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Association between consumption of Herbalife® nutritional supplements and acute hepatotoxicity☆

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***Background/Aims*: Nutritional supplements are frequently considered to be harmless but indiscriminate use of unlabelled ingredients may lead to significant adverse reactions.**

***Methods*: In 2004, identification of four index cases of acute hepatitis associated with Herbalife® intake led to a ministry of health investigation in all Israeli hospitals. Twelve patients with acute idiopathic liver injury in association with consumption of Herbalife® products were investigated.**

***Results*: Eleven of the patients were females, aged 49.5 ± 13.4 y. One patient had stage I primary biliary cirrhosis and another had hepatitis B. Acute liver injury was diagnosed after 11.9 ± 11.1 months of initiation of Herbalife® consumption. Liver biopsies demonstrated active hepatitis, portal inflammation rich with eosinophils, ductular reaction and parenchymal inflammation with peri-central accentuation. One patient developed sub-fulminant and two fulminant episodes of hepatic failure. Hepatitis resolved in eleven patients, while one patient succumbed to complications following liver transplantation. Three patients resumed consumption of Herbalife® products following normalization of liver enzymes, resulting in a second bout of hepatitis.**

***Conclusions*: An association between intake of Herbalife® products and acute hepatitis was identified in Israel. We call for prospective evaluation of Herbalife® products for possible hepatotoxicity. Until then, caution should be exercised by consumers, especially among individuals suffering from underlying liver disease.**

***Keywords*: Hepatitis; Hepatotoxicity; Herbalife®; Herbal supplements**

1. Introduction

Herbal preparations are common ingredients in complementary and alternative medications (CAM) and in nutritional supplements. Their use is prevalent worldwide because they are considered to be "natural" and hence free of adverse reactions [1]. It is estimated that up to 42% of Americans consume CAM annually [2], while one-third of patients examined in US liver clinics

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report the use of herbal agents [1]. In contrast to pharmaceuticals, CAM are usually distributed as 'food supplements'. As a result, in most countries their use is neither regulated nor controlled.

Toxic hepatitis is considered the most common adverse reaction resulting from use of CAM [3–5]. Hepatitis is often caused by either the concomitant consumption of hepatotoxic ingredients such as acetaminophen and non-steroidal anti-inflammatory agents or by hepatotoxicity of herbal ingredients themselves [6]. For the majority of herbal products, proof of efficacy by blinded controlled trials is often lacking. Anecdotal success and personal experience are frequently the driving force for acceptance of CAM in the population. On the other hand, reports on adverse reactions of CAM are numerous, but often lack the power to provide unequivocal evidence-based proof regarding the relative risk associated with intake of such agents [1].

In 2004, four index cases were identified at the Hadassah Medical Center, Jerusalem, Israel, consisting of patients suffering from acute unexplained liver injury, apparently associated with the recent consumption of Herbalife® products. This led to a joint Israel Ministry of Health (MOH) – Hadassah Hebrew University Medical Center investigation, aimed to identify additional cases, and to assess the hepatotoxic potential of Herbalife® products.

2. Methods

2.1. Study population

In 2004, four index cases were identified at the Hadassah Medical Center, Jerusalem, Israel, consisting of patients suffering from acute unexplained liver injury apparently associated with the recent consumption of Herbalife® products. To further investigate such a possible association, the Israel MOH issued a database search including files of all general Israeli hospitals ($n = 23$) for cases of unexplained acute hepatitis during 2004 (ICD-9 codes 570.0–573.3). Out of 30 cases with abnormal liver enzymes of unestablished etiology, ten patients (33%, including the four index cases) were identified with the exposure of interest (recent consumption of Herbalife® products prior to clinical symptoms). Following public notification, two additional cases (treated during 2002 and 2003) were recognized.

2.2. Data collection

Twelve patients (ten systematically-identified and two randomly-identified) underwent an interview which included a detailed questionnaire, after consent was obtained. All medical records were reviewed. Collected demographic and clinical data included age, gender, ethnic origin, occupation, height, weight, background illnesses, intake of medications, habitual alcohol consumption, and use of recreational drugs. The history of Herbalife® products' consumption as well as intake of other food supplements and CAM were recorded.

Laboratory records from hospital and outpatient clinics included blood counts, coagulation tests, aminotransferase activity, alkaline phosphatase, γ-glutamyl transpeptidase (γ-GTP), lactate dehydrogenase (LDH) and serum bilirubin levels. Investigation for causes of liver damage included viral entities (Hepatitis A, B, C viruses [HAV, HBV, HCV, respectively], HIV, Cytomegalovirus [CMV] and Epstein Barr Virus [EBV]), serologic markers for autoimmune disease (anti-smooth muscle [ASMA], anti-nuclear [ANA], and anti-mitochondrial antibodies), and metabolic entities (ferritin, ceruloplasmin, alpha-1-antitrypsin and TSH). Serum acetaminophen levels and urinary toxic screening were determined on admission. Results of all CT and ultrasonographic examinations were reviewed by expert radiologists. In four cases, in which liver biopsy was performed, sections were reviewed by a blinded expert pathologist. A histopathology report from a liver explant removed from patient number 5 was obtained from a German transplant center in Essen. Causality was graded according to the WHO criteria for Causality Assessment of Suspected Adverse Reactions (http://www.who-umc.org/DynPage.aspx?id=22682).

2.3. Data analysis

Demographic and clinical descriptive data are presented as numbers and percentages or as means and standard deviations. All analyses were done using the SPSS® statistical package for Windows.

2.4. Role of the funding source

The study was officially funded by the Israel Ministry of Health. No sponsor(s) were involved in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

3. Results

3.1. Characteristics of the study population

Characteristics of the patients, background illness and medications are depicted in Table 1. Eleven patients were females, mean age 49.5 ± 13.4 years (range 32–78 y). Nine patients resided in Central Israel, while three were from Northern Israel. Seven patients were Ashkenazi, four Sephardic, and one was of Israeli-Arab origin. Seven patients were employed in clerical jobs, two were housewives, and three were employed as Herbalife® distributors. All medications had been taken for at least 3 months prior to development of acute liver injury. Mean Body mass index (BMI) was 28.6 ± 4.2. All patients denied regular alcohol consumption or use of illicit drugs, and had no risk factors for HIV.

3.2. Consumption of Herbalife® products

Nine patients consumed Herbalife® products for weight reduction, and three for improvement of well-being. The three patients who were Herbalife® distributors self-administered the products. Two patients received the products from a family member who was a Herbalife® agent and seven by non-family-related distributors. The patients reported a wide array of consumed Herbalife® products, distributed in different combinations as part of a personalized Herbalife® kit (Table 2). Eleven patients consumed products at the recommended doses, while one increased the dose to three times the recommended dose after developing prodromal symptoms of acute hepatitis. Other than longstanding consumption

Table 1
Patient demographic and clinical characteristics

	Sex	Age	Background illnesses	Medications	BMI[a]	Latency (months)	Type of liver injury	Histology	Re-challenge	Outcome	**Causality (WHO)**
1	F	55	NIDDM[b] Hyperlipidemia	Aspirin, metformin, statins	33	6	Hepatocellular	ND[c]	Positive	Recovery	Certain
2	F	48	HTN[d]	Alpha adrenergic blocker	32	9	Hepatocellular	Hepatocellular hepatitis	Positive	Recovery	Certain
3	F	52	None	HRT	27	6	Hepatocellular	Hepatocellular hepatitis	ND	Recovery	Probable
4	M	65	None	None	25	35	Hepatocellular	Hepatocellular hepatitis+ Massive necrosis	ND	Recovery	Probable
5	F	33	HBV[e]	None	28	3	Hepatocellular	Massive necrosis, negative HBV staining	ND	Exitus	Possible
6	F	54	PBC[f]	Ursodecholic acid	32	2	Hepatocellular	ND	ND	Recovery	Probable
7	F	32	None	Oral contraceptives	22	7	Hepatocellular	ND	ND	Recovery	Probable
8	F	50	None	HRT[g]	23	25	Hepatocellular	Hepatocellular hepatitis+ massive necrosis	ND	Recovery	Probable
9	F	33	HTN	None	27	3	Mixed	ND	ND	Recovery	Probable
10	F	50	Hyperlipidemia	None	35	28	Hepatocellular	ND	ND	Recovery	Possible
11	F	44	None	None	32	7	Hepatocellular	ND	ND	Recovery	Possible
12	F	78	Psoriasis NIDDM	Bisphosphonates Aspirin	27	12	Hepatocellular	ND	Positive	Recovery	Certain

[a] BMI, body mass index (weight in kg divided by height in meters squared).
[b] NIDDM, non-insulin dependent diabetes mellitus.
[c] ND, not determined.
[d] HTN, hypertension.
[e] HBV, hepatitis B virus.
[f] PBC, primary biliary cirrhosis.
[g] HRT, hormone replacement therapy.

Table 2
Herbalife® products consumed by the patients

Herbalife® product consumed	Patients											
	1	2	3	4	5	6	7	8	9	10	11	12
Protein mix drink	+	+	+	+	+	+	+	+	+	+	+	+
Herbalifeline (fish oil concentrate)	+	+	+	+	+		+	+		+		+
Thermojetics performance protein powder	+	+	+	+								
Thermojetics herbal mix (tea)		+			+	+	+	+	+	+	+	+
Thermojetics Green and beige capsules (herbal extract)		+	+		+			+			+	+
Thermojetics snack	+	+				+	+	+	+		+	+
Snack defense	+	+	+				+	+				+
Aminogen		+	+				+					+
Tang Kuei Plus		+	+		+		+		+		+	+
Instant drink with plant extracts	+	+	+		+		+	+	+		+	+
Sesame and Herbs tablets	+	+	+	+	+	+	+	+	+		+	+
Activated fiber	+	+	+	+			+	+	+		+	+
N-R-G tablets	+	+	+				+	+	+			+
Safflower oil capsules	+	+	+	+	+	+	+	+	+		+	+
RoseOx (herbal extract)	+	+	+	+		+	+	+		+	+	+
Schizandra Plus tablets	+	+	+	+		+	+	+		+	+	+
Herbal Aloe	+	+				+	+	+			+	+
Skin activator replenishing cream										+		

of multivitamins by a single patient, no other CAM was reportedly consumed by any of the patients.

3.3. Clinical presentation

Acute liver injury was diagnosed on average after 11.9 ± 11.1 months of Herbalife® consumption (Table 1). Presenting symptoms were fatigue, jaundice, and weight loss in eleven patients, while one patient was identified during routine blood testing. Ten patients were hospitalized, while two were evaluated on an outpatient basis. Three patients developed severe hepatitis, one patient developed sub-fulminant hepatic failure, and two patients developed fulminant hepatic failure. Upon development of symptoms of acute hepatitis, two patients consulted their Herbalife® distributor and were advised to continue or even increase product doses.

3.4. Laboratory results

Peak serum ALT, AST, alkaline phosphatase, GGTP and LDH levels were $1{,}481 \pm 787$ U/L (normal range 6–52 U/L), $1{,}603 \pm 1440$ U/L (normal range 2–6 U/L), 210 ± 67 U/L (normal range 40–130 U/L), 282 ± 123 U/L (normal range 10–80 U/L) and 1177 ± 572 U/L (normal range 300–620 U/L), respectively. Serum bilirubin levels were 9.1 ± 4.95 mg/dl (normal range 0.3–1.0 mg/dl). Mean serum albumin was 34.5 ± 4.4 g/L (normal range 30–50 g/L), international normalized ratio (INR) 1.44 ± 1.1, and partial prothrombin time 34.4 ± 13.4 s. Eleven patients featured a hepatocellular liver enzyme elevation pattern, while a single patient had a mixed hepatocellular-cholestatic pattern.

Apart from positive HBsAg with anti-HBcIgM antibodies and a viral-load of 10^6 copies/ml in one HBV-infected patient, serology for HAV, HBV, HCV and HIV was negative in all. Primary infection or reactivation of CMV or EBV was excluded. Serum acetaminophen levels and urinary toxicology screen were unremarkable. Serum Ceruloplasmin, alpha-1-antitrypsin and TSH were normal. Ferritin was normal in nine patients and elevated in three patients during acute disease (mean 1543 ± 684 mg/l), returning to normal levels following recovery. Anti-mitochondrial antibodies were positive (+4/4) in one biopsy-proven PBC patient. ASMA and ANA were positive in a single patient during acute liver injury (titer 1:160 and 1:400, respectively) but became negative following recovery. In another patient ANA remained weakly positive following resolution of hepatitis. In both patients full recovery was achieved without corticosteroid treatment. Causality assessment (WHO criteria) yielded 3 cases as certain, 6 cases as probable, and 3 cases as possible (Table 1). Three certain cases were based on a positive rechallenge, while probable cases were based on the fact that no other potential cause could be elicited.

3.5. Imaging results

Abdominal ultrasound ($n = 12$) was normal in ten patients while one PBC patient had hepatomegaly. In one previously healthy patient with sub-fulminant hepatitis the liver was described as non-homogeneous, otherwise unremarkable. Liver CT scan ($n = 6$) was normal in four patients. One patient with sub-fulminant hepatitis featured irregular hepatic borders and mild ascites. Another patient with sub-fulminant liver failure demonstrated a lobular liver and periportal edema which resolved following recovery. No radiological evidence for non-alcoholic fatty liver disease (NAFLD) was found in any of the imaging studies. Gastroscopy ($n = 2$) revealed no evidence of portal hypertension.

3.6. Pathology results

Liver biopsy was performed in four cases. In all biopsies injury was predominantly hepatocellular, with lobular disarray, ballooning degeneration of hepatocytes, focal mild steatosis, spotty necrosis and extensive inflammation with Kupffer cell hypertrophy and hyperplasia. The inflammatory infiltrate was found in portal tracts, extending into the periportal area and throughout the parenchyma, with accentuation of zone 3, and consisted of lymphocytes accompanied mainly by eosinophils and plasma cells. Portal bile ducts and blood vessels were unremarkable, however ductular reaction was noted (Fig. 1). In one of the patients with sub-fulminant hepatic failure, evidence was also found for bridging necrosis and fibrosis (Fig. 2). A second biopsy in this patient, performed 6 months following complete recovery, revealed resolution of liver inflammation, parenchymal regeneration, and residual parenchymal fibrosis. No evidence for non-alcoholic fatty liver disease (NAFLD) was found in any of the biopsies. One HBsAg positive patient (number 5) underwent liver transplantation for fulminant hepatic failure. A written report noted nodular liver with massive necrosis (~80%), ceroid laden macrophages, sinusoidal congestion, ballooning degeneration of hepatocytes with occasional fatty infiltration

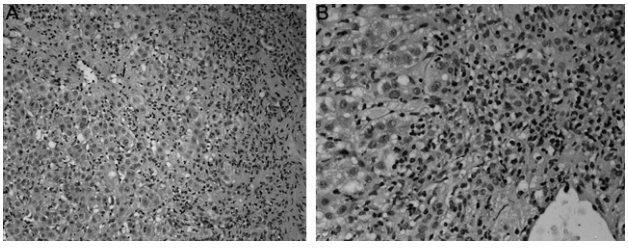

Fig. 1. Core biopsy from liver tissue showing acute hepatitis; (A) parenchymal disarray; ballooning degeneration, minimal steatosis, occasional acidophilic bodies with diffuse chronic inflammation and Kupffer cell hyperplasiaand hypertrophy. (B) Expansion of the portal tract as a result of chronic inflammation and ductular reaction.

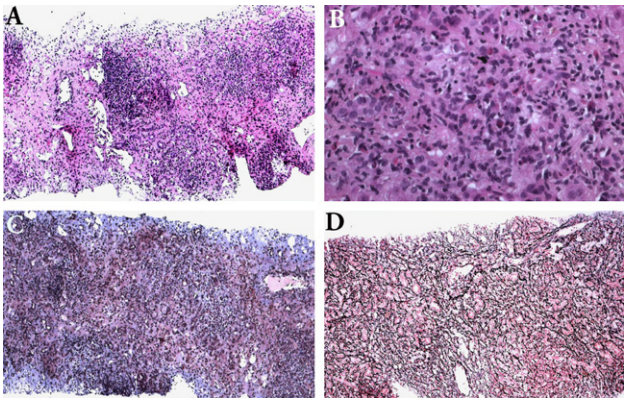

Fig. 2. Liver biopsy of a patient with sub-fulminant liver failure, featuring bridging necrosis and fibrosis and moderate inflammation. (A) Severe acute hepatitis with bridging necrosis linking central areas (H&E stain). (B) In the portal tract moderate inflammation rich in eosinophils with cholangiolar proliferation (H&E stain). (C) Early fibrosis (masson-trichrome stain). (D) Condensation of normal reticulin (reticulin stain).

and canalicular cholestasis. Orcein, HBsAg and HBcAg stainings were negative.

3.7. Treatment, outcome and complications

In all patients Herbalife® use was terminated on recognition of hepatitis. Four patients were treated with short courses of corticosteroids, four were treated with ursodeoxycholic acid and three (with fulminant or sub-fulminant hepatic failure) treated with intravenous *N*-acetyl cysteine. Hepatitis resolved completely in 11 patients. One HBsAg+ patient developed fulminant hepatic failure, underwent urgent liver transplantation, but succumbed to peri-transplantation complications. A 2-year follow up revealed no long-term complications in any of the remaining patients who did not resume intake of Herbalife®.

3.8. Rechallenge with Herbalife® products

Three patients resumed intake of Herbalife® following normalization of liver enzymes leading to a second episode of hepatic injury. In all cases, the decision to resume consumption of Herbalife products was made by the patients, without informing their physicians. The first (No. 1, Table 1) was a diabetic patient on 10-year long statin and metformin therapy. Upon development of acute liver injury medication and Herbalife® treatment were stopped, resulting in complete recovery. Two months later, the patient resumed consumption of Herbalife® products and a month later presented with a second bout of severe hepatitis, necessitating hospitalization and steroid treatment. Re-cessation of Herbalife® use resulted in complete recovery. The second patient (No. 2, Table 1) developed severe biopsy-proven hepatitis, which resolved following cessation of Herbalife® use. A month after discharge the patient resumed intake of Herbalife products and was re-admitted with a second episode of acute liver injury. The patient fully recovered upon re-cessation of use of Herbalife® products. The third patient (No. 12, Table 1) was re-administered Herbalife® by her daughter (a Herbalife® agent) and developed a second bout of hepatitis which was unresolved at the time of manuscript submission.

4. Discussion

The presented case series of 12 patients suggests a causal association between consumption of Herbalife® products and development of acute liver injury. Such cause and effect relationship is suggested by the temporal association between exposure to Herbalife® products and development of liver injury, the negative evaluation of other causes of hepatic injury, and the fact that cessation of Herbalife® was associated with normalization of liver enzymes (apart from the deceased patient). Furthermore, the possibility for a causal association is strongly substantiated by the three rechallenge cases. A closely similar case series from Switzerland (Schoepfer et al.) in this issue of the Journal strongly supports our results. As far as we know, these two series are the first to report an association between Herbalife® products and a propensity for development of life-threatening hepatotoxicity.

It is quite possible that the detected cases represent only the tip of the iceberg, since our active investigation included mostly hospitalized patients, labelled under pre-determined ICD-9 codes, and diagnosed during a limited time period (2004, apart from two randomly-identified patients). Acute liver injury in one patient was incidentally discovered during routine blood testing, supporting the possibility that milder undetected cases of Herbalife®-induced hepatotoxicity may occur. Determination of the incidence of hepatotoxicity in Herbalife® consumers requires full disclosure of the precise number of Herbalife® customers in the Israeli population at time of the study. Such information has yet to be provided by Herbalife®.

The use of herbal preparations has been vastly expanding over the past decade, with hepatotoxicity being the most frequently reported adverse reaction [1–5,7]. Examples of hepatotoxic herbal agents include Chaparral, Germander, Kava Kava, Jin Bu Huan, and Ephedra [1,8–13]. In recent years, several cases of severe hepatotoxicity occurred in association with consumption of seemingly harmless nutritional supplements [14]. Herbalife®, one of the largest weight management and nutritional supplement companies in the world, is active in almost 60 countries. Its nutritional supplements are aimed at weight reduction and improvement in well-being (“wellness”). In recent years, due to safety

concerns and in association with a 1998 FDA inquiry, Herbalife® excluded Ephedrine from their products [15]. Current Herbalife® kits contain a multitude of products, for which ingredient lists are not fully provided. Laboratory analysis of potentially-hepatotoxic ingredients in these products is difficult, without full disclosure of all components including the manufacturing processes.

The presented cases were identified in different regions of Israel over a period of 2 years, while those in Switzerland occurred over a 6-year period. The relatively short period of identification of the cases in Israel raises the possibility that a corrupted batch was accountable for hepatotoxicity. During the investigation the company has taken one product 'Sesame and Herbs tablets' off the market, that is the only product distributed exclusively in Israel which could possibly account for Herbalife®-induced hepatotoxicity. However, not all affected Israeli patients consumed this product, and the recognition of similar cases in Switzerland makes the possibility of locally-contaminated hepatotoxic product improbable. The hepatitis injury described herein, with an eosinophil-rich inflammation, ductular reaction and pericentral accentuation in seronegative patients with continuous product exposure, is highly compatible with drug-induced hepatitis. Of note is that this hepatitic reaction is more often the result of the unpredictable type of drug injury than of a predictable one. Despite similarities between the clusters in Switzerland and Israel, the histopathological manifestations are not completely identical, with variations which could have been induced by different combinations or dosages of hepatotoxins.

Four patients in this series had evidence for possible underlying conditions which could have contributed to liver enzyme abnormalities while consuming Herbalife® products. The first was HBsAg+/anti-HBcIgM+ with viremia who apparently was HBsAg−/anti-HBc− with normal ALT 17 months before developing fulminant hepatitis. This patient consumed large amounts of Herbalife® during the incubation period of acute hepatitis B. Indeed, this patient was anti-HBc IgM positive prior to liver transplantation and the macroscopic appearance of the liver explant was nodular. Nevertheless, negative staining for HBcAg and HBsAg may suggest co-morbidity by an unidentified agent. It should however be noted that HBV replication may cease at the peak of hepatocellular necrosis. Thus, it is impossible to differentiate between acute HBV infection and Herbalife®-induced toxicity. The second patient suffered from longstanding serologically and biopsy proven stage I PBC. Following resolution of acute liver injury associated with Herbalife® consumption, her PBC remained at its prior low-grade stage. Two additional patients had hyperlipidemia associated with an increased BMI, a condition often associated with non-alcoholic fatty liver disease (NAFLD). In both patients no radiological evidence was noted for NAFLD. In three of the four patients (apart from the HBV carrier who died as a result of fulminant liver failure) full resolution of acute hepatocellular injury occurred following discontinuation of Herbalife®-products.

Thus, patients with underlying liver disorders may be more susceptible to Herbalife®-induced liver injury. A similar herbal-induced aggravation of underlying liver disease has been described with the herbal agent Ma-Huang (Ephedra) [16]. Other predisposing unidentified risk factors may include genetic susceptibility such as P450 enzyme polymorphism and individual aberrations in immune response. The exact mechanism of liver injury in our patients is not established, but the plasma-cell rich infiltrates in four biopsies and occasional transient presence of autoantibodies suggest the possibility of immune-mediated liver toxicity. Indeed, metabolism of one or more constituents may trigger an immune response, such as that described in halothane and anti-convulsant hepatotoxicity [17].

Despite the alleged association between Herbalife® consumption and hepatic toxicity noted in the two case series, it is not possible to conclude at present whether consumption of Herbalife® products pose a major health threat to the general public. Toxicity occurred in a minority of consumers, and may result from a hepatotoxic ingredient, overdose of an otherwise safe ingredient or contamination during product processing, in combination with individual predisposition. Nevertheless, disturbing public concerns arise from our investigation. The majority of CAM are sold as nutritional supplements and are thus neither regulated nor subjected to routine state-sponsored medicinal quality control in most countries [18]. Thus, listing of ingredients as well as potential adverse reactions is often missing. This stands in contrast to conventional pharmaceuticals, approved only after toxicity studies, clinical trials and notification of observed adverse reactions and contraindications. As a result, consumers and distributors of nutritional supplements, who are often avid believers in the product(s), remain unaware of potential adverse reactions.

In conclusion, we call for an expanded investigation into Herbalife® products for possible hepatotoxic adverse reactions. Until such research is completed, we advise increased awareness by practicing physicians, pharmacists, and the general public for possible Herbalife®-induced liver toxicity. Caution should be greatest among individuals with chronic underlying liver diseases. In addition, we call for a change of regulations concerning nutritional supplements and natural remedies that will establish ingredient-listing, toxicological testing, and mandatory reporting of all adverse events. This will ensure that manufacturers become responsible and accountable for their product's safety, efficacy and quality.

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