



CASE REPORT

A Case of Serial Liver Injury Induced by Plant Food Supplements in a Young Healthy Man

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Introduction

The use of botanicals is increasingly throughout the world. They are ingredients of different types of products, such as herbal medicinal products, Plant Food Supplements (PFS), and functional foods. They are commonly taken to promote health and treat or prevent diseases, even if, in most of cases, there is no clear evidence of their clinical efficacy. In recent years, several reports have highlighted the beneficial effects of botanicals or PFS in the prevention of some chronic diseases [1,2]. But these positive effects are accompanied by the increased incidence of hepatic damage caused by herbal medicines, including PFS [3-7]. We are presenting two repeated cases of acute hepatitis occurred in the same patient for two consecutive years, after taking the same PFS.

Case Presentation

A 40-year-old male, healthy, with no morbidities, was hospitalized with nausea, vomiting, pruritus, and headache. Symptoms were started two days before. At clinical examination skin and sclera were yellow; these signs in association with symptoms were suggestive for acute hepatitis. There was no other sign of chronic liver disease. He reported a 14-day ongoing natural therapy

of two different PFS (once a day each) to prevent seasonal allergy and a recent consumption of raw fish. No other medical treatment was taking by the patient in the same period. PFS composition is reported in Table 1.

Laboratory test revealed normal blood count and basic metabolic panel. Liver tests showed Alanine Aminotransferase (ALT) level of 2605 IU/L, aspartate aminotransferase of 918 IU/L, and a total bilirubin of 17.35 mg dl-1 (directed 13.44 mg dl-1) (Table 2). Both hepatitis B and C testing were negative.

Instrumental investigations to rule out all other causes of jaundice were performed. Imaging studies for biliary obstruction were negative. He was discharged with the diagnosis of "food acute hepatitis" and a bland diet and biliary salt therapy was provided. Symptoms disappeared in 3 months, with the normalization of serum liver enzyme (Table 2).

One year later, in the same season, patient was re-admitted because of jaundice, with similar symptoms described before, including nausea, vomiting, headache, and yellow skin. On admission Alanine Aminotransferase (ALT) level was of 2158 IU/L and the aspartate aminotransferase was of 924 IU/L, while total bilirubin was 10.12 mg dl⁻¹ (Table 2). He reported the consumption of the same PFS of the previous year (PFS ingredients are reported in Table 1), started 10 days before. PFS consumption was immediately interrupted and the patient was treated again with a bland diet and biliary salt. This new episode of acute hepatitis was re-

Table 1: Pfs ingredients, standardization and *in vivo* Cyp3a4 modulation.

PFS-1 Composition*	<i>In vivo</i> CYP3A4 Modulation	Standardization of Active Compounds	PFS-2 Composition#	<i>In vivo</i> CYP3A4 Modulation	Standardization of Active Compounds
<i>Ginkgo biloba</i> L. dried extract from leaves	CYP3A inhibition in rats [16,17]; slight CYP3A induction in humans [18,19]; CYP3A4 inhibition in humans [20]	24% Ginkgo flavonoids, 5% terpenes lantons	<i>Perilla frutescens</i> L. dried extract from leaves and seeds		2.5% total polyphenols
<i>Schisandra chinensis</i> Turcz. dried extract from fruits	CYP3A4 induction in rats [21]	5% schizandrin	<i>Scutellaria baicalensis</i> Georgi root extract	Baicalin inhibits CYP3A4 in rats [22]	30% baicalein
<i>Camellia sinensis</i> Kuntze (green tea)	CYP3A inhibitor [23]; potent inhibitor CYP3A4 [24,25]	95% total polyphenols	<i>Citrus x sinensis</i> L.	The aglycone of hesperidin (hesperetin) inhibits CYP3A4 in rats [26]	60% hesperidin

*Composition included vitamin B12 (0.1%) and DL-phosphoserine; #Composition included quercetin and maltodextrine from *Zea mays* L.

Table 2: The evolution of the liver enzymes at the first and second year.

Examination	1 st case	Day 15	Day 30	Day 60	Day 90	2 nd case	Day 30	Day 60	Day 90
	05-07-2014					04-28-2015			
Tot Bilirubin mg dl ⁻¹	17.35	8.45	3.95	2.60	1.98	10.12	3.45	2.40	2.29
Directed mg dl ⁻¹	13.44	6.36	2.41	1.41	0.70	6.35	2.35	1.45	0.66
ALT mU/ml	2605	829	225	74	31	2158	260	80	20
AST mU/ml	918	453	196	78	15	924	170	65	18
LDH mU/ml	325	225			190	385			170
YGT mU/ml	157				29	188			15
ALP mU/ml	154				38	175			39
IgM	Neg					Neg			
Hepatitis E	Neg					Neg			
IgM Hepatitis A	Neg					Neg			
IgG Hepatitis A	Neg					Neg			
Chronic viral hepatitis	Neg					Neg			

solved in further 3 months with the complete normalization of serum liver enzyme. The new imaging showed the presence of mild steatosis.

Discussion

In this report, the etiology of the acute liver injury is resulted unequivocal the second year considering the consumption of the same PFS of the previous year. Identifying any toxic component(s) in herbal mixtures is a major problem since such supplements contain multiple ingredients. Each component may not be pure compounds and not all components occurring in the extracts could be listed as ingredients. Among all the botanicals present in the PFS of this case, hepatotoxic reactions have been reported after ingestion of *Scutellaria* spp. (skullcap)-containing preparations, alone or combined with other plant extracts [8,9]. Accordingly, the Food and Drug Administration (FDA) has listed skullcap as an herb of undefined safety. Moreover, some skullcap preparations available from wholesale suppliers contain species belonging to the *Teucrium* genus, including the hepatotoxic plant Germander (*Teucrium chamaedrys* L.) [10]. This observation strongly highlights the need for an accurate identification of the plant material [11]. LC-

MS/MS analysis on the acetone extract prepared from the PFS capsules allowed us to exclude the presence of teucriin A, which is the main hepatotoxic neo-clerodane occurring in Germander.

Neo-clerodane diterpenoids with cytotoxic activity have been identified from the whole plant of *Scutellaria* spp. and from the aerial parts of *Scutellaria baicalensis* [12], thus suggesting that these compounds, which effects in humans have not been still identified, could have toxic effects comparable to those exerted by teucriin A.

Although skullcap seems to be the candidate mostly responsible for the adverse effect, the contribution of other botanicals occurring in both the formulations cannot be excluded.

Hepatotoxicity of green tea preparations, mainly containing unusual concentration of catechins, has been reviewed [7,13]. Although the bioavailability of catechins is low after oral administration, plasma levels can reach toxic levels under fasting or repeated administration. Green tea hepatotoxicity has been imputed to the capability of Epigallocatechin-3-O-Gallate (EGCG) or its metabolites to induce oxidative stress in the liver [13].

Several herbal ingredients, occurring within both the above-mentioned PFS, have been identified as modulators of various cytochrome P450 enzymes, particularly CYP3A4 [9]. CYP3A4 modulators could potentiate the intrinsic hepatotoxicity of other substances, including neo-clerodane diterpenoids, by an increased conversion to toxic metabolites. Table 1 reports the *in vivo* modulation of cytochromes by ingredients included in PFS.

The hepatocellular (not cholestatic) injury with the combination of increased aminotransferase and serum total bilirubin could lead to consider the patient as a Hy's law case [14]. Unfortunately, botanicals are not included among Drug-Induced-Liver-Injury (DILI) [15], but considering symptoms and the clinical history of the patient, we cannot exclude a Hy's law case.

The current case report suggests the potential hepatotoxicity of some PFS commercially available; since they are accessible to the public and used as self-medication, the risk of adverse effects is high. This highlights the need for an active surveillance on PFS to provide detailed information on their safety. Further, the possibility of interactions among PFS ingredients before commercialization should be considered as well as new data on the safety of neo-clerodanes in skullcap.

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Conflicts of Interest

None.

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