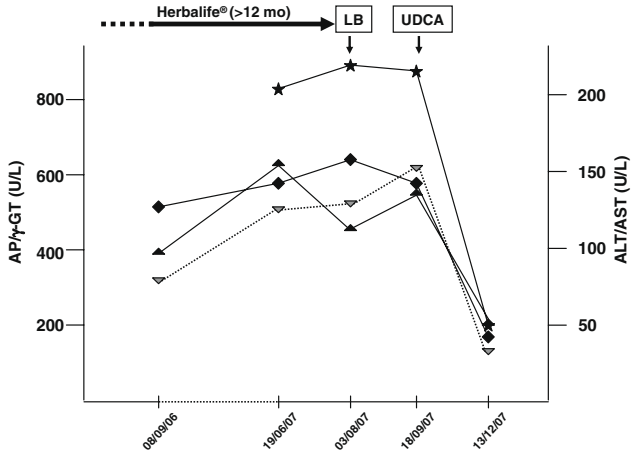

Fig. 3. Course of standard liver laboratory values of case 2. Cholestatic hepatitis was present several months prior to recognition of Herbalife® as the precipitating cause. Liver biopsy (LB) was performed at the peak of laboratory abnormalities, followed by the administration of ursodeoxycholic acid (UDCA) 6 weeks later. (▲, AST; ▽, ALT; ♦, alkaline phosphatase [AP]; ★, γ-GT).

3. Methods

3.1. Toxicological evaluation

A test for bulk toxicity was performed by extracting 100 mg of Herbalife® F1 Shake Strawberry (see case 1) with 100 mL of analytical grade methanol. This extract was directly injected into a gas chromatograph with mass spectrometric and nitrogen–phosphorus specific detection as described [20]. Also, a part of this extract was evaporated and derivatized with acetic acid anhydride, in order to protect thermally instable compounds from decomposition with the gas chromatographic inlet. In addition, 1 mL of the methanolic extract was evaporated and extracted under basic conditions. The extract was again injected with or without chemical derivatization. Subsequent mass spectra interpretation was performed using MassLib with update mass spectrometry libraries [21]. No evidence of bulk contamination or bulk toxicity was found. Specific and sensitive analyses for traces of pesticides and toxic metals were performed by the state food control laboratory in Bern [Kantonales Labor, Bern] using standard mass spectrometry procedures, but no contaminants were detected.

3.2. Testing for immunoallergic sensitization

Peripheral blood mononuclear cells (PBMC) were prepared over Ficoll gradient density centrifugation and processed as described [22]. The powder of Herbalife® – Shape Works Shake Formula 1 (Strawberry) was dissolved in RPMI-1640 medium and used in non-toxic concentrations (1, 10 and 100 μg/mL) in cell cultures with the PBMC. Stimulation was evaluated with ^{3}H-thymidine incorporation after 6 days. The product was also dissolved in 5% petrolatum and applied for epicutaneous patch tests in Finn-chambers for 24 h. Evaluation at 48 and 72 h did not register any reaction.

3.3. Testing for microbiological contamination

For microbiological analysis of Herbalife® products all samples ingested by both patients and two sealed Herbalife® products (Shape Works Shake Formula 1 Cappuccino) were processed and cultured using standard laboratory procedures. DNA was extracted from culture by using the PrepMan® Ultra Sample Preparation Reagent (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instruction. *Bacillus subtilis* was identified by sequencing the16S rRNA and *gyrB* genes, and analysis of the cellular fatty acids. Amplification and sequencing of the 16S rRNA was performed by using the MicroSeq® 500 16S rDNA Bacterial Identification Kit (Applied Biosystems) according to the manufacturer's instructions. A GeneAmp® PCR System 9700 (Applied Biosystems) was used for amplification and cycle sequencing. Capillary electrophoresis of sequencing products was performed using an ABI 310 Genetic Analyzer (Applied Biosystems). Further sequencing analysis was based on the amplification and sequencing of the *gyrB* gene of *Bacillus* spp. by using a BigDye® Terminator Sequencing Kit v1.1 (Applied Biosystems) as described [23] using sequencing primers displayed in Table 1. DNA sequences were assembled and analyzed with SeqMan and MegAlign computer programs (DNASTAR, Madison, USA). Comparison of DNA sequences and their corresponding amino acid sequences with sequences in the GenBank database were performed with BLAST [24].

Table 1
Primers used for sequencing of the *gyrB* gene of *Bacillus* spp.

Sequence	Primer
gyrB_Bsub_SF_2	5′-TGA AGA GCC GAT TTA CAT TGA AGG-3′
gyrB_Bsub_SF_3	5′-AAA GGT TTA ATG GCG GCA AGA G-3′
gyrB_Bsub_SR_2	5′-GTC TGT CGC GTC CTT GTT T-3′
gyrB_Bsub_SR_3	5′-CGC TTA GGT TTG GAT CAT TTT CTT-3′
gyrB_Bsub_SR_4	5′-GCA GAT CGT AAT CAT ACT CGG TT-3′

3.4. Cell culture experiments

Cellular toxicity of bacterial supernatants was assayed using HepG2 cells (ATCC, Rockville, MD, USA) grown in DMEM supplemented with 10% fetal calf serum (FCS), 200 IU/mL penicillin, 200 μg/mL streptomycin (all from Biochrom, Berlin, Germany). To test for direct cytotoxicity of bacterial supernatants, lactate dehydrogenase (LDH) leakage was measured in the supernatants with an autoanalyzer (Olympus Autoanalyzer AU 2700, Kobe, Japan). Total LDH activities were determined by sonicating a parallel cell monolayer and LDH leakage was expressed as the percentage of LDH in the medium relative to the total LDH content. The release of LDH into the medium from cells reflects cytolysis.

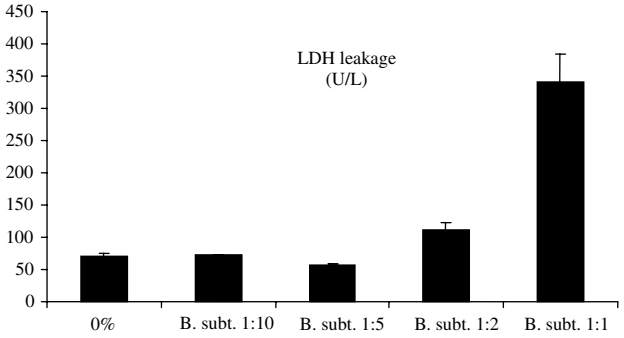

Fig. 4. LDH leakage from HepG2 after incubation of 24 h with serial dilution of bacterial supernatant from *Bacillus subtilis* cultures.

4. Results

Toxicology screening of the Herbalife® F1 Shake revealed no relevant contamination with pesticides, heavy metals, antibiotics, alkyl phosphates, and softeners which were either not detected or below the thresholds that are considered safe (data not shown).

Immunoallergic activation towards the used Herbalife® products was not detectable neither by skin hypersensitivity testing nor by assaying lymphocyte stimulation indicative of drug-induced hypersensitivity.

Herbalife® F1 Shake and Personalized Protein Powder Mix Formula 3 were subjected to a standard microbiology screening. Four samples of Herbalife® products, namely two of seven ingested by the female patient and the only sample ingested by the male patient as well as one sample of a sealed batch of Shape Works Shake Formula 1 Cappuccino showed growth of Gram positive rods after 48 h of incubation. Bacteria from three out of four were subsequently identified by sequencing the 16S rRNA gene as *Bacillus* spp. (one product sample ingested by the female patient also harboured *Paenibacillus* spp.). *Bacillus* spp. was analyzed to the species level by perfoming *gyrB* gene sequencing and identified as *Bacillus subtilis* (Table 2).

Bacterial supernatants were collected and used in incremental dilutions for cell toxicity assays. As shown in Fig. 4, bacterial supernatants from cultures of *B. subtilis* caused a dose-dependent increase of LDH leakage from HepG2 cells into the culture media.

5. Discussion

The consumption of remedies containing certain "active" nutrients, herbals and combinations of traditional medicines is rising steadily, partly due to easy access to commercial products [25]. Concerns over their safety were raised after incidents of adverse hepatic reactions had been recorded in Europe and the US [11–14,26]. Recently, severe liver injury associated with the consumption of Herbalife® products was described ranging from reversible cholestatic hepatitis to acute

Table 2
Herbalife® products tested for bacterial contamination.

Product	Bacterial Culture	*gyrB* gene sequencing
Patient 1		
Herbalife – Shape Works Shake Formula 1 (Strawberry)	*Bacillus subtilis*	*Bacillus subtilis*
Herbalife – Shape Works Shake Formula 1 (Cappuccino)	*Brevibacillus parabrevis*	Not assayed
Herbalife – Shape Works Shake Formula 1 (Cappucino)	No growth	–
Patient 2		
Herbalife – Personalized Protein Powder Formula 3	*Bacillus subtilis* *Paenibacillus polymyxa*	*Bacillus subtilis* *Paenibacillus polymyxa*
Vitamin C tablets	*Bacillus subtilis* *Bacillus cereus*	*Bacillus subtilis* Not assayed
Tang Kuei Plus tablets	No growth	
RoseOx tablets	No growth	
Multivitamin tablets	No growth	
Thermojetics granules	No growth	
Herbalifeline omega 3 fatty acids capsules	No growth	

liver failure requiring liver transplantation, and death from post-transplant complications [15–17]. The details provided in the Israeli, Swiss and Spanish series leave little doubt over consumption of (a) Herbalife® product(s) as the precipitating cause of liver damage in at least some of the patients, but it remains entirely speculative what mechanism might have precipitated the reported incidents. As in the case of patient 2 of our report, most previously documented cases occurred in individuals who consumed several Herbalife® products which makes it difficult to identify the toxic product or, let alone, substance. In this study we were able to retrieve all Herbalife® preparations that patients had consumed for a detailed scrutiny for toxic, immunoallergic, and infectious etiologies. No toxins could be found in any of the 10 Herbalife® products tested, and no sensitization towards the ingested preparations. However, four batches of Herbalife® products revealed bacterial contamination with Gram positive rods identified as *B. subtilis* of which the bacterial supernatant caused dose-dependent increase of LDH leakage in HepG2 cells. Causality of Herbalife® products as the precipitating factor of liver damage was assessed according to CIOMS and scored "probable" in both cases due to exclusion of other causes and immediate resolution of liver damage after dechallenge [18].

Adulteration of nutritional and herbal supplements with bacterial pathogens of which some may produce hepatotoxins has been described [27,28]. In fact, microbial contamination can be quite extensive as demonstrated by a recent FDA-initiated investigation of commercial ginseng supplements in the US detecting a high concentration of yeasts and fungi including *Aspergillus flavus* well above the microbial limits established by the US Pharmacopeia [29]. These investigators also detected *Bacillus* spp. forming highly processing-resistant endospores which cannot be easily eliminated by standard decontamination. In our report, detailed characterization of bacterial cultures revealed growth of *Bacillus subtilis*. It is unknown whether *Bacillus subtilis* colonies can be routinely detected in sealed Herbalife® products, or rather reflect contamination during usage. However, one unopened batch of Herbalife® F1 Shake also revealed growth of *B. subtilis* which raises concerns over improper production, handling, packaging, and/or storage. *B. subtilis* is not generally considered a strong human pathogen [30], but *B. subtilis*-related food poisonings and an isolated case of cholangitis in a patient receiving immunosuppression after kidney transplantation have been described [31]. Better known to potentially precipitate fatal human disease is *B. anthracis* causing anthrax and *B. cereus* as the cause of two types of food poisoning, the emetic and diarrheal syndromes. Mahler et al. described two dramatic cases of *B. cereus*-related food poisoning with fulminant liver failure after the ingestion of reheated pasta sauce contaminated with *B. cereus* [32]. Indeed, *B. cereus* was also detected in a single batch of Herbalife Vitamin C tablets ingested by patient 2 who presented with chronic liver injury unlike the two patients reported by Mahler et al. [32] who developed fulminant liver failure, and only *B. subtilis* was detected in Herbalife® batches from both patients. So, we considered *B. cereus* as the less likely cause of liver injury. Nevertheless, the documentation of two pathogenic species in the tested Herbalife® products further underscores the need for their bacteriologic testing.

Lack of standardization, quality and safety shortcomings of herbal and nutritional supplements are major concerns of advocates of a tighter regulation of these products since several reports depicting contamination with heavy/toxic metals, pesticides, and drugs including antibiotics, non-steroidal anti-inflammatory drugs and anabolic steroids [28,33,34]. However, screening of Herbalife® products ingested by our two patients detected no chemical contamination.

Both patients in this report had remarkably advanced liver injury with incomplete cirrhosis in the male patient, and ductopenia and partially complete fibrotic septa in the female patient. The prevailing histological pattern of liver injury in the previous case series on Herbalife®-related liver injury was acute and chronic cytolytic or cholestatic hepatitis, but established liver cirrhosis was also noted in one patient [15,16]. So, advanced fibrosis could relate to long-term intake of Herbalife® products, possibly by a yet unknown profibrotic component, and acute decompensation may be related to contamination with *B. subtilis*. The natural course of drug-induced liver injury was assessed in previous retrospective studies which demonstrated that patients are more prone to chronicity despite withdrawal of the precipitating agent if fibrosis and/or cholestatic injury was present on histology than patients who present with acute cytolytic liver injury [35–37].

Elevated autoantibodies were found in two patients of the Israeli series, in none from Switzerland, and were unreported in the Spanish series. It can be argued that autoantibodies in case 1 indicate autoimmune hepatitis (AIH), particularly, since the patient rapidly responded to steroid treatment. Unlike with genuine AIH, in this case steroid treatment could be ceased after 3 months without adding another immunosuppressant, and the patient has remained in remission without specific treatment since. Also, a favourable response to steroids is compatible with AIH, however, not diagnostic. To screen for the possibility of underlying AIH as the underlying cause of hepatitis, the patient was subjected to a diagnostic score recently developed and validated by the International Autoimmune Hepatitis Group which assigns 1 or 2 points for positive ANA/SMA, elevated IgG levels, compatible or typical liver histology, and the exclusion of viral hepatitis, respectively [38]. It was proposed that the diagnosis of AIH is probable at >6 points, and

definite at >7 points. Applying these criteria, case 1 scored 5 points which does not rule out AIH. However, absence of certain characteristic features suggesting AIH such as elevated immunoglobulins type G or plasma cellular infiltrates and interface lesions on histology, patient's advanced age and male gender, and the pattern of therapeutic response weaken the suspicion of typical AIH. In our view, a more likely explanation for the patient's presentation is drug-induced autoimmunity, particularly, since elevated autoantibody titres are frequently observed both along with synthetic [39] and herbal drugs [40,41]. Conceptually, metabolites derived from the metabolism of xenobiotics may bind to cellular proteins or macromolecules, leading either to a direct toxic effect on hepatocytes or the formation of protein adducts recognized by the immune system as neoantigens. Lymphocyte activation may then stimulate autoantibody production and cell-mediated immune responses [42].

We found no evidence for immunoallergic sensitization as both lymphocyte stimulation test and epicutaneous patch test resulted negative. The lymphocyte transformation test is able to detect drug specific T cells with a high sensitivity and specificity in allergic reactions to drugs involving the skin and the liver, especially in recently introduced drugs [22,43]. However, in cases in which immunoallergic reactions are restricted to the liver, its sensititvity is low even with optimized assays [44]. So, a negative test cannot rule out involvement of a particular drug, while a positive test is reliable prove of a sensitization as false-positive results are rare.

These two novel cases on Herbalife®-related hepatic damage add to the growing body of scientific evidence of nutritional supplements as a rare, but worrisome cause of severe adverse hepatic reactions considering the widespread use of "neutraceuticals" by individuals practising self-medication. So, similar incidents may be observed as the awareness of physicians and consumers towards their potential hazards increases.

Until recently, nutritional supplements and functional food preparations were exempt from strict licensing regulations but, in our view, these well-documented incidents of adverse hepatic reactions call for caution and safety actions from health authorities. In this regard, the European Union has set forth legislative measures relevant to the distribution of nutritional supplements and functional foods that are outlined in the European Commission 2000 White Paper on Food Safety. Among others, it foresaw the establishment of a General Food Law Regulation, laying down the principles of food law and the creation of an independent Food Authority endowed with the task of giving scientific advice on issues based upon risk assessment, management and communication [45,46]. Legislation acknowledges the fact that botanical and nutritional supplements harbour specific problems because of their complex composition particularly with respect to quality aspects. Also, guidelines for conducting *in vitro* and *in vivo* studies and their relevance for clinical safety data are defined. Apparently, these initiatives are necessary since efficacy and safety of dietary supplements and herbals is poorly documented, and the awareness of consumers and health professionals towards nutritional supplements as a potential source of health damage is low [4,47].

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