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Case Report

HERBALIFE® ASSOCIATED SEVERE HEPATOTOXICITY IN A PREVIOUSLY HEALTHY WOMAN

Dragan Jurčić[1,2], Maruška Gabrić[2,] Rosana Troskot Perić[1,2,3], Ana Marija Liberati Pršo[4], Jure Mirat[1], Aleksandar Včev[1], Ivan Alerić[1,5] and Barbara Ebling[1]

[1]Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia;
[2]Department of Gastroenterology and Hepatology, Sveti Duh University Hospital, Zagreb, Croatia;
[3]Faculty of Health Studies, University of Rijeka, Rijeka, Croatia;
[4]Department of Endocrinology, Diabetes and Metabolic Diseases, Sveti Duh University Hospital, Zagreb, Croatia;
[5]Jordanovac Hospital for Lung Diseases, Zagreb University Hospital Centre, Zagreb, Croatia

SUMMARY – Lately there has been an increased consumption of herbal preparations, distributed as nutritional supplements, often claimed to be 'natural' and harmless. However, as their use is not subjected to strict pre-marketing testing and regulations, their ingredients are not clearly defined and there is no quality control or proof of their effectiveness and safety. A growing body of references accentuate their harmful effects, in particular hepatotoxicity, which varies from minimal hepatogram changes to fulminant hepatitis requiring liver transplantation. This case report describes liver damage that was highly suspected to originate from Herbalife® products consumption. We excluded alcohol, viral, metabolic, autoimmune and neoplastic causes of liver lesions, as well as vascular liver disease, but we noticed a connection between the use of Herbalife® products and liver damage. The exact mechanism of liver damage in our patient was not determined. After removing the Herbalife® products, liver damage resolved and there was no need to perform liver biopsy. Taking into consideration the growing consumption of herbal products and their potential harmfulness, we consider that more strict regulations of their production process and sale are necessary, including exact identification of active substances with a list of ingredients, toxicologic testing and obligatory side effect report.

Key words: *Herbalife; Plant preparations; Dietary supplements; Liver failure*

Introduction

Lately there has been an increase in the use of herbal preparations, which are important components of supplemental and alternative products[1]. Their popularity is based on their wide availability and the belief that they are 'natural' and therefore harmless[2]. In many western countries, herbal products are distributed as nutritional supplements. Their use is not subjected to strict pre-marketing testing and regulations, therefore, their ingredients are not defined, there is no quality control or proof of their effectiveness and safety[3]. Many references accentuate harmful effects of herbal products. Their most frequent harmful side effect is hepatotoxicity[4]. Herbalife® products are connected to various grades of liver damage, from minimal hepatogram changes to fulminant hepatitis that requires liver transplantation[5-7]. This case report describes liver damage that was likely associated with the use of Herbalife® products.

Case Report

A 54-year-old female patient was admitted to the Department of Gastroenterology and Hepatology for icterus, abdominal pain, pale stool, tiredness and general weakness, which occurred several days prior to hospital admission. The patient did not have any severe

Correspondence to: *Asst. Prof. Ivan Alerić, MD, PhD*, Ljudevita Posavskog 19A, HR-10000 Zagreb, Croatia
E-mail: ivan.aleric@kbc-zagreb.hr
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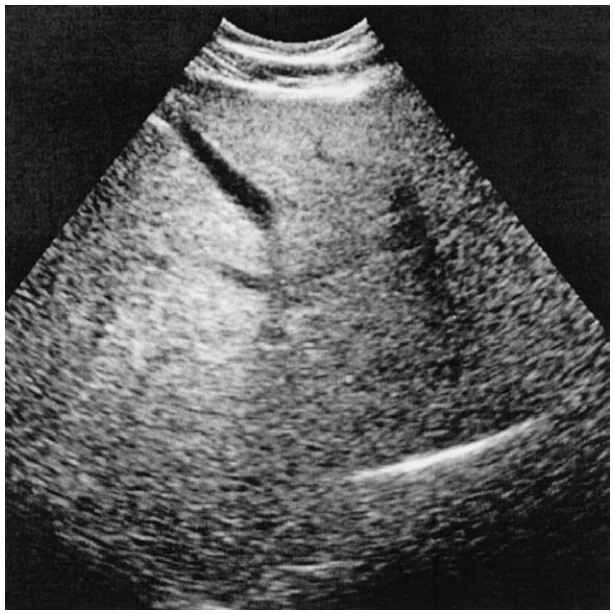

Fig. 1. Ultrasound showing a diffuse liver lesion.

Source: Ultrasound Unit, Department of Gastroenterology and Hepatology, Sveti Duh University Hospital, Zagreb, Croatia.

illnesses or any similar problems before. She denied alcohol or drug addiction, taking any medicine as acute or chronic therapy, receiving blood transfusions and/or any blood products. Epidemiology and family history were negative. At admission, she was hemodynamically stable and not febrile. Icterus was noticed during physical examination, however, there was no chronic liver disease stigmata. Initial laboratory tests showed significantly elevated markers of hepatocellular damage (Table 1). Coagulation parameters and proteinogram were normal. Complete blood count, inflammation parameters, glucose, electrolytes, kidney function parameters, thyroid hormones and thyroid-stimulating hormone were also normal (Table 2). Serologic tests excluded hepatitis B and C infection, as well as cytomegalovirus and Epstein-Barr virus infection or reactivation. Positive anti-hepatitis A virus (HAV) antibodies pointed to HAV. The levels of serum copper, ferritin and transferrin saturation were normal. Immunologic examination (antinuclear antibodies [ANA], antimitochondrial antibodies [AMHA], antibodies against smooth muscle cells [AGLM], antibodies against liver or kidneys [LKM]) excluded autoimmune etiology of liver damage. Upper abdomen ultrasound revealed normal size but diffuse hyperechoic liver. There were no signs of lithiasis or biliary obstruction (Fig. 1). Gastroscopy confirmed *Helicobacter (H.) pylori* positive chronic gastritis, but no signs of portal hypertension. Considering elevated hepatogram values, eradication therapy of *H. pylori* infection was conducted in later therapeutic period.

Subsequently, we found out that the patient had been using the following Herbalife® products: Guarana comprese, RoseOx, Herbalifeline, Tang Kuei Plus and Formula 4 at recommended dosage (10 tablets *per* day in total) (Table 3), for approximately half a year before admission. During her stay at the Department of Gastroenterology and Hepatology, these products were excluded from therapy; soon after, the clinical picture regressed and the initially high hepatogram values decreased (Table 1, Figs. 2 and 3).

According to the World Health Organization criteria (WHO-UMC Criteria) for the cause and effect of liver failure and Herbalife® products, the patient's toxic hepatitis was probably the result of taking the aforementioned products[8].

Discussion and Conclusion

Liver damage frequently occurs as a result of using medicines and their byproducts, since it is the most important organ for metabolizing medicines[1]. Hepatotoxicity occurs in 10% of cases and is the most common cause of side effect reporting, as well as putting medical products off the market. Harmful effects of conventional medical products are well known, however, side effects of herbal products are becoming more frequent as they are being more widespread. It is known that up to 67% of Americans use herbal products[9], and their use is steadily increasing[1].

Hepatotoxicity due to herbal products is more frequently caused by an idiosyncratic reaction than by toxic damage. There is a wide span of liver damage manifestations caused by harmful effects of medicinal products, starting from highly elevated liver enzymes to steatosis, acute and chronic hepatitis, hepatic fibrosis and cirrhosis, partial or diffuse necrosis, cholestasis, veno-occlusive disease, carcinogenesis, up to acute liver failure that requires transplantation[10]. In addition, the same medicinal product produced in different countries can cause different types of liver damage. The risk factors that influence the tendency towards developing liver lesions caused by medication are older age, female gender, parallel use of other drugs that induce cyto-

Table 1. Hepatogram values on admission and follow-up measurements

	Days after admission								Month	Year
	1	3	6	8	9	13	16	20	1	2
AST	1411	1450	1055	688	544	227	143	78	45	17
ALT	2196	2132	1932	1393	1184	587	330	156	58	11
GGT	252	216	213	187	168	131	110	84	55	30
ALP	216	199	188	164	142	121	104	82	68	60
Conj. bil.	123.6	146.2	160.7	107.8	86.2	49.2	39.8	28	22	22
Dir. bil.	69.8	79.6	82.1	50.8	38.8	19.5	13.9	10.1	87.0	8.7

AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = gamma-glutamyl transferase; ALP = alkaline phosphatase; Conj. bil. = conjugated bilirubin; Dir. bil. = direct bilirubin

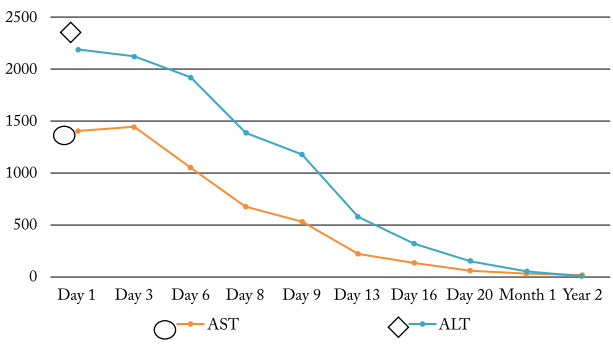

Fig. 2. AST and ALT values on admission and follow-up measurements.

AST = aspartate aminotransferase; ALT = alanine aminotransferase

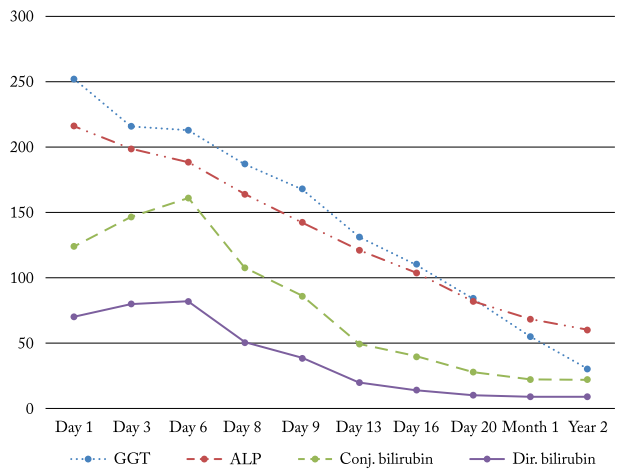

Fig. 3. Other hepatogam findings on admission and follow-up measurements.

GGT = gamma-glutamyl transferase; ALP = alkaline phosphatase; Conj. bilirubin = conjugated bilirubin; Dir. bilirubin = direct bilirubin

chrome P450 and genetic polymorphism of pathways included in the drug metabolism[11,12]. One of the most important predisposing factors is a pre-existing liver disease.

Some of the herbal preparations connected to hepatotoxicity are Kava Kava (*Piper methysticum rhizoma*), Jin Bu Huan (*Lypocodium serratum*), Ma Huang (*Ephedra* spp.), Germander (*Teucrium chamaedrys*), Chaparral *(Larrea tridentata)*, and pyrrolizidine alkaloids (*Heliotropium, Senecio, Symphyium* and *Crotalaria* spp.). In the last few years, there have been more than 50 cases of liver damage connected with Herbalife® use, some of them even life threatening.

Herbalife® is one of the world's leading companies that manufacture supplements, with internet sales of approximately 1.2 billion dollars *per* year. It sells products for weight loss, improving general wellbeing, as well as personal hygiene products, and it has widespread distributers in 59 countries. Some products are registered as dietary supplements, whereas others are not registered at all.

Herbalife® products contain herbal extracts enriched with vitamins, minerals and oligo-elements. Because of the lack of the production process standardization, which varies among countries, and because of the complexity and variability of herbal extracts, their exact ingredients are unknown. Besides being contaminated by other chemicals such as softeners, preservatives, flavor enhancers and pesticides, we can also find traces of heavy metals which were added during the production process or are found in unprocessed raw materials[13]. A number of heavy liver failure cases caused by Herbalife® products that were contaminated with *Bacillus subtilis* have been described[14]. Considering everything mentioned above and the fact that patients use more than one product at the same time, it is difficult to identify the exact culprit substance.

Table 2. Laboratory parameters (values other than hepatogram) on follow-up measurements

	Days after admission								Month	Year
	1	3	6	8	9	13	16	20	1	2
L	6.5	4.64								5.58
RBC	4.49	4.43								4.72
Hb	136	130								136
Htc	0.41	0.39								0.4
T	238	209								275
CRP	5	5								3.8
Na	138	138					138			139
K	4.1	4.1					4.7			3.7
Urea	2.3	2.1								2.9
Creatinine	88	87								81
BG	5.6	4.7					4.1			5.5
S. amylase	58	52				58				
Albumins		40								
PT	0.9	0.84	0.78		0.86	0.91			0.97	
INR	1.05		1.12			1.05				
AFP		12.1				27.6				

L = leukocyte count; RBC = red blood cell count; Hb = hemoglobin; Htc = hematocrit; Plt = platelet count; CRP = C-reactive protein; Na = sodium; K = potassium; BG = blood glucose; S. amylase = serum amylase; PT = prothrombin time; INR = International Normalized Ratio; AFP = alpha fetoprotein

There is a proof of harmful effects of green tea and aloe vera, which are the two main ingredients of some Herbalife® products. There have been case reports of hepatotoxicity (4 in Spain[15], 9 in France[16]) in 2003 caused by the product Exolise, which contains the ethanol extract of green tea, which was taken off the market in Spain. Not one Herbalife® product containing green tea has the type of extract and its amount specified. Several authors state that there is a connection between liver damage and oral use of products containing aloe vera[17-19]. Aloe vera is the main ingredient of Herbalife® drink Herbal Aloe.

The exact mechanism of liver damage is unknown. Most probably, it is immune mediated hepatotoxicity, where genetic susceptibility plays an important role[4]. Family connection in two cases of hepatitis in Spain, one of which was autoimmune hepatitis, favors this statement[20]. It is possible that autoimmune mechanisms lead to compromised liver microcirculation, the same as in veno-occlusive liver disease. It is also known that one of the causes for this condition is the use of herbal products containing pyrrolizidine alkaloids.

We excluded alcohol, viral, metabolic, autoimmune and neoplastic causes of liver lesions, as well as vascular liver disease, and we noticed a connection between the use of Herbalife® products and liver damage. The exact mechanism of our patient's liver damage was not determined. After removing the Herbalife® products, liver damage resolved and there was no need to perform liver biopsy.

In two series of hepatotoxicity cases caused by Herbalife® described in Switzerland and Israel, the histopathologic forms of liver damage were different. In the Switzerland cases, there was predominantly cholestatic hepatitis with two cases of giant cell hepatitis/sinusoid obstruction syndrome[5], whereas in Israel cases there was predominantly hepatocellular hepatitis[4]. In the case described in Argentina, there was also predominantly hepatocellular hepatitis[7]. Different mechanisms of liver damage are caused by 'geographical' variations of Herbalife® product ingredients, and the aforementioned fact that the same substance can cause various types of liver failure.

Even though Herbalife® products are very widely used, the recorded frequency of their side effects is low. The real side effects are actually unknown because of imprecise data on total consumption of Herbalife® products, as well as the fact that liver damage

Table 3. Product labels/ingredients as claimed by the manufacturer (Herbalife®)

Product name	*Per* serving
Guarana	202 mg calcium carbonate, 800 mg guarana seed blend, microcrystalline cellulose, hydroxypropyl cellulose, silicon dioxide, stearic acid, magnesium stearate, maltodextrin, sodium carboxy methylcellulose, dextrin, dextrose, soy lecithin
RoseOx	Calcium carbonate 140 mg, exclusive herbal blend 620 mg (dried rosemary extract – leaf, cruciferous vegetable concentrate – broccoli, cauliflower, cabbage and carrot extracts, dried turmeric extract – root, tomato concentrate – fruit, sage – leaf, cloves – flower), corn starch, croscarmellose sodium, stearic acid, hydroxypropyl cellulose, silicon dioxide, magnesium stearate, microcrystalline cellulose, ethylcellulose, hydroxypropyl methylcellulose, guar gum, propylene glycol, vegetable oil, carnauba wax
Tang Kuei Plus	Vitamin C as ascorbic acid 8 mg, Tang Kuei root extract 200 mg, passionflower extract 30 mg, microcrystalline cellulose, modified food starch, stearic acid, croscarmellose sodium, magnesium stearate, silicon dioxide, sodium carbomethylcellulose, dextrin, dextrose, soy lecithin
Herbalifeline	Vitamin E as D-alpha tocopherol 8 IU, marine lipid complex as fish oil 758 mg, omega-3 fatty acids from fish oil 336 mg, gelatin, glycerin, soybean oil, white thyme oil, clove oil, peppermint oil, ethyl vanillin
Formula 4	Safflower oil 171 mg (linoleic acid 73%, oleic acid 13%, linoleic acid 0.3%), natural peach flavor (genetically modified)

may be occult and asymptomatic, and therefore undetected.

Taking into consideration the growing consumption of herbal products and their potential harmfulness, we consider that more strict regulations of the manufacture process and sale of herbal products are necessary, including exact identification of active substances with the list of ingredients, toxicologic testing and obligatory side effect report. Until then, the public at large, physicians and pharmacists have to be informed about the potential risk of their use.

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Sažetak

OZBILJNA HEPATOTOKSIČNOST UDRUŽENA S PRIPRAVKOM HERBALIFE® U PRETHODNO ZDRAVE ŽENE

D. Jurčić, M. Gabrić R. Troskot Perić, A. M. Liberati Pršo, J. Mirat, A. Včev, I. Alerić i *B. Ebling*

U novije vrijeme bilježi se porast upotrebe biljnih pripravaka koji su važan sastojak komplementarnih i alternativnih pripravaka te su široko dostupni pod krinkom "prirodnosti" i neškodljvosti. No budući da njihova upotreba ne podliježe strogim predmarketinškim testiranjima i regulativama, često nemaju jasno i detaljno definiran sastav, osiguranu kontrolu kvalitete, kao niti dokaz o učinkovitosti i sigurnosti. Štoviše, sve je više literaturnih podataka koji svjedoče štetnim učincima biljnih pripravaka, a kao najčešća posljedica njihove upotrebe navodi se hepatotoksičnost s različitim stupnjevima jetrenog oštećenja, od minimalnih promjena hepatograma sve do fulminantnog hepatitisa koji zahtijeva transplantacijsko liječenje. Prikazuje se slučaj jetrenog oštećenja visoko povezanog s uporabom određenih proizvoda Herbalife®, nakon što su kao moguć uzrok jetrenog oštećenja isključeni alkohol, virusne bolesti, metabolička, vaskularna, autoimuna i neoplastična zbivanja. Točan mehanizam jetrenog oštećenja u prikazane bolesnice nismo otkrili, a budući da su se jetrena funkcija i morfologija u potpunosti oporavile nakon ukidanja sumnjivih pripravaka Herbalife® nije bilo potrebe za biopsiju jetre. Imajući u vidu sve učestaliju konzumaciju biljnih pripravaka s potencijalno štetnim djelovanjem, smatramo da je neophodno uvođenje kako stroge regulacije proizvodnih i prodajnih procesa, tako i točne i detaljne identifikacije aktivnih tvari na popisu sastojaka te toksikološka testiranja uz obvezu prijavljivanja nuspojava.

Ključne riječi: *Herbalife; Biljni pripravci; Prehrana, dodaci; Zatajenje jetre*