

Postpartum hepatotoxicity due to herbal medicine *Teucrium polium*

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The hepatotoxicity cases due to herbal medical products have been increased in recent years. *Teucrium polium* (TP) (mountain germander) is one of the most popular species of the Lamiaceae family and is commonly used for increasing breast milk formation and for relieving gastrointestinal complaints in the last months of pregnancy and postpartum periods. Here are presented 3 cases of serious hepatotoxicity due to TP. Three female patients aged 33, 31, and 37 years were admitted to clinic with jaundice and serious elevated liver enzymes for a period of 2 years. The patients were using TP for approximately 40 days to 3 months. Two of the 3 used TP during their previous pregnancies and were monitored for similar complaints by another center. After discontinuation of TP and supportive care, the liver function tests were decreased to normal limits within 3 months in all 3 patients. In addition to the potential hepatotoxic effect of TP, physiological changes in the postpartum period may increase the severity of hepatotoxicity. TP should be considered in differential diagnosis in patients presenting similar history and complaints, where it is used commonly.

The use of herbal medical products has increased gradually in recent years. Such products are consumed in Western countries as commonly as in Eastern, Asian, and African communities.¹ The increased use of herbal products is based on the recognition of their efficacy on prevention and treatment of many diseases and the belief of their reliability and natural structure.² However, effects of these herbal medical drugs on the liver are limited.

Teucrium polium (TP) (mountain germander) is one of the most popular species of the Lamiaceae family and grows wild in Mediterranean and Middle Eastern countries. Tea and powder forms of the aerial part of this plant are used commonly for wound healing, headache, gastrointestinal disorders, and diabetes in traditional folk medicine.³ Apart from beneficial effects of TP, hepatotoxicity cases have been reported with TP.^{4,5} During pregnancy and postpartum periods, various physiological changes occurred in the liver.⁶ Here we, presented 3 cases of severe hepatotoxicity due to TP in the last 2 months of pregnancy and postpartum periods.

CASES

Case 1

A 33-year-old female patient was admitted to clinic with jaundice, complaint of fatigue, and elevated transaminase level. There were no extraordinary findings in physical examination except for icterus on skin and sclera. The medical history of the patient presented that the patient gave birth 40 days ago; it was noticed that she had yellow skin and sclera for the last 1 week and received the traditional herbal drug TP as 2 to 3 tablespoon of dry powder per day for 2.5 months for dyspeptic complaints and to increase breast milk secretion. According to the ultrasonographic examination, liver size, parenchymal structure, and other abdominal organs were normal. Laboratory tests were demonstrated in **Table 1**. The liver biopsy could not be performed due to patient refusal. With supportive treatment and the initiation of 1500 mg/d of ursodeoxycholic acid, the serum aminotransferase levels decreased rapidly; bilirubin decrease was much slower as compared to liver enzymes. The patient's clinical symptoms were regressed

Table 1. Laboratory results of patients.

Laboratory	Patient I	Patient II	Patient III
ALT (10-40) IU/L	1673	2397	1212
AST (5-34) IU/L	1198	2039	1127
ALP (30-120) IU/L	586	466	200
GGT (9-64) IU/L	127	118	165
Total bilirubin (0.2-1.2) mg/dL	22	23	14
Direct bilirubin (0-0.5) mg/dL	14	20	13
Prothrombin time (11-14.2 s)	20	18,4	20
Albumin (3.5-5) g/dL	4.3	3.7	3.8
Glucose (70-110) mg/dL	85	91	86
Whole blood count	Normal	Normal	Normal
Hepatotropic viruses serology ^a	Negative	Negative	Negative
Autoimmune hepatitis markers ^b	Negative	Negative	Negative
Alpha-1 antitrypsin	Normal	Normal	Normal
Ceruloplasmin	Normal	Normal	Normal
Ferritin	Normal	Normal	Normal

^aHepatitis viruses A, B, C, E, adenoviruses, parvo B19, herpes viruses, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus; ^bantinuclear antibodies, antismooth muscle antibodies, antiliver-kidney-microsomes type 1 antibodies, antimitochondrial antibodies. ALT: Alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase.

significantly, and she was discharged after 10 days. Liver function tests were normal within 3 months, and these remained within normal limits over 2 years of the follow-up period.

Case 2

A 31-year-old female patient presented with jaundice, nausea, and vomiting. Her physical examination revealed icterus on skin and sclera. The patient had given birth 45 days ago, and she had used TP as 2 tablespoon per day to increase breast milk secretion in the last 2 months of pregnancy and postpartum periods. She had similar complaints in her previous pregnancy due to the use of TP. The abdominal ultrasound examination was unremarkable. Laboratory tests are shown in **Table 1**. A liver biopsy could not be performed due to unacceptance of the patient. Both supportive treatment and 1500 mg/d of ursodeoxycholic acid were given to the patient. The liver tests reduced normal levels at the end of the third month, and the liver function tests remained normal during 2 years of the follow-up period.

Case 3

A 37-year-old female patient was admitted to clinic with

jaundice and complaint of weakness. Physical examination was normal except jaundice and icteric sclera. Her medical history revealed the use of TP for increasing breast milk secretion and treating dyspeptic complaints for 1 month and postpartum. The ultrasonographic examination was normal, and laboratory tests were demonstrated in **Table 1**. The patient refused liver biopsy. With supportive treatment and 1500 mg/d of ursodeoxycholic acid, the serum liver enzyme levels decreased to normal levels within 3 months. After 6 months of treatment, the liver function tests were still normal.

DISCUSSION

Common reasons for using herbal medicines are as follows: loss of efficiency, adverse effects of prescribed drugs, and difficulty in accessing health care providers. On the contrary, easy access without prescription and low costs are important advantages of herbal medicine.² Diagnosis of hepatotoxicity caused by the use of herbal medicine is very difficult for patients without having specific histopathological features, and also hepatotoxicity cannot be tested by giving the suspected agent again. Therefore, an exact anamnesis should be taken for a definitive diagnosis, and herbal toxicity should be considered in differential diagnosis.¹ In our second and third cases, hepatotoxicity developed due to TP during first and second pregnancies, and it reoccurred as a result of the repeated use of TP in the late postpartum period. Besides determined hepatotoxicity in mothers, there was no congenital deformity or hepatotoxicity in infants. The general health status of all babies was good.

The liver diseases in pregnancy can be classified as follows: hyperemesis gravidarum, preeclampsia or eclampsia, HELLP syndrome, acute fatty liver of pregnancy, and intrahepatic cholestasis of pregnancy. These diseases are seen only during pregnancy and chronic liver diseases accompanying pregnancy such as viral hepatitis, autoimmune hepatitis, Wilson disease, and cholestatic liver diseases.⁷ The increased volume of hepatocytes in liver, formation of cytoplasmic fatty vacuole and hypertrophy of Kupffer cells, decreased serum albumin levels, and decreased bilirubin transport due to reduced activity of cytochrome p450 and glucuronyl transferase are observed during normal pregnancy.⁶ Pregnancy-specific diseases of the liver were not considered since the symptoms occurred during postpartum periods in all 3 cases. The tests performed to reveal other etiological causes were all negative. The regression of the symptoms and normalization of laboratory results after discontinuation of TP strongly indicated herbal hepatotoxicity. In all 3 cases, the severity of hepatotoxicity was associated with exposure time and dose of TP

as well as physiological changes occurred in liver during pregnancy.

The hepatotoxic effects of TP are shown in many case reports and experimental studies.^{4,8-10} Savvidou et al.⁵ and Starakis et al.¹¹ described cases of hepatotoxicity due to the use of TP. Kawther et al. demonstrated that increasing the dose of TP tea elevated liver enzymes and caused histopathological changes in mice models.¹² Several cases of hepatotoxicity have been also reported for other types of the genus *Teucrium*.¹³⁻¹⁵ Perhaps, it is the first case series in the published studies demonstrating TP-induced hepatotoxicity during pregnancy and postpartum periods.

In addition to hepatotoxic features, the hepatoprotective effects of TP have also been demonstrated in many experimental studies.^{16,17} Shtukmaster et al demonstrated hepatoprotective effects of TP through glutathione homeostasis.¹⁶ Amini et al. showed that TP improved the damage in an experimental rat model of steatohepatitis.¹⁷ The hepatoprotective and the hepatotoxic effects of TP are attributed to dose and duration of usage.¹⁸

The histopathological properties of liver toxicity due to herbal medicines are non-specific and show a wide clinical spectrum. Hepatic findings were moderate or severe necroinflammatory activities, and various levels of cholestasis accompanying these findings were described in case reports regarding histological properties of hepatotoxicity due to TP.^{5,9} The histopathological examination could not be performed in 3 cases because of the unacceptance of the patients.

The particular mechanism of hepatotoxicity arising from TP is not known; however, it was demonstrated that furano-diterpenoids generate harmful metabolites through oxidation by cytochrome P450 3A 9,19.

In conclusion, unconsciously using herbal products in various diseases can cause hepatotoxicity. Similar to other types of genus *Teucrium*, TP has a potential hepatotoxic effect; however, physiological changes during pregnancy and postpartum periods may increase the severity of such toxicity. The TP should be considered in differential diagnosis and should be asked insistently in medical history for patients presenting with abnormal liver function tests, where it is used commonly.

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