

REVIEW ARTICLE

Review of liver injury associated with dietary supplements

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Keywords

anabolic steroids – *Camellia sinensis* –
cholestasis – hepatitis – retinoid toxicity –
toxic liver injury

Abbreviations

ALF, acute liver failure; DILI, drug-induced liver injury; DS, dietary supplements; FDA, Food and Drug Administration; HSC/MFB, hepatic stellate cells/portal myofibroblasts.

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Abstract

Dietary supplements (DS) are easily available and increasingly used, and adverse hepatic reactions have been reported following their intake. To critically review the literature on liver injury because of DSs, delineating patterns and mechanisms of injury and to increase the awareness towards this cause of acute and chronic liver damage. Studies and case reports on liver injury specifically because of DSs published between 1990 and 2010 were searched in the PubMed and EMBASE data bases using the terms 'dietary/nutritional supplements', 'adverse hepatic reactions', 'liver injury', 'hepatitis', 'liver failure', 'vitamin A' and 'retinoids', and reviewed for yet unidentified publications. Significant liver injury was reported after intake of Herbalife[®] and Hydroxycut products, tea extracts from *Camellia sinensis*, products containing usnic acid and high contents of vitamin A, anabolic steroids and others. No uniform pattern of hepatotoxicity has been identified and severity may range from asymptomatic elevations of serum liver enzymes to hepatic failure and death. Exact estimates on how frequent adverse hepatic reactions occur as a result of DSs cannot be provided. Liver injury from DSs mimicking other liver diseases is increasingly recognized. Measures to reduce risk include tighter regulation of their production and distribution and increased awareness of users and professionals of the potential risks.

The use of dietary supplements (DS) containing vitamins, anti-oxidants, fibre, trace elements, proteins, amino acids and herbal constituents has become a major health trend in affluent societies (1, 2). Consumption of DS in the USA has doubled to 18.9% of adults admitting their use only between 1999 and 2004 (3, 4); some investigations report their consumption up to 47% in certain subgroups such as among elder, non-smoking females with higher education (5). The rising popularity of DS is probably because of an increased awareness of consumers towards health in general and the desire to prevent diseases by an optimized nutritional status, and the persuasion that these treatments are safe (1, 2, 5, 6). Further, DS do not require prescriptions from health professionals allowing largely unrestricted access to relatively cheap products. Consequently, marketing such products has become a multibillion business largely unregulated by official health authorities (6–8).

In the USA, DS are expected to meet the standards outlined in the Dietary Supplement and Health Education Act published in 1994, which allows distribution without prior approval of their efficacy and safety by the

Food and Drug Administration (FDA) (9). This simplified licensing practice does not ensure efficacy and safety in the same strict way as with the approval of conventional medications and treatments. Similarly, the European Union has set forth legislative measures for the distribution and marketing of DS and functional foods that are outlined in the European Commission 2000 White Paper on Food Safety (10, 11). This set of legislation pays tribute to the fact that DS may harbour specific problems because of their complex composition, particularly with respect to quality aspects, and defines guidelines for conducting premarketing *in vitro* and *in vivo* studies.

While adverse hepatic reactions from xenobiotics are well documented by pre- and post-marketing pharmacovigilance, the situation for DS is less well depicted as widespread and uncontrolled use and under-reporting prevent the determination of their true incidence. Additionally, a low awareness of users and providers towards their potential harms impedes their recognition as the causative agent in incidents of hepatotoxicity. Consequently, estimates of the frequency of DS-associated

Table 1. Nutritional supplements associated with liver injury ($n > 1$ case)

Dietary supplement	Indication for use	Liver lesion	Toxicity mechanisms
Herbalife®	Various (weight loss, nutritional support, 'well-being')	Variable (acute and chronic hepatitis, cholestasis, cirrhosis, hepatic failure)	Unknown; autoimmunity? Bacterial contamination?
<i>Camellia sinensis</i> (green tea)	Weight loss	Acute hepatitis	Oxidative stress from (–)-epigallocatechin gallate?
LipoKinetix®	Weight loss	Acute hepatitis	Uncoupling of respiratory chain?
Hydroxycut	Weight loss	Acute and/or cholestatic hepatitis, liver failure	Unknown
Senna (<i>Cassia angustifolia</i>)	Constipation	Variable (acute hepatitis, granulomatous hepatitis, cirrhosis)	Drug idiosyncrasy (CYP2D6 variation)?; uncoupling of respiratory chain?
Noni juice (<i>Morinda citrifolia</i>)	'Immunostimulation', health tonic	Acute hepatitis, hepatic failure	Unknown; drug-induced autoimmunity?
Ma huang (<i>Ephedra sinica</i>)	Weight loss	Acute hepatitis, hepatic failure	Unknown; drug-induced autoimmunity?
Germander (<i>Teucrium chamaedrys</i>)	Weight loss	Acute, and fulminant hepatitis, chronic hepatitis with fibrosis/cirrhosis	Oxidative stress? Hepatocyte apoptosis from toxic neoclerodane diterpenoids
'Onshidou-Genbi-Kounou', 'Chaso' (Japanese herbals)	Weight loss	Acute hepatitis, hepatic failure	Hepatocyte apoptosis due to <i>N</i> -nitroso-fenfluramine
Vitamin A	Disease prevention, immune function	Chronic hepatitis, cholestasis, cirrhosis	Fibrosis from HSC/MFB activation; formation of toxic polar retinoid metabolites with concomitant alcohol consumption
Anabolic steroids	Muscle build-up	Cholestasis, benign/malignant liver tumours	Dysfunction of biliary transporter

HSC, hepatic stellate cells; MFB, portal myofibroblasts.

hepatic injury are likely imprecise and, possibly, too low. The proportion of hepatotoxicity ascribed to DS varies from 2% in a Spanish study (12) describing 531 cases of drug-induced liver injury (DILI) to approximately 10% in a series from the US Drug-Induced Liver Injury Network (DILIN) (13). Figures were as high as 35% in a small series of 20 patients developing acute liver failure with DS exposure as the only identifiable cause of liver damage (14).

Our article aimed to review and describe the literature on liver injury because of DS, delineate patterns and mechanisms of injury and to increase the awareness towards this possible cause of acute and chronic liver damage.

Literature search methodology

In February 2010, case reports and series thereof on liver injury specifically occurring following the consumption of DS published between 1990 and 2010 were searched in PubMed and EMBASE data bases using the terms 'adverse hepatic reactions', 'anabolic steroids', '*Camellia sinensis*', 'dietary/nutritional supplements', 'Herbalife', 'hepatitis', 'Hydroxycut', 'green tea', 'liver failure', 'liver injury', 'Noni', 'retinoids', 'vitamin A' and critically reviewed. Retrieved publications were searched for yet unidentified publications. Remedies were considered DS if consumed as an aid to improve nutritional status, to lose weight or to treat constipation. Cases of liver injury from preparations taken

for other causes than nutritional purposes were not included. No language restriction was used.

While hepatotoxicity from herbal medicines in general has been addressed in several reviews (15–18), summaries specifically devoted to liver-related risks along with DS are scarce (19). In the following, a panel of rather distinct DS preparations associated with liver injury are described (Table 1).

Specific dietary supplements associated with liver injury

Herbalife®

Herbalife® (Los Angeles, CA, USA) sells nutritional and herbal supplements as tablets, capsules, drinks and energy bars for weight control, improvement of nutrition, 'well-being' and cosmetics. In 2006, the stock market quoted that Herbalife® company had a revenue of US\$3.1 billion via online marketing or through independently operating sales agents.

There are so far six published reports on liver damage following the intake of Herbalife® products since 2007 describing 34 cases from five countries (Switzerland, Israel, Spain, Argentina and Iceland), although Herbalife® products are sold in at least 60 countries worldwide (20–25). Individual data of all reports are displayed in Table 2. Pattern of injury was mostly hepatocellular, but mixed and

Table 2. Case reports on liver injury following the intake of Herbalife® products

Author	Patients (n)	Type and number of products	Duration of intake (months)	Type of injury	Outcome	Causality assessment
Elinav <i>et al.</i> (20)	12 (11F)	Variable; between 6 and 17 different products	2–28	Hepatocellular (n = 11), mixed (n = 1)	Recovery (n = 11), death (n = 1)	WHO score; certain (n = 3; positive rechallenge); probable (n = 6); possible (n = 3)
Schoepfer <i>et al.</i> (21)*	10 (7F)	Variable; between 3 and 13 different products	2–26	Hepatocellular (n = 9), mixed (n = 1)	Recovery (n = 8), liver transplantation (n = 1), cirrhosis (n = 1)	WHO score; certain (n = 2; positive rechallenge); probable (n = 7); possible (n = 1)
Duque <i>et al.</i> (22)	4 (4F)	Nine different products	1–26	Hepatocellular (n = 2); mixed (n = 2)	Recovery of all four	Not assessed
Chao <i>et al.</i> (23)	1 (F)	Three different products	2.5	Mixed	Recovery	WHO score; probable
Stickel <i>et al.</i> (24)	2 (1F)	Variable; between six and eight different products	12–36	Mixed (n = 1), cholestatic (n = 1)	Recovery (n = 1), cirrhosis (n = 1)	CIOMS; probable (n = 2)
Johannsson <i>et al.</i> (25)	5 (4F)	Variable; between two and five different products	1–7	Hepatocellular (n = 3), cholestatic (n = 2)	Recovery (n = 5)	RUCAM; probable (n = 3), possible (n = 2); WHO; certain (n = 1), probable (n = 2), possible (n = 2)

*Contains case reported in Hoffmann *et al.* (28):

F, female; M, male.

cholestatic enzyme patterns were also observed. Severity ranged from mild to severe hepatic damage including cirrhosis and acute liver failure requiring liver transplantation, which was successful in one patient while the second died because of post-operative complications. Causality between intake of Herbalife® products and the evolution of liver injury was assessed by widely used scores (26, 27) in five of the six reports and considered 'certain' in at least five patients by a positive rechallenge reaction and 'probable' in the majority of the remaining cases (20, 21).

Since Herbalife®-related liver injury was first reported in 2005 in Switzerland (28) and Spain (29), some countries (Israel and Switzerland) have not noticed further incidents after publication of corresponding series, while other investigators continue to see new cases (G. Manso and M. Johannsson, personal communication). However, Herbalife® representatives have so far denied the causal relationship between the consumption of their products and cases of liver injury (30).

It still remains entirely speculative what might have been the cause of liver damage in the published cases as patients took up to 17 different Herbalife® products at the same time, which makes it extremely difficult if not impossible to identify the crucial compound(s). Based on the observation of plasma cell infiltrates in some patients, Elinav *et al.* (20) hypothesized that immune-mediated liver injury could be a possible explanation in some cases. Moreover, speculations over possibly adulterated products evolved after a report on two patients of which one developed cirrhosis (Fig. 1) demonstrated bacterial contamination of several Herbalife® products with *Bacillus subtilis* as a possible explanation of liver injury (24).

Herbalife® runs numerous production sites worldwide that deliver products to different regions, suggesting that spoiled products contaminated with certain germs, chemicals such as softeners, preservatives, flavour enhancers, pesticides or heavy metals either intentionally added during the manufacturing process or accidentally contained in the unrefined raw products, i.e. herb extracts, could have been responsible for locally restricted series of hepatotoxicity.

Camellia sinensis (green tea)

Green tea is among the most frequently consumed drinks in the USA and often used as a DS. The first report on liver injury following the ingestion of green tea extracts and preparations thereof was published in 1999 (31), and since then, numerous consecutive cases were reported to regulatory agencies worldwide. With effect of April 2003, the manufacturer of Exolise® (Arkopharma, Carros, France), a hydro-alcoholic extract of *C. sinensis*, has revoked all of their products after altogether 13 cases of acute liver damage following its intake were reported to the French pharmacovigilance authorities (Agence Française de Sécurité Sanitaire de Produits de Santé; <http://www.afssaps.sante.fr>). As a reaction to these accumulating reports, the US Pharmacopeia performed a systematic review of all cases accessible from PubMed, EMBASE and pharmacovigilance data bases in the USA, Canada, UK and Australia reporting on 34 single cases of liver injury following the ingestion of numerous different green tea preparations (32). Herein, case reports were retrospectively evaluated according to the Naranjo

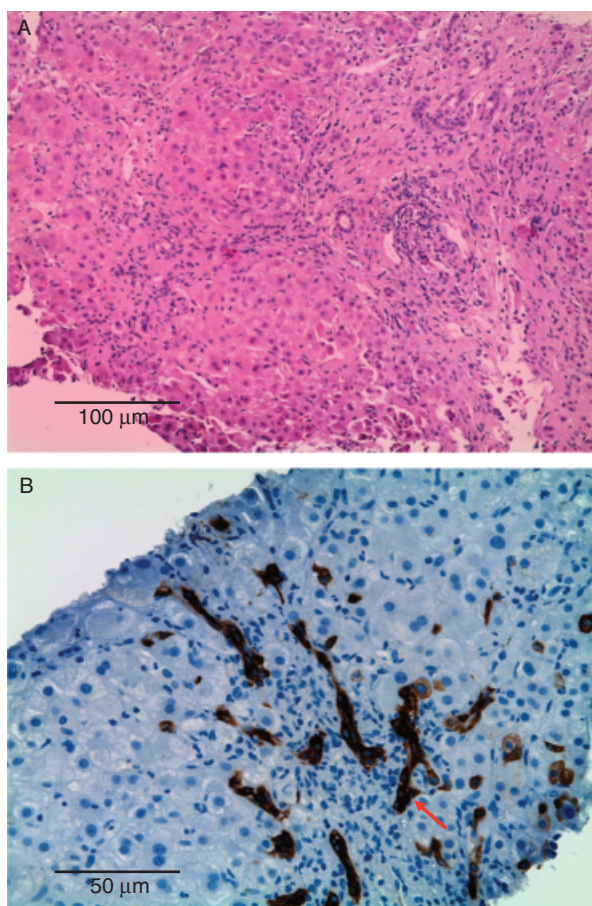


Fig. 1. Liver histology from a patient with secondary biliary cirrhosis following long-term intake of numerous Herbalife[®] nutritional supplements contaminated with *Bacillus subtilis*. (A) Enlargement of portal tracts with fibrosis, chronic inflammation and porto-lobular interface activity as well as ductular proliferation of the bile ducts with reactive changes of the epithelium (HE staining). (B) Immunohistochemistry with anticytokeratin 7 indicating bile duct such as loss of biliary lumina and significant lympho-epithelial infiltration (see arrow).

causality algorithm scale (33), and 27 reports pertaining to liver damage were labelled as 'possibly' and the remaining seven cases as 'probably' linked to green tea. Another Medline search review of cases on green tea liver injury from the same year also retrieved 34 published reports and described two further yet unpublished cases (34). On histological examination, livers of patients revealed inflammatory reactions, cholestasis, occasionally steatosis and necrosis. Although there was some overlap of single reports between these two review articles, collected case reports were not identical and jointly provided details on 58 cases of hepatotoxicity along with the intake of green tea extracts, powdered leaves, green tea infusions and hydro-alcoholic and aqueous extracts. In Mazzanti's summary, no causality re-evaluation was performed, but information on de- and rechallenge is provided for every case indicating a

positive rechallenge response with accelerated recurrence of liver injury in seven of 36 incidents, which strongly suggests a causal relationship between the observed liver injury and green tea consumption. Of concern is that there was one reported death. However, a note of caution is warranted in many of the cases regarding an exclusive assignment of causality to green tea, because many patients who experienced adverse hepatic reactions also took numerous other products with a published record of hepatotoxicity, such as *Cassia angustifolia*, Hydroxycut and *Ephedra sinica* (for all three, please see below). Since these two review articles, additional cases have been published from Belgium reporting on a 42-year-old female patient who developed cholestatic hepatitis 6 months after starting Densitive[®] (Kerastase Nutritients, L'Oréal, Paris), which contains *C. sinensis* (35). Upon dechallenge, a full recovery was recorded. Other causes of liver injury were carefully excluded, but formal causality assessment using an established score was not performed. In the second case, jaundice, weight loss and subacute hepatitis developed in a 76-year-old man who regularly drank green tea infusions (36). Histology showed marked necro-inflammation, and transiently elevated anti-smooth muscle auto-antibodies were suggestive of auto-immunity induced by green tea constituents.

The mode of toxicity derived from green tea still remains incompletely understood but could be because of (–)-epigallocatechin gallate or its metabolite (–)-epicatechin gallate, which, under certain conditions such as fasting, can induce oxidative stress-related liver damage (37). Interestingly, *in vitro* and *in vivo* experimental studies have demonstrated both hepatoprotective as well as hepatotoxic properties (37–40). Along this line, support for potentially hepatoprotective activity from green tea extracts comes from clinical studies studying its therapeutic effects in humans with liver diseases including liver cancer, cirrhosis and steatosis. Four randomized-controlled clinical trials, two cohort, one case–control and three cross-sectional studies from China, Japan and the USA were recently subjected to a systematic review and found overall favourable effects from green tea as reflected by reduced mortality, attenuated steatosis and reduced incidence of primary liver cancer (41).

Whether the risks from green tea consumption outweigh their benefits remains open, but current evidence as outlined above suggests a causal relationship between intake of green tea-containing products and hepatotoxicity. Consequently, in their systematic review, the US Pharmacopeia included a cautionary statement on green tea indicating this possibility (32).

Usnic acid

Some years ago, several cases of acute liver failure requiring liver transplantation following the intake of LipoKinetix[®], a product extracted from lichens and fungi and sold as DS capsules, were reported (42–45). Onset of liver injury was usually acute with a maximum

latency of 3 months and the injury pattern hepatocellular with massive elevations of ALT and AST. LipoKinetix contained usnic acid and was marketed as a weight-loss remedy. Efficacy for this indication was postulated based on its function as an uncoupler of the respiratory chain, which in principle can augment weight loss (46). Apart from usnic acid, LipoKinetix[®] contained norephedrine hydrochloride, diiodothyronine, yohimbine hydrochloride and caffeine, which were confirmed by analysing the used LipoKinetix[®] lots. None of the ingredients were associated previously with liver damage and inadvertent contamination was excluded. These serious events caused the withdrawal of LipoKinetix[®] from the market.

Hydroxycut

Only recently, several Hydroxycut products were retracted by the manufacturer following a warning posted by the FDA in May 2009 because of 23 reports of liver injury including cases with acute hepatic failure and subsequent liver transplantation (47–49). Hydroxycut preparations were sold as powder, capsules and tablets by conventional retailers, through Internet sources and via direct television marketing. Hydroxycut was used to support weight loss and by body builders. The manufacturer had been charged previously with several lawsuits for unfounded health claims. Before May 2009, its primary ingredients included *Garcinia cambogia*, *Gymnema sylvestre*, chromium polynicotinate, caffeine and green tea. Published cases were recently reviewed and showed acute onset after several weeks of intake with high levels of serum aminotransferases in the majority of cases, while others presented with a more insidious, usually cholestatic course (50).

Miscellaneous

Various other DS have been associated with acute and subacute liver damage such as Senna (*C. angustifolia*), which is used as a powder, tea or suppository to treat constipation. According to our search, a total of five reports with altogether five individual cases describe the evolution of variable liver pathologies including acute cytolytic hepatitis, subacute cholestatic hepatitis, acute liver failure and portal vein thrombosis upon consumption of Senna products (51–55). In some reports, Senna preparations were self-made or ingested excessively such as in a young woman taking approximately 10 times the recommended dose who developed cytolytic hepatitis, which completely subsided after stopping Senna (51). The causal relationship between the preparation and hepatitis was confirmed through a positive rechallenge in two cases (51, 52). Senna is biotransformed via intestinal bacteria to rhein anthrone, which is highly reactive and requires binding to glucuronide and sulphate via phase I oxidation for renal excretion (56). Rhein anthrone is suspected to function as an uncoupler of the respiratory chain, and can therefore possibly affect hepatocyte integrity under certain circumstances, such as

in genetically predisposed individuals. Seybold *et al.* (52) describe a case of increased toxicity of Senna tea in a homozygous carrier of a genetic cytochrome P450 2D6 variant rendering the individual a poor metabolizer for phase I hepatic detoxification reactions.

Noni juice (*Morinda citrifolia*) has become increasingly popular in Western countries as a health tonic. Consumption of Noni was the presumed cause of acute hepatitis in a 45-year-old man who drank a glass of this tropical fruit over several weeks for preventive reasons and for 'strengthening the immune system' (57). Other possible aetiologies of acute hepatitis were ruled out and liver tests rapidly turned normal after the cessation of Noni intake. Since this first report in 2005, five additional cases have been published from Austria, Germany and Spain (58–61). Remarkably, two patients experienced liver failure of which one required liver transplantation. The pattern of liver injury was hepatocellular in all cases and occurred rapidly within a few weeks of exposure. Causality was formally assessed in two publications, but not considered 'certain' in any of the cases because no rechallenge was used. Also, at least two of totally six patients had concomitant medication with known hepatotoxic potential, such as interferon- β (62) and a Chinese herbal mixture (63) respectively. Responsibility of Noni preparations as the cause of liver injury in these cases is challenged by one of the manufacturers of Noni products (64, 65) by demonstrating experimental evidence of no dose-dependent hepatotoxicity and even hepatoprotective properties in some animal models of chronic liver injury (66, 67). However, a lack of dose-dependent hepatotoxicity does not exclude idiosyncratic drug toxicity, e.g. by inducing autoimmune reaction as shown by Yuce *et al.* (59) who found excessively high liver–kidney microsomal antibodies of 1:3840 in a patient drinking Noni juice for 4 weeks. Nevertheless, the true underlying pathophysiology of Noni-associated liver injury remains elusive because active components within Noni extracts such as flavonoids, glycosides, vitamins, anthraquinones and polyunsaturated fatty acids are not known to be hepatotoxic.

Chinese herbs have become highly popular among consumers in Western countries because of a prevailing belief in their efficacy and safety. Among many others, Ma huang (*E. sinica*) is marketed in the USA as a nasal decongestant and bronchodilator, and more recently as a weight-loss remedy. The first report of Ma huang-associated liver injury was about a woman developing acute hepatitis together with elevated antinuclear antibodies (ANA) and smooth muscle antibodies (SMA) after only 3 weeks of intake of Ma huang, but liver abnormalities resolved after its discontinuation (68). Another report suggested that intake of Ma huang was the cause of acute liver failure in a 58-year-old patient initiating her listing for high-urgency liver transplantation who also presented with elevated titres of SMA (69). Another report suggested an association of Ma huang-related liver injury with compound heterozygosity for the C282Y and H63D mutation in the haemochromatosis gene, proposing that

excess hepatic iron could aggravate hepatotoxicity, possibly via enhancing oxidative stress (70). The largest series on severe liver injury because of the intake of Ma huang by Neff *et al.* (71) describes 10 cases of acute cytolytic hepatitis of which two subjects required liver transplantation and one died, while the remaining seven patients recovered spontaneously. These cases of severe liver damage and others referring to cardiac toxicity have prompted a warning by the FDA for the use of *Epedra*-containing DS such as Ma huang (72).

In 1986, *Germander* (*Teucrium chamaedrys*) was approved as a drug for the supportive treatment of obesity in France. Its subsequent widespread use precipitated numerous reports on acute, chronic and even fulminant hepatitis to the French pharmacovigilance authorities in 1992 (73–75). Within a median of 2 months, intake of daily doses between 600 and 1600 mg/day precipitated acute cytolytic hepatitis or chronic hepatitis with fibrosis and even cirrhosis (74, 76). All patients recovered after the discontinuation of treatment, but some relapsed under re-exposure. *Germander* contains saponins, glycosides, flavonoids and neoclerodane diterpenoids, which were shown to be converted into diterpenoid toxic metabolites by cytochrome P450 3A in mice (77). In conditions of glutathione depletion – such as during fasting – or after induction of cytochrome P450 3A, toxic diterpenoids are potent inducers of hepatocyte apoptosis (78, 79). Hence, in 1992, the license for *Germander*-containing products was withdrawn.

'Onshidou-Genbi-Kounou', another herbal marketed for weight loss, seemed the likely cause of chronic hepatitis in a 52-year-old Japanese woman who took this preparation for 2 months (80). Serum levels of liver enzymes were elevated to >1500 IU/l and ANA were positive with 1:160. All other possible causes for chronic hepatitis were excluded, and liver histology was compatible with drug-induced autoimmune hepatitis. The patient recovered completely without intervention on cessation of 'Onshidou-Genbi-Kounou' intake. In a larger series from Japan describing 12 patients with acute hepatitis after taking 'Onshidou-Genbi-Kounou' and 'Chaso' for weight loss, two patients developed liver failure of which one survived after successful liver transplantation and the other one died (81). 'Onshidou-Genbi-Kounou' contains several natural compounds (amachazuru, tea leaf, barbaloin, total saponin and polyphenols) and *N*-nitroso-fenfluramine. The latter demonstrated induction of mitochondrial permeability transition and hepatocyte apoptosis following uncoupling of oxidative phosphorylation and intracellular ATP depletion (82, 83).

Vitamin A-associated liver injury

DS fortified with vitamin A are used to prevent night blindness, to increase immune function and to promote health in general. Liver injury related to hypervitaminosis A is well known for many decades and comprises mild elevations of serum liver enzymes, cholestatic hepatitis, non-cirrhotic portal hypertension, progressive fibrosis and

cirrhosis (84–87). Toxicity does not usually occur with standard doses below 50 000 IU/day as contained in common multivitamin preparations, but individual tolerability may vary (88). Pre-existing liver lesions including steatosis, chronic alcohol consumption, comedication with other potentially hepatotoxic drugs and young age may predispose certain individuals to develop vitamin A hepatotoxicity (89, 90). Several case reports have demonstrated significant hepatotoxicity with vitamin A doses as low as 20 000 IU/day (91), and upper limits of tolerability may even be lower in regular alcohol consumers (92).

Toxicity is mediated to the dose-dependent effect of retinoids on hepatic stellate cells/portal myofibroblasts (HSC/MFB), which are the key effector cells in the evolution of fibrosis and cirrhosis (93). Upon excessive vitamin A exposure, HSC/MFB start to produce collagens, down-regulate collagenase activity and acquire the ability of contraction leading to elevation of blood pressure in the portal vein. In addition to this direct impact on HSC/MFB function and activity, retinoids can be transformed into metabolites that affect mitochondrial function and hepatocyte viability with resulting liver cell apoptosis (94, 95). This was shown to occur particularly when co-administered with alcohol. Dan and colleagues showed that retinoids can be transformed via alcohol-induced cytochrome P450 2E1 into highly reactive and toxic polar metabolites, which cause hepatocyte apoptosis upon caspase 3 activation (Fig. 2). Hence, health professionals should consult users carefully about the potential dangers of vitamin A, particularly when intended for longer period, in children and regular alcohol consumers.

Anabolic steroids

Anabolic steroids are an integral part of the nutritional concept of many athletes to improve fitness, muscle gain and exercise performance. Their use is widespread although anabolics are classified as class III substances and therefore subdued to strict rules (96). However, access via unofficial and sometimes illegal sources is easy, and therefore, in spite of tight rules, further adverse hepatic reactions following the consumption of anabolic steroids can be expected. Hepatotoxicity has been frequently described and patterns of injury delineated. Liver lesions include intrahepatic cholestasis, hepatitis, adenoma and hepatocellular carcinoma and rare malformations such as peliosis hepatis, a rare pathological entity characterized by the gross appearance of multiple cyst-like, blood-filled cavities within the liver (97, 98). A recent case series demonstrated the evolution of cholestasis 2 weeks after the intake of anabolic steroids had been stopped. All patients recovered fully after intake had been terminated (99). Even more worrisome is the observation that some DS may contain anabolic steroids sufficient to precipitate liver injury, as demonstrated by a recent case report showing cholestasis in two young men who took DS to enhance their body-building performance (100). Another case presented with a less favourable course as prolonged

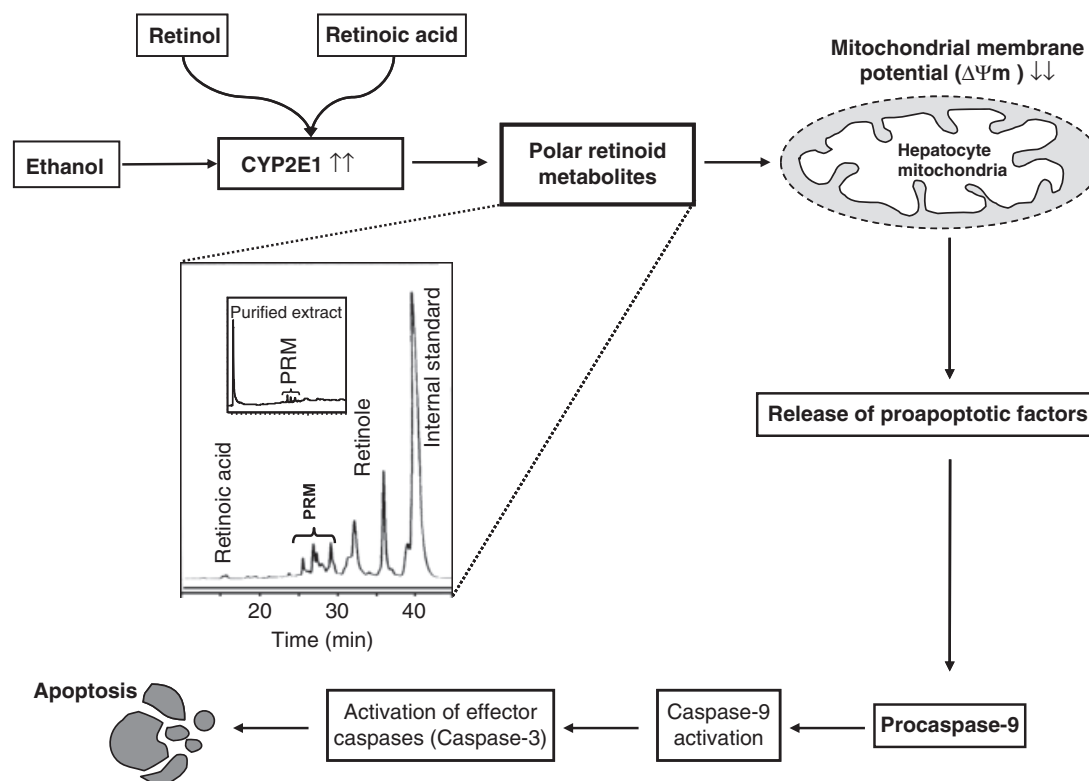


Fig. 2. Retinoids are substrates of cytochrome P450 2E1 and may be transformed into toxic polar retinoid metabolites. These can damage mitochondria by disrupting the mitochondrial membrane potential, releasing pro-apoptotic factors (e.g. cytochrome C) and initiating caspase activation and hepatocellular apoptosis.

intrahepatic cholestasis and subsequent kidney failure developed (101). The precise mechanism underlying toxicity is yet unclear, but experimental data indicate direct hepatocellular toxicity from steroids via increased oxidative stress and subsequent impairment of function of the canalicular bile salt export pump (100).

A recent case-control study from Brazil suggested that anabolic steroids could be a cause of toxicant-associated non-alcoholic fatty liver disease (TAFLD) by comparing 95 recreational body builders using anabolic steroids with 85 non-users. In those consuming anabolic steroids, 12.6% of subjects revealed criteria compatible with TAFLD such as steatosis on ultrasound imaging, elevated serum transaminases and exclusion of relevant alcohol intake or concomitant medication, but no overweight or insulin resistance suggestive of metabolic NAFLD. In turn, 2.4% of body builders not using anabolic steroids showed clinical signs and findings suggestive of NAFLD. The authors concluded that the intake of anabolic steroids could be a cause of non-metabolic, but toxicant-associated NAFLD (102).

Conclusion

Hepatic injury secondary to consumption of DS is recognized, although its exact frequency remains unclear,

mostly because evidence relies exclusively on case reports. Lack of stringent diagnostic criteria, poor awareness of consumers and prescribers, easy and uncontrolled access and under-reporting account for this epidemiological gap of knowledge. Diagnostic assessment of DS-associated should be made more consistent, and customized specifically to DS. Although causality categories reached in many of the published reports suggest a causal relationship between liver injury and the intake of certain DS products, pitfalls exist related to the used diagnostic scales, which have all been criticized for variable reasons and of which none is unequivocally accepted as being suitable for the evaluation of DS as a cause of liver injury. While the WHO score is not specifically designed to evaluate DILI (103), the Naranjo adverse drug reaction probability scale (33) was recently found to have low sensitivity (54%), poor negative predictive value (29%) and to lack reproducibility in a large series of cases of suspected hepatotoxicity (104) when compared with the Roussel Uclaf Causality Assessment Method (RUCAM) (26, 105). A clinical diagnostic scale has been suggested as a simple tool to assess adverse hepatic drug reactions and showed good correlation with RUCAM in one study (106), but not in another (107). To conclude, all used scores reveal merits and limitations, but a common consensus on which one is the best to

apply in causality assessment of DS-associated liver damage has never been reached. In an approach to compensate for this lack of common agreement, recently, the DILIN was established to advance our understanding and research into DILI by initiating a prospective registry of patients with DILI for future studies into host clinical, genetic, environmental and immunological risk factors, and to develop standardized nomenclature, terminology and causality assessment instruments (108). Patients with liver injury because of herbal products are also eligible to be included. Herein, a causality score ranging from 1 (definite) to 5 (unlikely) as well as a severity score ranging from 1 (mild) to 5 (fatal) is applied by three hepatologists of the DILIN study group, thereby minimizing individual biases. In addition to accounting for the input of the reporting investigator who took the history, performed the physical examination and supervised the data collection, a prospective evaluation of other potential causes of liver injury and serial laboratory data through at least 6 months of follow-up are offered. However, the DILIN expert opinion is limited by its lack of generalizability and a low level of agreement between the three hepatologists (109). Hence, a certain degree of inaccuracy in assigning causality remains until better diagnostic measures are established.

Apart from diagnostic measures, better regulatory measures to assure safety and timely recognition of potentially harmful products require improvement and, thus, efforts of pharmacovigilance authorities and healthcare providers must jointly act to minimize risks and protect consumers. Manufacturers must spend utmost care in providing users with clean and unadulterated products and should be held liable if this accidentally or carelessly fails. Finally, consumers should develop a more critical attitude towards the expectations and hopes associated with DS use in largely healthy individuals, and turn to measures for which safety data are known, and efficacy is proven.

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