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Letter to the Editor

Hepatotoxicity of Green Tea Extract: Idiosyncratic or Indirect Drug-induced Liver Injury?

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In 2021, the American College of Gastroenterology published the latest version of the guidelines for the diagnosis and management of drug-induced liver injury. The guidelines indicated that green tea extract (GTE) could cause idiosyncratic hepatotoxicity, and *HLA-B*35:01* is its susceptibility gene.[1,2] We believe that the hepatotoxicity of GTE is mainly related to indirect drug-induced liver injury mediated by the starvation state after dieting or fasting, and liver injury is more likely to occur in patients with the *HLA-B*35:01* susceptibility gene.

GTE, a dietary supplement for weight loss, is popular in the United States and Europe and contains a variety of polyphenol flavonoids and catechins, including epigallocatechin gallate (EGCG), which is abundant in GTE and has been associated with liver toxicity.[3] Based on our research and literature analysis, EGCG is more easily absorbed fully in dieters because they tend to be in a state of low food intake or fasting with less digestion and absorption burden on the gastrointestinal tract. Concurrently, owing to the excessive control of the caloric intake, dieters tend to have an insufficient energy supply, which weakens the activity of the hepatic microsomal enzymes. The decreased detoxification ability of the liver thus leads to the accumulation of EGCG and its metabolites in the liver.[4–7] In addition, long-term oral administration of EGCG could cause metabolic enzyme saturation or inactivation leading to a time-related increase in the EGCG exposure *in vivo*.[8] In conclusion, the impaired physical and metabolic conditions of dieters may lead to increased accumulation of EGCG in the liver, thus increasing the risk of liver injury caused by EGCG. Once the liver is damaged by stress, the released or newly produced antigen may be recognized and presented by antigen-presenting cells expressing *HLA-B*35:01*; consequently, the immune response would be activated resulting in immune-mediated damage in the liver. One possible risk factor for liver injury caused by GTE is starvation with differences in effects among individuals. If dieters carry the *HLA-B*35:01* susceptibility gene, they would have an increased risk of liver injury (Fig. 1).

In recent years, we found that liver injury caused by the well-known Chinese herbal medicine *Polygonum multiflorum* (PM) was highly correlated with susceptibility genes. Furthermore, the incidence of PM-induced liver injury has been a worldwide concern for many years. Experimental studies have also confirmed that PM is safe without hepatotoxicity in normal animal models.[9] Based on large-scale clinical cases and biospecimen studies, we found that liver injury from PM had a significant episodic character that individuals with immune hyperactivation or autoimmune diseases would be more susceptible to liver injury from PM, and that there would be no obvious correlation with the dose or regimen. Moreover, further studies have revealed that *HLA-B *35:01* is a human susceptibility gene for liver injury from PM.[10,11] Although the susceptibility gene for liver injury caused by GTE and PM is *HLA-B*35:01*, the clinical characteristics of liver injury are significantly different between PM and GTE, thus suggesting that genetic susceptibility may not be the only risk factor for liver injury from GTE.

According to the latest classification of drug hepatotoxicity established by Hoofnagle *et al*.,[12] we considered that hepatotoxicity of GTE is related to indirect liver injury mediated by the starvation state after dieting or fasting, where *HLA-B*35:01* susceptibility gene carriers would be more prone to liver injury. For instance, alcohol has direct liver toxicity, and excessive alcohol consumption could lead to alcoholism.[13,14] In the fasting or starvation state, alcohol could be absorbed more quickly, and rapidly absorbed alcohol would be difficult to quickly metabolize; therefore, people who drink on an empty stomach would become inebriated more easily. If a fasting drinker is also deficient in acetaldehyde dehydrogenase, this could further increase the risk of drunkenness and even cause severe alcoholism.[15]

Hence, the above analysis would suggest that diet and high EGCG intake are the two key factors of liver injury induced by GTE. Therefore, we suggest the following measures to prevent GTE-induced hepatotoxicity:

GTE products should be used with caution in people on weight-loss diets. When consuming EGCG-enriched products, attention should be paid to supplementing nutrition and energy to maintain

Keywords: Green tea extract; Epigallocatechin gallate; Drug-induced liver injury; Idiosyncratic hepatotoxicity; Indirect drug-induced liver injury.

Abbreviations: EGCG, epigallocatechin gallate; GTE, green tea extract; PM, *Polygonum multiflorum*.

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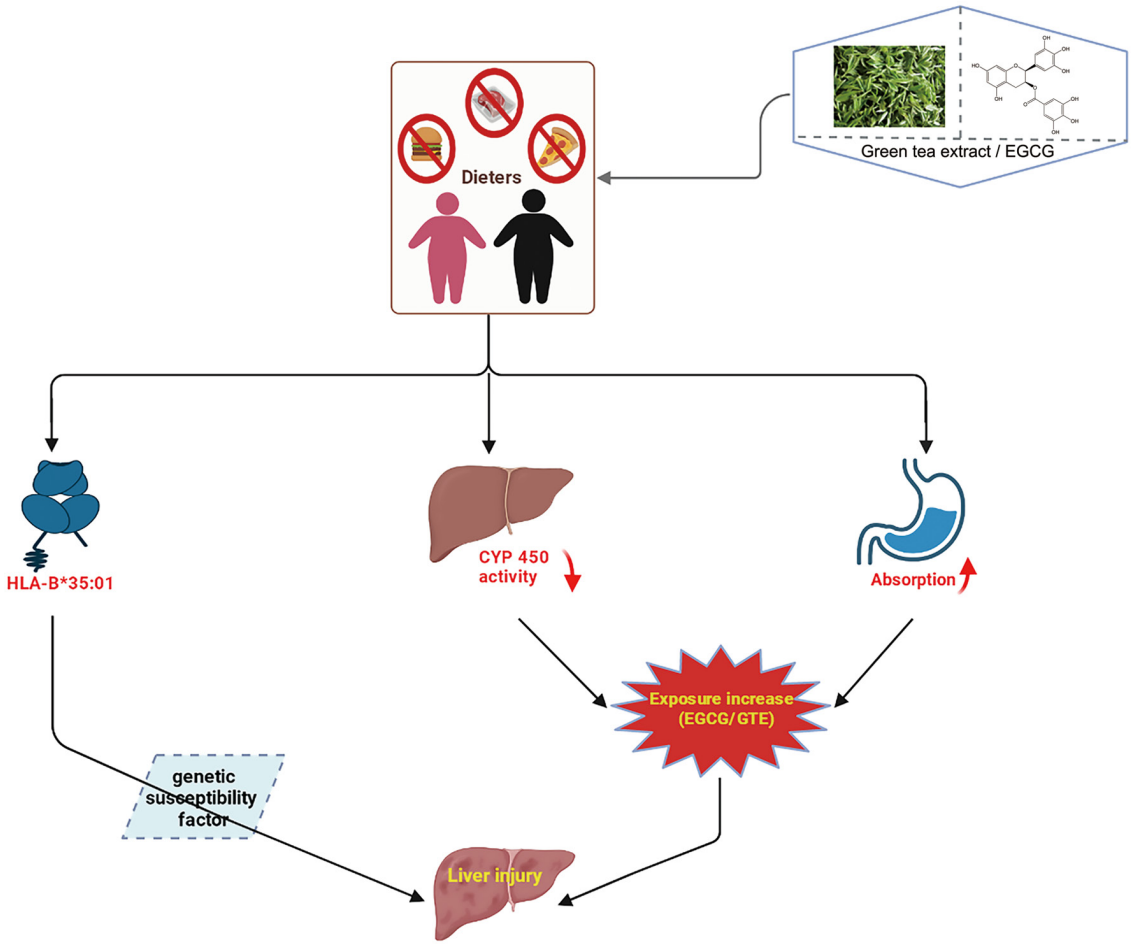

Fig. 1. Hepatotoxicity of green tea extract.

the normal metabolic detoxification ability of the liver.

To reduce the risk of liver injury, GTE products should be used in moderation by avoiding long-term use and reducing exposure.

The risk of liver injury due to the consumption of GTE products does not have the same effect as the consumption of green tea. People usually drink approximately 10 g of natural tea once a day, which corresponds to an intake of 75 mg of EGCG,[16] which is much lower than that consumed when using GTE products (125-900 mg/day). In China, a large green tea consuming country, there are currently no reports describing liver injury caused by green tea consumption.

In future studies, using an intravital imaging device for monitoring the pathway of the GTE products inside the body in general, and especially the liver, would clarify the effect in an imaged manner and would unveil the missing link of hepatic hazards.

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Conflict of interest

XHX has been the Honorary Editor-in-Chief of *Future Integrative Medicine* since September 2021. The other authors declare that they have no conflict of interest related to this publication.

Author contributions

Study concept and design (XHX, ZFB, XZ, and DKX), acquisition of the literature and data (YJG and CZW), drafting of the manuscript (YJG, XZ, DKX, WS, and HJY), and critical revision of the manuscript for important intellectual content (XHX, ZFB, XZ, and YJG), All authors have made a significant contribution to this letter and have approved the final manuscript.

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