

Review Article

Green Tea Consumption Is Increasing but There Are Significant Hepatic Side Effects

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Herbal medicines including teas and plant extracts have been in use for thousands of years. There are reports of the use of herbal preparations in Egypt, China, India, and Samaria. Many patients consider “natural” herbal teas to be completely free of unwanted side effects. Many herbal products, however, have biological activities that can result in severe hepatic cell toxicity or interact with other herbal products or prescription medications. Their use is increased dramatically. The most common herbal teas and nonmineral natural products are used as self-medication, principally for health improvement. However, these products are potentially dangerous to some individuals. Monitoring for liver injury is an important aspect of drug and herbal safety assessment. When present, herbal-induced liver injury (HILI) may limit the use or result in the discontinuation of these agents. HILI can exhibit with a wide spectrum of clinical and laboratory manifestations, ranging from asymptomatic elevations in aminotransferases to acute liver failure. Most cases of HILI resolve within several weeks after herbal remedy discontinuation. However, some cases can persist as low-level aminotransferase elevations. Our review aims to (1) describe the possible significant discrepancies between the ingredients listed on the label and the actual contents of the preparation; (2) evaluate teas containing multiple plants or herbs which may be adulterated by more toxic herbs, heavy metals, microbials, pharmaceuticals, and medicines; (3) describe pathophysiologic events in herbal tea-induced hepatotoxicity; and (4) discuss the key elements required for attributing the consumption of tea to the induction of liver injury. The widespread use of mixed heterogeneous remedies and the lack of randomized trials are an obstacle to providing safe use of plant-derived teas.

1. Introduction

The worldwide epidemic of obesity has a severe impact on health. The body mass index (BMI) is a central component of the metabolic syndrome which plays an important role in the development of metabolic (dysfunction)-associated fatty liver disease (MAFLD).

The only proven treatment for MAFLD is lifestyle changes including weight loss and moderate physical activity and coffee consumption. No current investigational agents have been shown to reverse fibrosis and decrease clinical events.

Achieving and maintaining weight loss is a difficult endeavor for many patients. There is a range of options available from

medications to bariatric surgery and endoscopic procedures. In addition, dietary treatment of obesity is a multibillion-dollar industry.

Green tea, derived from the tea plant (*Camellia sinensis*), is the second most popular beverage in the world. Green tea contains polyphenols, including catechins (flavanols), flavonoids, and flavonols. Green tea polyphenols (GTP) consist of 70–80% catechins.

The health-promoting effects of green tea have been intensively investigated. There have been reports of a beneficial effect in cancer prevention [1], anti-inflammatory actions [2], cardiovascular and metabolic disorders [3], antiarthritic [4], antibacterial [5], antiangiogenic [6], antioxidative [7], antiviral [8], and

also neuroprotective [9]. Much of the health-promoting effect of green tea is attributed to its high polyphenol content [10].

2. Methods

Using the PubMed bibliographic database (provided by <http://www.ncbi.nlm.nih.gov/pubmed>, US National Library of Medicine, National Institutes of Health, United States), we examined the potential liver injury induced by tea. We also reviewed the results from cellular and animal experiments with proposed mechanisms of action. Studies were included if they described case reports or studies with known amounts of tea from the same plant or plant combinations.

3. Beliefs and Evidence

Chinese tradition is that green tea washes out fat [11]. There is evidence from clinical trials, analyzed in meta-analyses of the effect of green tea in weight management [12, 13]. In addition, a meta-analysis has shown an effect of green tea on decreasing fasting glucose and insulin levels [14]. Investigation of possible mechanisms in animal studies and cell lines has shown a reduction of food intake, interruption of lipid emulsification and absorption, suppression of adipogenesis and lipid synthesis, and increased energy expenditure via thermogenesis, fat oxidation, and fecal lipid excretion [11].

It is for these reasons that green tea has been examined as part of the treatment of the metabolic syndrome and its complications including MAFLD. Green tea has a beneficial effect on liver diseases, including cirrhosis, hepatocellular carcinoma, and steatosis [15].

Evidence has been accumulated regarding a green Mediterranean diet and its effects on obesity and MAFLD.

The DIRECT-PLUS trial included 296 subjects with abdominal obesity and hyperlipidemia who were split into three groups. One group received standard healthy dietary guidelines (HDG) and one group a calorie-restricted Mediterranean diet (MED) which was rich in vegetables and with poultry and fish replacing beef and lamb, as well as 28 g per day of walnuts (which contribute 440 mg of polyphenols per day). In addition, there was another group, the green Mediterranean diet (Green-Med) restricted in processed and red meat and richer in plants and polyphenols. In addition, the participants received 3-4 cups of green tea per day as well as 100 g per day of frozen *Wolffia globosa* (Mankai strain) cubes as a green shake that replaced the evening meal [16]. This regimen has been shown to decrease weight circumference in men and decrease in both LDL cholesterol, diastolic BP, HOMA score, and Framingham risk score in men and women [17].

A subsequent study from the same group obtained stools after the weight loss phase and produced capsules of frozen stools for autologous microbial transplantation in all categories of participants. Autologous fecal microbial transplantation (aFMT) in the green Mediterranean group decreased the gain in waist circumference and insulin rebound compared to all the other groups including the green Mediterranean diet that received placebo fecal capsules [18]. In

addition, the administration of a FMT resulted in maintaining the significant change in the microbiome achieved in the weight loss phase. This resulted in the preservation of weight loss-specific bacteria and microbial sugar transport pathways. This was also shown in mice that received stools from the Mankai-modulated FMT group and an improvement in glucose tolerance.

It is likely that there will be a marked increase in the consumption of green tea for weight loss purposes because of these recent studies. The global market for green tea was \$12.8 billion dollars in 2019 and is projected to reach \$23.66 billion by 2027.

There is, however, a potential danger associated with an increase in green tea consumption. The liver can suffer injury from drugs (drug-induced liver injury (DILI)) and herbs (herb-induced liver (HILI)). HILI has been linked to green tea consumption.

Since MAFLD is associated with obesity and metabolic syndrome and green tea is advertised for weight reduction, it is to be expected that there will be a large increase in the number of obese individuals receiving green tea.

Green tea extracts have been linked to several cases of hepatotoxicity and exacerbated by fasting. In a mouse model, decaffeinated green tea extract did not cause hepatotoxicity [19].

There are more than 100 cases of hepatotoxicity related to green tea extract in the literature and summarized with Liver Tox. The US Pharmacopeia reported a systematic review of green tea extracts [20]. The GTE composition and catechin profile differ between varying manufacturing processes. The USP review found hepatotoxicity to be related to epigallocatechin (EGCG) in daily amounts ranging from 140 mg to 1000 mg. There was interindividual variability in susceptibility which could reflect genetic factors. Decaffeinated green tea did not cause hepatotoxicity in a mouse model [19].

4. Pathophysiology of HILI Resulting from Different Tea Drinks

HILI resulting from the consumption of direct toxic effects of botanical toxins is due to either contamination of cultivated or wild tea with plants containing pyrrolizidine alkaloids [20, 21]. Clinically, there may be congestive hepatopathy and ascites that can progress rapidly to venocclusive disease (VOD) of the liver. There are partial or total occlusions of central (efferent) venules and hepatic necrosis. In France, cases of hepatotoxicity including acute hepatitis and liver failure were reported. The mechanism of injury appears to be metabolic activation to a toxic intermediate (furan-containing neoclerodane diterpenoids) [22–24].

Herbal tea containing germander can result into hepatocellular injury [25, 26]. The lesion is typically used in women drinking tea for weight loss purposes. The histology reveals necrosis especially in zone 3. Ben Yahia et al. and the group of French pharmacovigilance reported 3 cases of chronic active hepatitis and cirrhosis induced by wild germander. Two women and one man developed jaundice approximately 6 months after starting germander (bilirubin 6.3,

2.3, and 15.6 mg/dl; ALT 20-50 times ULN; and alkaline phosphatase 1-3 times ULN). The biopsies were showing chronic hepatitis with fibrosis or cirrhosis and enzymes improving rapidly on stopping the herbal remedy.

Pyrrrolizidine alkaloids (PAs) and P-N oxides are naturally occurring alkaloids based on the structure of pyrrolizidine identified in over 6000 species throughout several continents. PA-containing teas are used for complaints, including arthritis, gout, and/or infections [27, 28].

Hepatotoxicity, which has been long recognized, is predominantly observed after exposure to the following species: *Heliotropium* sp., *Trichodesma* sp., *Symphytum* sp. (*Comfrey*), *Senecio* sp. (Bush Teas), and *Eupatorium* sp. German-der (*Teucrium chamaedrys*) [29–35]. Tea that is used especially in Chinese medicine was shown to produce acute liver injury [29].

The diagnosis of HILI is difficult. The relationship between exposure and liver injury is not always clear [36]. In addition, patients may be taking multiple preparations, not permitting the identification of a single offending agent. Moreover, the patients may also have concomitant liver disease, such as alcoholism or hepatitis B or C virus infection, which can produce similar clinical features and biochemical parameters [33]. Moreover, the medication used to treat human immunodeficiency and viral infection may contribute to herbal toxicity.

We have employed a specific test, the lymphocyte toxicity assay, to confirm a diagnosis of drug-induced liver injury (DILI) from either a medication [37, 38] or a herbal remedy [28].

Moreover, we also have to consider that epigallocatechin gallate, which is considered the most important of the catechins found in tea, has a hepatoprotective role [39].

Confirmation of a diagnosis of HILI requires fulfillment of both chronological and clinical criteria. We also consider a future review and meta-analysis on the green tea-induced injury to the liver, using the PRISMA criteria [40].

Krishnankutty et al. bring the possibility of the toxic effect of the water used for teas [41]. Fluoride exposure increases with tea consumption, which has been linked to developmental neurotoxicity in pregnant women. As the fluoride release from tea varies widely, the fluoride concentration should be indicated on tea packages to allow consumers to make informed decisions on minimizing their fluoride exposure [41]. Another group of researchers measured the fluoride content in infusions of commercially available black, green, and white teas [42]. The brewing time (5, 10, and 30 min) increased the fluoride content, in which infusion of black tea (5 min brewing) was higher than that in the other types of tea, with contents ranging between 0.32 and 4.54 mg/l for black tea and 0.37 and 0.54 mg/l for white tea and with even lower values for herbal tea infusions of 0.02-0.09 mg/l. The fluoride intake resulted from the regular consumption of black tea infusions was raised as compared to the other types of teas as well as herbal teas. The control of tea quality is important to protect human against high uptake of this element from tea.

Zimmerman observed that drug-induced hepatocellular jaundice potentially predicted serious and even fatal out-

comes [43]. “Hy’s law” is defined as serum alanine aminotransferase (ALT) levels $> 3 \times$ ULN combined with total bilirubin levels $> 2 \times$ ULN, after the exclusion of other underlying causes to help identify patients most likely to progress to serious liver injury.

Elevated ALT levels are sensitive for liver injury. Healthy liver tissue has excess bilirubin-excreting capacity; therefore, hepatic injury sufficient to cause hyperbilirubinemia ($2 \times$ ULN) represents a degree of hepatocyte loss that may become irreversible [43].

Hy’s law criteria have been historically useful for predicting serious drug-induced hepatocellular liver injury, with approximately 1 in 10 Hy law cases leading to death from liver-related causes or the need for liver transplant [43, 44, 45]. The detection of ≥ 2 Hy law cases in DILI-HILI is a strong predictor of significant risk and may prevent further development [45–51].

An important point is the fact that there is also the intentional addition of substances, to enhance the efficacy of herbal products [52]. Adulteration is common practice in Chinese [53], Ayurvedic [54, 55], South American [56], and South African [57] herbal remedies. The main adulterants were found to be metals (mercury, lead, arsenic, and copper) [58]. Ayurvedic formulations are widely used, they are incorrectly perceived as the safer medicinal alternative and are permitted to be self-prescribed [59].

5. Conclusion

HILI resulting from green tea is rare. Cessation of drinking green tea is advised and recovery can take up to 2 months. It is important for physicians to be aware of the potential hepatotoxicity related to green tea, especially in view of the increasing numbers of consumers of this product.

Data Availability

The data was obtained from published peer review articles.

Conflicts of Interest

There are no conflicts of interest to declare.

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