



## Case Report of A Hepatotoxicity Related to Plane Leaf Tea

### Çınar Yaprığı Çayına Bağlı Gelişen Bir Hepatotoksisite Vakası

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**ABSTRACT** Herbs are used in our country and worldwide till ancient times. Although we know about the benefits of some of the herbs and use as herbal medicines, medically proven ones limited and these are used as medicines. These herbal remedies are sold out widely under name of medication by herbalists, or even by pharmacies, without strict surveillance, although they may cause serious adverse reactions. Acute liver injury is one of the most frequently encountered adverse reactions by herbal remedies. As an herbal medicine, plane leaf tea is used widely for analgesic effects in our country. We present a woman patient who admitted to our clinic with acute hepatitis after consumption of this plant in tea form.

**Keywords:** Herbal medicine; chemical and drug induced liver injury

**ÖZET** Bitkiler ülkemizde ve dünyada eski zamanlardan beri tedavi amacıyla kullanılmaktadır. Bazı bitkilerin yararlarını bilmemize ve bitkisel ilaçlar şeklinde kullanmamıza rağmen, tıbbi yararı kanıtlanmış olanları sınırlıdır ve bunlar ilaç olarak kullanılmaktadır. Bu bitkisel çareler, ciddi advers reaksiyonlara yol açsalar da, herbalistler ve hatta eczaneler tarafından, sıkı bir denetleme yapılmaksızın ilaç tedavisi adı altında yaygın olarak satılmaktadır. Akut karaciğer hasarı, bitkisel ilaçlarla en sık rastlanan yan etkilerden biridir. Ülkemizde bitkisel ilaçlardan çınar yaprağına rastlanılmakta olup sıklıkla analjezik etkileri için kullanılmaktadır. Bu bitkinin çay şeklinde tüketilmesinden sonra kliniğimize akut hepatit ile başvuran bir kadın hastayı sunuyoruz.

**Anahtar Kelimeler:** Bitkisel tıp; kimyasal ve ilaç ilişkili karaciğer hasarı

**H**erbals and dietary supplements (HDS) are worldwide used to improve health. They are supposed to reduce body fat, increase immunity, modify glucose and lipid metabolism, and enhance performance. They may help to cause weight gain and muscle building beside from antipyretic, analgesic, antioxidant, antimicrobial and anti-inflammatory properties.<sup>1-4</sup>

Natural and synthetic chemicals need metabolic degradation to be eliminated after entering the body. Hepatotoxic metabolites may be generated in some patients. Herbal products may be contaminated with aflatoxins, *Bacillus subtilis* and chemicals. Heavy metals may be added as adulterant; which may remain unlabeled. These may all cause liver injury.<sup>3,5</sup>

## CASE REPORT

A 66-year-old woman with essential hypertension was admitted to the emergency clinic with nausea and abdominal pain. She had a history of

drinking plane leaf tea for three days because of the pain at her knees. Physical examination was unremarkable except for right upper quadrant tenderness. The laboratory findings revealed elevated aspartate aminotransferase (AST) 1002 U/L, alanine aminotransferase (ALT) 1042 U/L, gamma glutamyl transpeptidase (GGT) 577 U/L, alkaline phosphatase (ALP) 226 U/L, total bilirubin: 2.40 mg/dl, direct bilirubin: 1.40 mg/dl, albumin: 4.1 g/dl. Coagulation tests were within normal limits. She was on hypertension medication which the drug was unknown. There wasn't any other herbal remedy, illegal drug or alcohol use, and mushroom ingestion. She was interned with an initial diagnosis as toxic hepatitis. On admission her blood pressure was 190/100 mmHg which was treated with nifedipine. ELISA tests for viral markers were as follows: Anti-HCV and anti-HBs were positive; Hbs Ag, anti-HBc IgM, anti-HAV IgM were negative. Autoimmune markers were negative. Serologic evidence for recent infections with Epstein-Barr-virus, Herpes simplex virus, Cytomegalovirus and Toxoplasma were negative. Blood sample was obtained for HCV RNA analysis. Liver biopsy was performed on the fifth day of admission to differentiate between toxic and viral hepatitis. Biopsy specimen reflected slight mononuclear inflammatory infiltration, focal bile duct damage, ductular metaplasia, a region of focal lytic necrosis, and hepatosteatosis (Figure 1, Figure 2). On the follow ups, she was hemodynamically stable, with no fever, pain or nausea. Transaminase levels decreased gradually to levels of AST: 58 U/L, ALT: 230 U/L, GGT: 305 U/L, ALP: 210 U/L. Coagulation tests were normal. After she was discharged from the hospital, liver enzymes and coagulation tests returned to normal within 4 months of follow-up. On control we learned that she had used ramipril which was her drug before admission for hypertension, without any adverse effect. Upon re-administration she didn't have any complaint either. Her test for HCV RNA was found negative.

After the patient recovered, we searched medical literature about the plane (*Platanus orientalis*) leaf toxicity, but we could not reach specific knowledge in this field. Because she had no herbal

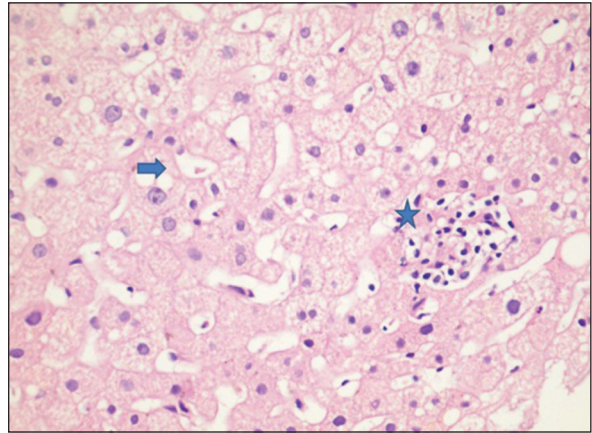


FIGURE 1: Ductular metaplasia (arrow) and focal lytic hepatocellular necrosis (H&E stain).

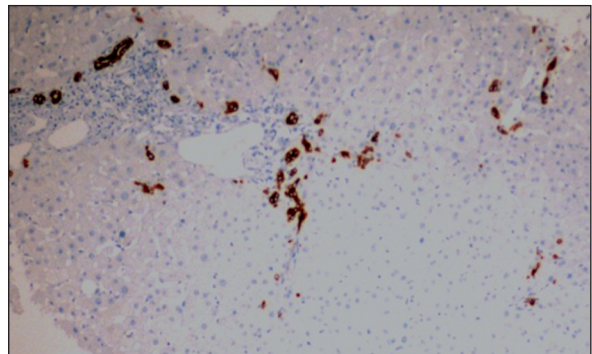


FIGURE 2: Moderate ductular reaction highlighted with cytokeratin-7 immunohistochemistry.

product left, we couldn't make any analysis about the culprit structure. For the benefit of further medical practice knowledge, she gave informed consent for the case to be reported.

## DISCUSSION

Hepatotoxicity may be the most frequent adverse reaction to herbal remedies. Acute or chronic hepatotoxicity reactions may be predictable or unpredictable with immunologic or metabolic origin. The more frequently reported noxious herbs include Chinese remedies and teas, germander, valerian, mistletoe, skullcap, chaparral comfrey herbal teas, green teas, and kava.<sup>2,6,7</sup> Use of herbal remedies must be considered as a possible etiology in any setting of liver injury which may present as asymptomatic liver enzyme elevations, jaundice,

hepatitis, acute liver failure, or with signs and symptoms of cirrhosis.

Key elements for attributing liver injury to HDS are:

- Exposure must precede the onset of liver injury
- Underlying liver disease should be excluded
- Injury may improve when the HDS is stopped
- Liver injury may have recurred more rapidly and severely after repeated exposure.

Alanine aminotransferase and/or alkaline phosphatase values are used as the laboratory criteria of herbal induced liver injury (HILI), which are expressed as N in multiples of the upper limit of their normal range. Recommended values for ALT were initially and currently at  $>2N$  and at  $>5N$  respectively. The basis for classification is the ratio R and is calculated as the ALT/ALP, both should be the values that are measured when the liver injury is suspected and expressed as multiples of N, the upper limit of the normal range. Liver injury is evaluated as hepatocellular if  $R \geq 5$ ; cholestatic if  $R \leq 2$ ; and is mixed if  $2 < R < 5$ . Analytical methods that identify cases of hepatotoxicity include genomics, proteomics, metabolomics, and assessing circulating micro-RNA in the serum of patients. It is not clear whether these new technologies can identify idiosyncratic HILI cases. In fact, in some HILI cases, the measurements of herbal toxins and their metabolites in the serum are also useful.<sup>3</sup> Our case had mixed injury. We could not make any analysis about the culprit product as there was not any left.

Liver histology may show hepatitis, liver cell necrosis, bile duct proliferation, intrahepatic cholestasis. These findings may be seen in many other liver diseases.<sup>3</sup>

The mainstay of therapy is withdrawal of the offending toxin. Early diagnosis of herbal toxicity is

important to assess severity and monitor acute liver failure. Corticosteroids, glycyrrhizin, and ursodesoxycholic acid may be used.<sup>3</sup> After discontinuing the HDS recovery should be expected in the majority of patients. Some patients with liver failure may require liver transplantation. They should receive supportive therapy until surgery. Our patient did not use the herbal medicine anymore; she did not need any other therapy.

For prophylaxis the clinician should discuss the use of these products with the patient. Patients should also be educated about the potential adverse effects and herb-herb or drug-herb interactions. In cases of liver enzyme abnormalities herbal drugs must also be considered as a provoking agent along with other etiologies. Given that herbal drugs are used world-wide without strict surveillance subjects should be recommended not to use them without consulting their physicians.<sup>3,8</sup>

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#### **Conflict of Interest**

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

#### **Authorship Contributions**

**Idea/Concept:** Füsün Erdenen; **Design:** Füsün Erdenen; **Control/Supervision:** Füsün Erdenen; **Data Collection and/or Processing:** Muzaffer Ece Hakan Şahin; **Analysis and/or Interpretation:** Muzaffer Ece Hakan Şahin, Füsün Erdenen; **Literature Review:** Füsün Erdenen; **Writing the Article:** Muzaffer Ece Hakan Şahin; **Critical Review:** Füsün Erdenen, Muzaffer Ece Hakan Şahin; **References and Fundings:** Füsün Erdenen, Muzaffer Ece Hakan Şahin; **Materials:** Füsün Erdenen.

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