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SHORT REVIEW

Potential Risks of Plant-based Dietary Supplements: A Closer Look at Liver Toxicity and Safety Concern

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Abstract

Dietary supplements, which include a wide range of products such as vitamins, minerals, herbs, and botanicals, are commonly used to complement regular diets and provide nutritional or physiological benefits. Among these, plant-based supplements like Echinacea, Ginkgo Biloba, Ginseng, and Green Tea Extract (GTE) have gained significant popularity for their therapeutic uses. However, certain plant-based supplements have been linked to liver toxicity, raising concerns about their safety. Green tea extract, commonly consumed for its antioxidant properties and weight-loss claims, has been associated with acute liver injury, with case reports documenting jaundice and elevated liver enzymes in affected individuals. Other supplements, such as Kava, Germander, and certain weight-loss products, also carry risks of hepatotoxicity due to mechanisms involving oxidative stress, DNA interaction, and depletion of protective enzymes like glutathione. Herbal products, including Herbal life, have been implicated in liver damage, leading to clinical symptoms such as jaundice, fatigue, and elevated liver enzymes. Additionally, Comfrey, a plant known for its medicinal use, contains pyrrolizidine alkaloids that can result in severe liver damage, including cirrhosis. These findings highlight the need for caution when using plant-based supplements, particularly when consumed in excess or in combination with other medications. Despite the growing demand for alternative therapies, more research and regulatory oversight are necessary to ensure the safety of these products and prevent adverse health outcomes.

Major Findings: The major findings highlight that while dietary supplements, particularly plant-based products, offer health benefits; many are associated with hepatotoxicity and other adverse effects. Green tea extract, kava, germander, and Herbal life products have been linked to liver damage, often due to toxic metabolites, oxidative stress, and drug interactions. Regulatory gaps and inconsistent quality controls contribute to the risks associated with these supplements.

Keywords: Herbal Supplements, Hepatotoxicity, Liver Toxicity, Risks

1. Introduction

Dietary supplements are a wide range of products that include vitamins, minerals, herbs, botanicals, fish oils, glucosamine, creatine, and essential fatty acids[1]. The European Union's regulations on food supplements also categorize plant-based products as dietary supplements. These are concentrated forms of nutrients or other substances that offer nutritional or health benefits, commonly found in various formats like capsules, tablets, pills, powders, liquid ampoules, or droppers. The primary goal of these supplements is to enhance a person's regular diet. Some popular plant-based supplements are *Echinacea*, *Ginkgo biloba*, ginseng, and green tea extract[2]. These are commonly used not only as dietary supplements but also for therapeutic purposes. The growing acceptance of Complementary and Alternative Medicine (CAM) has contributed to the rising popularity of these products, driven in part by dissatisfaction with conventional medical treatments and a desire for greater control over personal health choices. Phytotherapy-the practice of using plant-based treatments-has been a foundational element of medical practice for centuries, and the World Health Organization (WHO) claims that roughly 80% of people on the planet still depends on herbal medicines for health management[3]. As a result,

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plant-based ingredients are found in various products like Herbal Medicinal Products (HMPs), Plant Food Supplements (PFSs), homeopathic remedies, teas, juices, and cosmetics. While in the past, herbal medicines were primarily regulated on the basis of traditional use, safety studies, clinical trials, and stringent quality controls, many herbal products today are marketed as PFSs[4]. These often lack firm evidence of efficacy and may not be subject to the same strict quality standards as their medicinal counterparts[5].

2. Green Tea Extract

Millions of people drink green tea every day, making it one of the most popular drinks in the world. The leaves of the *Camellia sinensis* plant are used to make Green Tea Extract (GTE), which is widely thought to have a number of health advantages. Among the most notable claims is its potential to support improving fat metabolism ("fat burning") to lose weight[6]. These claims are based on laboratory studies using concentrated GTE, which have demonstrated antioxidant properties, inhibition of fat cell formation, and the activation of various metabolic pathways. However, since 2006, more than 50 reported cases of acute liver injury, including jaundice, have been associated with GTE consumption[7]. Initially, the connection between GTE and liver damage was thought to be linked to rare cases of acute hepatitis[8]. Although the precise mechanism underlying GTE-induced liver damage is unclear, research on mice has revealed that elevated GTE levels catechins, particularly Epigallocatechin Gallate (EGCG)- which accounts for 30% to 50% of GTE's dry weight-can result in hepatotoxicity. While the usual human dosage of EGCG (typically less than 12 mg/kg per day) is not considered excessive and is lower than the threshold known to cause direct toxicity, with an estimated 30-90 mg/kg some individuals may experience adverse reactions[9,10]. This suggests that liver damage from GTE may be an idiosyncratic reaction, much like traditional Drug-Induced Liver Injury (DILI). Some case reports have provided additional insights into this phenomenon (Table 1).

3. L-Carnitine

Fatty acid β-oxidation requires the movement of acyl-CoA from the cytosol into the mitochondrial matrix, which is facilitated by L-carnitine (L-carnitine), the active form of carnitine. In 1986, the US Food and Drug Administration (FDA) recommended a daily dosage of 1 gram of L-carnitine for duration of 2 to 4 months to address primary carnitine deficiency[11]. L-carnitine is also a component of infant diets for those who cannot produce it during early stages of life and is commonly used to aid in weight management for both humans and animals. Research conducted by the National Institutes of Health suggests that L-carnitine supplementation typically has no severe adverse effects, though minor side effects like nausea, vomiting, diarrhea, cramping, a fishy odor on the body, and, in some cases, muscle weakness and seizures may occur. A reduction in body fat can sometimes result in metabolic disturbances, such as insufficient energy reserves, subcutaneous fat tissue dysfunction, and damage to the cell membranes of vital organs. Additionally, L-carnitine supplementation has been noted to increase insulin secretion, which disturbs blood glucose regulation without changing serum levels of non-esterified fatty acids, more in lean people than in obese people[12,13]. This calls into question how it regulates the β-oxidation of fatty acids and the balance of energy in general[14,15]. Supplementing with L-carnitine has more recently been connected to an increased risk of cardiovascular disease in both humans and rats. Enhanced fatty acid β-oxidation within the Reactive Oxygen Species (ROS) are produced in greater quantities by mitochondria, which triggers the NLRP3 inflammasome[16,17]. Pro-inflammatory cytokines, IL-1β and IL-18, are released as a result of this activation and are important players in the inflammatory response that lead to liver and kidney damage[18-20].

4. Whey Protein

About 20% cow's milk protein, 50% lactoglobulin, 25% β-lactalbumin, 7% serum albumin, and 5% immunoglobulins make up whey protein[21]. Whey protein is essential for protein synthesis and the metabolism of carbohydrates because of its high amino acid chain content, which gives it energy when exercising. Protein supplements are used by many bodybuilders and athletes to increase strength, muscular mass, and growth hormone production. Among the most widely utilized supplements are casein, whey, and soy proteins; whey is the most widely used because of its greater calorie content

and ability to promote muscle growth. TNF-α, IL-6, and Interleukin 1β (IL-1β) are pro-inflammatory cytokines that are necessary for liver protection and regeneration. Stressors such as surgical problems cause the release of these cytokines into the bloodstream[22]. Stressors like infections and surgical problems cause these molecules to be released into the bloodstream; the intensity of the response varies according to the stressor's severity[23].

5. Kava-Kava

Kava (*Piper methysticum* Frost F), a perennial plant native to the South Pacific Islands, is commonly used in Western countries as a herbal therapy for anxiety and sleeplessness[24]. The World Health Organization declared in 2005 (WHO) reported 55 instances of liver damage linked to kava, including two cases of hepatic coma and three cases of liver failure. As a result, several European countries imposed a ban on kava, although it remains available in the United States despite warnings from the FDA liver damage has been linked to both commercially processed solvent-based kava supplements and conventional water-based kava extracts. Kava is thought to induce liver damage through various mechanisms (Table 2)[24-26].

Table 1. Clinical insights into green tea extract-induced liver injury

Observation	Associated Toxicity and Mechanism	References
Causal link between liver injury and green tea	Green tea drinking may be linked to liver damage, according to a review of 36 case studies.	29
Histological findings	The majority of cases of liver injury were hepatocellular in type, and histological analysis revealed cholestasis, inflammation, and occasionally steatosis and necrosis.	29
Fatality in case report	In one case, liver damage proved deadly.	29
Positive rechallenge	A positive rechallenge (re-exposure to green tea causing recurrent liver injury) was described in 7 cases (20%).	29
USP review	The US Pharmacopeia was examined 34 case reports linking green tea extract to potential herbal-induced liver damage and suggested incorporating warnings about liver injury symptoms into its monographs. Despite this recommendation, the proposal has not been implemented.	29
Clinical presentation of toxicity	In addition to abnormal laboratory results including increased transaminase, alkaline phosphatase, conjugated bilirubin, and an elevated International normalized ratio (INR), patients may also have jaundice in the skin or sclera.	30

Table 2. Unraveling the mechanisms behind kava-induced liver toxicity

Mechanism	Associated Toxicity and Mechanism	References
Kavalactones, pipermethystine, flavokavain B	These chemical entities found in kava may contribute to hepatotoxicity. While the mechanisms have been theorized, none have been definitively confirmed.	24
Interaction with DNA and proteins	Kavalactone metabolites and quinoids may interact with cellular proteins and DNA in the liver, which causes DNA alkylation and enzymatic activity to be disrupted.	24
Suppression of (COX-2) activity	COX-2inhibition may decrease the production of hepatoprotective substances, potentially resulting in hepatotoxicity. This theory is supported by studies demonstrating liver damage caused by other COX-2 inhibitors.	24
Drug interactions with CYP metabolized drugs	The risk of liver damage may increase if kava is used concurrently with other medications that are broken down by CYP enzymes.	24
Depletion of glutathione and oxidative stress	Kava metabolites have the potential to reduce glutathione levels, leading to oxidative stress and cytotoxicity in liver cells. This effect is especially associated with the extraction methods employed in commercial production.	28
High demand for glutathione in Phase II metabolism	The conjugation of kavalactones can deplete glutathione during phase II metabolism, increasing the liver's vulnerability to reactive oxygen species, which are normally neutralized by enzymes that depend on glutathione.	28

6. Germander

Teucrium is a Mediterranean shrub belonging to the mint family, with around 250 species. The plant's aerial parts are used to create germander, a traditional herbal remedy[27]. It is sold in various forms, including capsules and tea, and is known for its antimicrobial, anorexic, diuretic, diaphoretic, antipyretic, antispasmodic, anti-inflammatory, and antihypertensive qualities[28]. *Teucrium*'s lipid-lowering and hypoglycemic properties have also drawn interest[29]. It is frequently used as a spice or as a herbal tea and is well-known for its antioxidant properties[30]. However, germander has been associated with potential liver damage through different mechanisms (Table 3)[31,32].

7. Herbal-life Product

Herbal-life products are eaten for many reasons, including improved wellness and weight loss. Herbal-life supplements may include hepatotoxic pollutants, according to research and case series [33]. Clinical signs frequently observed include weariness, loss of appetite and jaundice, a case study found contamination in Herbal-life products consumed by two individuals [34]. The supernatant from *Bacillus subtilis* induced hepatotoxicity in a dose- and time-dependent manner, as evidenced by increased lactate dehydrogenase release in HepG2 cells (Table 4).

7.1 Black Cohosh (*Cimifuga racemosa*)

A warning monograph was released by the U. S. Pharmacopoeia in response to complaints of liver damage caused by black cohosh, a herb used to treat menopausal symptoms. However, DILI's concerns were not this conclusion was confirmed by a later meta-analysis of five small, randomized trials. These conflicting opinions must be settled. One possible cause of injuries is mitochondrial damage[36-39].

7.2 Comfrey

Comfrey tea contains pyrrolizidine alkaloids that cause sinusoidal obstruction syndrome and can contaminate food. In 2009, the FDA warned against using it as a dietary additive. Hepatomegaly, ascites, and ultimately, cirrhosis are the clinical symptoms. Injury occurs when CYPs convert pyrrolizidine alkaloids into hazardous adducts[40-44].

Table 3. Hepatotoxicity mechanisms of neoclerodane diterpenoids from the *Teucrium* genus

Mechanism	Associated Toxicity and Mechanism	References
Binding to proteins and glutathione depletion	These reactive metabolites can bind covalently to proteins, leading to a depletion of glutathione. This depletion may cause cell damage, contributing to hepatotoxicity.	25
Neoclerodane diterpenoids in *Teucrium* genus	Neoclerodane diterpenoids, found commonly in the *Teucrium* genus, are identified as chemotaxonomic markers and are linked to hepatotoxicity based on studies involving purification, metabolic profiling, and bioactivity tests.	26
CYP-3A4 enzyme involvement	The CYP-3A4 enzyme plays a role in oxidizing the furan ring of neoclerodane diterpenoids, which results in the formation of reactive epoxides.	26

Table 4. Herbal life and liver toxicity

Observation	Associated Toxicity	References
Review of Herbal-life-induced liver damage in Spanish	A review of 20 cases revealed that 60% of patients required hospitalization, 53% exhibited jaundice, and hepatocellular damage was the most common finding. One patient developed cirrhosis, and two had a positive rechallenge.	34
Iceland review of Herbal-life-induced liver injury	A review in Iceland identified 5 cases of liver damage after 1 to 7 months of Herbalife use. Four patients had hepatocellular damage, and one had cholestatic damage. Liver biopsies of two patients revealed toxic hepatitis, with abnormal bilirubin, transaminases, and alkaline phosphatase levels.	34
Herbal-life-induced hepatotoxicity: Case report (37-year-old female)	Jaundice, scleral icterus, and markedly increased liver enzymes (AST: 2199 U/L, ALT: 2068 U/L, alkaline phosphatase: 185 U/L, total bilirubin: 15. 3 mg/dL) were observed in a 37-year-old female who was taking Herbalife to lose weight. Acute necrotizing hepatitis with periportal bridging fibrosis was discovered during a liver biopsy.	35

8. Herbal Product Used for Height Loss Cause Hepatotoxicity

There are many herbal products on the market for weight loss, both online and in physical locations. Green tea extracts (as previously noted) and Hydroxycut are two proprietary formulations that have caused liver damage. The weight-loss and muscle-building supplement Hydroxycut has been connected to sudden hepatic failure that may necessitate liver transplantation. Green tea, *Gymnema sylvestre*, caffeine, and chromium polynicotinate are a few of the compositions. These products were taken off the market after the FDA issued a warning. In 2013, the FDA warned about Oxy-Elite Pro's serious hepatotoxicity, which could result in death or liver transplantation. A cluster of occurrences among Asians and Pacific Islanders in Hawaii points to a behavioral pattern or genetic susceptibility, even though the underlying cause is unknown[45-48].

8.1 Chaparral (*Larrea tridentata*)

Commonly used for weight loss and other disorders, has been linked to liver harm[49-51]. According to an FDA report, liver dysfunction can range from enzyme increases to fulminant hepatitis, with the majority of cases presenting as cholestatic damage. The damage is believed to be caused by inhibiting prostaglandin G/H syntheses and CYP.

8.2 Hydroxycut

One of the most well-liked weight-loss dietary supplements available today is Hydroxycut, which comes in two formulations: Hydroxycut and Hydroxycut hardcore. A variety of herbs are included in Hydroxycut, such as *Camellia sinensis, G. sylvestre* extract, chromium polynicotinate, and *Garcinia cambogia* extract (Tables 5 and 6)[52].

8.3 G -Cambogia

The fruit *G. cambogia*, which is native to Southeast Asia and western Africa, is used to make food

Table 5. Case series and reports involving liver injury due to Hydroxycut and OEP

Study or Case Series	Number of Patients	Common Symptoms	Severity	References
Hydroxycut (8 patients, larger case series)	8	Hepatocellular (R > 5)	3 required liver transplantation	62
Hydroxycut (6 case reports, 2007-present)	9	Hepatocellular	7 had severe injury	63
OEP (Roytman *etal.*)	8	Hepatocellular	Correlation between INR and severity	64
OEP (Foley *et al.*)	7	Hepatocellular	Severity related to INR elevation	65

Table 6. Herbaldrugs linked to liver toxicity-mechanisms of action unveiled

Herbal Drug	Scientific Name	Mechanism of Action	References
Kava	*Piper methysticum*	Kavalactones cause oxidative stress, protein binding, and depletion of glutathione.	66
Green tea extract	*C. sinensis*	High levels of catechins, particularly EGCG, generate damage to the liver caused by Reactive Oxygen Species (ROS).	67
Germander	*Teucrium chamaedrys*	Neoclerodane diterpenoids deplete glutathione and bind to proteins, leading to hepatotoxicity.	68,69
Black Cohosh	*Actaea racemosa*	May alter liver enzymes and cause liver dysfunction through unknown mechanisms.	70
Comfrey	*Symphytum officinale*	Pyrrolizidine alkaloids cause hepatocellular injury and veno-occlusive disease.	71,72
Chaparral	*Larrea tridentate*	Nordihydroguaiaretic Acid (NDGA) causes hepatocellular damage.	72-74
Boldo	*Peumusboldus*	Overuse may cause hepatotoxicity due to high concentrations of alkaloids.	75
Feverfew	*Tanacetum parthenium*	Contains parthenolide, which can stress the liver, especially with prolonged use.	75

appear "filling"[53,54]. By inhibiting the citrate cleavage enzyme (ATP citrate lyase), its primary constituent Hydroxycitric Acid (HCA) prevents the synthesis of fatty acids from scratch[55-60]. When HCA was first investigated as a dietary therapy for obesity in rodents, the findings appeared encouraging[61].

9. Conclusion

Supplements like Green tea extract, Kava, and Germander are popular for their health benefits, and they can pose risks of liver toxicity. Cases of liver injury, including jaundice and liver failure, have been linked to these products. The mechanisms behind this toxicity involve oxidative stress and enzyme depletion. Given these risks, further research, stricter regulation, and increased awareness are needed to ensure the safe use of these supplements. Health professionals should be cautious when recommending them, particularly for individuals with existing liver conditions.

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11. Author Contribution

Jyoti Yadav: Conceptualization, writing and literature search; Dr. Avijit Mazumder: Reviewing and verification; Dr. Saumya Das: Editing and literature review. All authors have read and agreed to the published version of the manuscript.

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