An Overview about Adverse Hepatic Effects of the Plants Used in Turkey

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Abstract

Herbal supplements are widely used for improving health and treating diseases in nearly all cultures of the world. However, the efficacy, safety, and drug interactions of many of the herbal treatment modalities are not known scientifically, and they are generally used without professional health assistance. Injudicious plant usage has been shown to be a risk factor for serious and unexpected side effects, and from this perspective, herbal drug usage is related to 25%–30% of drug-induced liver injury cases. Plant usage as an alternative therapeutic modality is common in Turkey. In this study, the adverse hepatic effects of the commonly used plants in Turkey has been reviewed. More than 400 plants that are sold by herbalists in different regions of Turkey have been obtained from various studies on this topic, and these plants were investigated for their hepatic effects in PubMed and Science Direct databases. The adverse hepatic outcomes of 27 of the researched plants. Studies about plant hepatotoxicity, plant-plant interaction, and plant-drug interaction have been reviewed in this article. Herbal modalities are widely used as an alternative and complementary treatment method in the population; however, the basic hepatotoxic compounds and the liver injury mechanism of many of the frequently used plants and the molecular action mechanism of most of the ingredient compounds of the plants are not exactly known. Multidisciplinary studies on the mentioned topics will be helpful in understanding the role of plants and hepatotoxicity in medical approaches.

Keywords: Plants, adverse effects, liver, Turkey

Türkiye'de Kullanılan Bitkilerin Karaciğer Üzerine Olumsuz Etkilerine Genel Bir Bakış

Öz

Bitkisel takviyeler, dünyanın neredeyse tüm kültürlerinde sağlığı iyileştirmek ve hastalık tedavisi için yaygın olarak kullanılmaktadır. Bununla birlikte, kullanılan bitkisel tedavi yöntemlerinin birçoğunun etkinliği, güvenliği ve ilaç etkileşimleri bilimsel olarak bilinmemektedir ve genellikle profesyonel sağlık yardımı olmadan kullanılırlar. Bilinçsiz bitki kullanımının ciddi beklenmedik yan etkiler için bir risk faktörü olduğu gösterilmiştir ve bu açıdan bitkisel ilaç kullanımı ilaca bağlı karaciğer hasarı vakalarının %25-30'u ile ilgilidir. Alternatif bir tedavi yöntemi olarak bitki kullanımı Türkiye'de de yaygındır. Bu araştırmada, Türkiye'de yaygın olarak kullanılan bitkilerin karaciğer üzerine olumsuz etkilerinin gözden geçirilmesi planlanmıştır. Türkiye'nin farklı bölgelerinde aktarlar tarafından satılan 400'den fazla bitki bu konudaki çeşitli araştırmalardan tespit edilmiş ve belirlenen bitkiler Pubmed ve Science Direct veritabanlarında hepatik etkileri açısından araştırılmıştır. Belirlenen bitkilerin yirmiyedisinin olumsuz hepatik sonuçları olduğu saptandı. Bitki hepatotoksisitesi, bitki-bitki etkileşimi ve bitki-ilaç etkileşimi konuları hakkında belirlenen çalışmalar ana metinde ele alınmıştır. Bitkisel yöntemler toplumda alternatif ve tamamlayıcı bir tedavi metodu olarak yaygın olarak kullanılmalarına rağmen, sık kullanılan bitkilerin çoğunun temel hepatotoksik bileşikleri ve karaciğer hasar mekanizması, ve bitkilerin bileşiklerinin çoğunun moleküler etki mekanizması tam olarak bilinmemektedir. Bahsedilen konularda yapılacak multidisipliner çalışmalar, tıbbi yaklaşımlarda bitkilerin rolünü ve hepatotoksisiteyi anlamada yardımcı olacaktır.

Anahtar Kelimeler: Bitki, yan etki, karaciğer, Türkiye

Physical health is one of the main components of life expectancy. Not only curative methods but also preventive and complementary modalities gain importance in maintaining health. At this point, populations in different parts of the world refer to various alternative and complementary methods (ACTMs) besides the modern medicinal techniques to maintain their health. Among ACTM, herbal preventive and treatment facilities are extensively used [1, 2]. However, studies indicate that plants are generally used without the knowledge and control of professional healthcare practitioners [3-6].

The belief that herbal applications do not have negative effects on the health, efficacy, safety, and drug interactions of many of the commonly used herbal modalities is not scientifically known and/or approved [7]. Moreover, use of plants in combined preparations has a complicated impact on human health [7, 8]. Till date, multiple studies have reported on the negative

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effects of uncontrolled herbal products on health [9-12]. Among these, plant and liver toxicity interactions are the most important ones [9, 11]. The liver has a critical role in many physiological functions, such as metabolism of nutrients, regulation of blood volume, synthesis of plasma proteins, support of the immune system, endocrine control of some mechanisms, lipid and cholesterol homeostasis, and breakdown of xenobiotic substances like drugs [13]. Liver failure can cause various health problems with significant morbidity and mortality [14]. It has been determined that the rate of herb-induced liver injury (HILI) may have a ratio of 25%–30% among all the drug-induced liver injury (DILI) cases [15, 16]. HILI ratios have been reported as 35.7% in China, 24.4% in South Korea, 8.1% in Western nations, and 5.4% in South-East Asia [16]. Plant usage as an alternative and complementary treatment method is also very common in Turkey [17, 18]. Some plants, which have been reported to cause liver damage, are traditionally consumed in the country, whereas some plants from the other parts of the world can also be easily supplied by the widespread herbal product market [16, 18]. There exist various case reports and interdisciplinary studies about the plants and their adverse hepatic effects in Turkey [19-22]. However, there is still a significant lack of knowledge about herb usage as an alternative health method, both in the general population and among health care professionals [23]. It is important to be aware of the potential side effects of the commonly used herbal products to prevent undesired outcomes.

Therefore, we decided to evaluate the adverse hepatic effects of the commonly used plants in Turkey. The commonly used plants in Turkey have been determined by detailed analyses of the herbalists' studies performed in different parts of Turkey, such as Konya, Çanakkale, Adana, and Istanbul [17, 24-26]. After listing the names of the plants in every article, duplications were determined and removed from the list, which finally included more than 400 plants. Every plant in the list was searched with "liver," "liver injury," and "hepatotoxicity" keywords on PubMed and Science Direct databases. There was no study about 98 of the listed plants, but there existed hepatoprotective and/or no liver injury studies about the majority of the plants. Hence, 27 of the listed plants have been reported to have an adverse liver injury or hepatotoxic effects *in vivo* and/or *in vitro*. Normally, there exist more than 60 plants (Chaparral, *Corydalis yanhusuo*, Jin Bu Huan, *Polygonum multiflorum*, *Psoralea corylifolia*, *Rheum officinale*, Syo Saiko, and so on) in literature that have been reported to have HILI potential [1, 7, 16, 18, 27]. However, because this study was conducted according to the herbalists' reports about the plants used in Turkey, the review has been performed with the determined plants in the list. At the end of the search, studies about the adverse hepatic effects of the determined plants, which can be summarized as single-plant effect, plant-plant interaction, plant-drug interaction, and the effects of plants on the liver through different systems, have been evaluated.

Clinical and Research Consequences

The identified plants and the determined *in-vivo* and/or *in-vitro* liver injury and/or hepatotoxicity studies about them with the detected injury pathways are as follows:

***Acorus calamus* L.** (Hazanbel, Eğir in Turkish)

Acorus calamus root has antimicrobial, antiviral, antifungal, and anti-inflammatory effects and is used for stress disorders, asthma, itching, ulcers, and rheumatic diseases [24, 25, 28]. Moreover, it is widely used for its neuroprotective and antiepileptic effects [29, 30]. Methanolic extract of *Acorus calamus* is known to have hepatoprotective properties [31]. However, − and −asarones, which are found specifically in Acorus (Araceae), have been determined to cause structural alterations, triacylglycerol accumulation, and protein synthesis inhibition in cultured rat hepatocytes and had hepatotoxic and carcinogenic potential in experimental studies [30, 32]. Therefore, it is advised that the asarone ingredient of daily food products are to be controlled, and a maximum of ~2 μg/kg body weight/day asarone exposure from herbal products is recommended in European countries [30].

Aloe vera L. (Aloe, Sarı Sabır in Turkish)

Aloe vera has known antioxidant, anti-inflammatory, and immune enhancement effects, and its leaves are widely used in skin diseases and cosmetology [17, 18, 25]. Although aloe vera has been shown to have hepatoprotective activity with its antioxidant capacity [33, 34], there are controversial studies about the plant [27, 35]. Aloe-emodin (AE) is the primary bioactive anthraquinone in aloe vera, and it has been determined to inhibit the transport activity of the multidrug resistance protein 2 (ABCC2/MRP2) and downregulate its expression. A study by Liu et al. [36] reported that ABCC2 degradation induces experimental hepatotoxicity. In recent studies, AE has been found to activate nuclear factor-−B inflammatory pathway and P53 apoptosis pathway from the mRNA and protein levels [35], inhibit cell proliferation, and induce apoptosis in the hepatic cells by reactive oxygen species generation (probably with Fas death and the mitochondrial pathway involvement) [37]. Teschke et al., [27] in their detailed herbal hepatotoxicity case analysis research, have reported

aloe to be "highly probable" for hepatocellular injury according to the scale of the Council for International Organizations of Medical Sciences (CIOMS).

***Cannabis sativa* L.** (Kenevir in Turkish)

Cannabidiol in *Cannabis sativa* is widely used for its anticancer, anti-inflammatory, antiepileptic, sleep promoting, relaxing, antioxidant, and painkiller effects [17, 38]. *C. sativa* is considered illegal in many parts of the world; however, cannabidiol usage as a treatment modality is increasing in the recent years [39]. Huestis et al. [40] have reported various probable drug-drug interactions with cannabidiol usage in which aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels have increased 3–12-fold, and worsened chronic cholecystitis cases have been indicated. In addition, in a recent experimental study, Ewing et al. [38] determined *C. sativa* to have cholestatic hepatotoxic outcome in mice. Further research about the hepatic effects of *C. sativa* will be valuable to understand its effects on liver functions.

Camellia sinensis (Yeşil çay in Turkish)

Camellia sinensis, also known as "green tea," has stimulant, diuretic, and constipatory effects. It is widely grown and consumed in Turkey [18, 24]. Apart from its antihepatotoxic, antioxidant, and anticancer (breast, ovarian, and colorectal) effects, green tea's potential hepatotoxic effect, especially in high doses, has been the subject of recent research [16, 27, 41]. Green tea increases the catechin bioavailability and decreases cytochrome P450 (CYP) 3A4 activity [16, 26, 42]. The activity of the CYP450 enzyme family is important for hepatic drug metabolization, and these results indicate that the use of *C. sinensis* is a risk factor for herb-drug interaction. Green tea has been reported to be "probable" and "highly probable" for hepatocellular injury according to the causality reports of different cases, and people have been warned about the undesired effects of repeated oral intake of green tea extracts in high doses (140 mg to 1,000 mg/day based on individual differences) during fasting [27, 42].

Cassia sp. (Sinameki in Turkish)

Cassia (also known as senna) leaves have diuretic, vasodilatory, and anti-eczematous properties and are widely used for constipation [17, 18]. Cassia decreases CYP3A4 levels, and multiple studies have reported senna hepatotoxicity, which may be related to the toxic metabolites of anthraquinone in senna [16, 26, 27, 43]. Turtay et al. [22] in Turkey have reported "probable" senna hepatotoxicity with a 100–200-fold increase in the hepatic markers and multiorgan failure. Causality evaluations of the plant are generally admitted as "probable" according to different reports [16, 27].

Citrus sp. (Turunçgillerin Turkish)

Citrus species are popularly consumed in many parts of the world as well as in Turkey [17, 44]. In a recent study, Xia et al. [44] determined that raw orange intake caused an increase in nonalcoholic fatty liver disease prevalence, and the authors associated the situation with the high fructose content of the plant. However, there exist totally disparate experimental studies, which report the use of *Citrus sinensis* to be effective in reducing liver fat and insulin resistance (mainly via the antioxidant properties of the ingredient phenolic compounds) [45, 46]. Further research about *C. sinensis* and liver interaction will be required to understand the detailed mechanism.

***Chelidonium majus* L.** (Kırlangıç otu, Kaşıntı otu, Hilaliye in Turkish)

Parts of *Chelidonium majus* (greater celandine) that are above the ground have spasmolytic, analgesic, sedative, bile secretion enhancing, diuretic, and anticancer effects and are widely used in Turkey [17, 18, 25, 28, 47]. Apart from its positive curative effects, high hepatotoxicity and potential for liver injury have also been reported [27, 47]. Sanguinarine, coptisine, and chelerythrine have been identified as the main hepatotoxic constituents of *C. majus* in a recent study [48]. *C. majus* has been reported to be "probable" and "highly probable" for hepatocellular injury according to the CIOMS scale [27, 47].

Chondrus crispus (Deniz kadayıfı in Turkish)

Chondrus crispus has anticoagulant and antilipidemic properties and is used in ulcer treatment. Although it does not grow in Turkey, it is sold in the country [49]. No research about the hepatotoxic potential of the plant could be determined in the scanned databases. However, it has been reported to have hepatotoxic effect in a study by Byeon et al., [16] in which they conducted a general systematic evaluation of the research with the plant's hepatotoxic causality reports.

***Chrysanthemum cinerariaefolium* vis.** (Dalmaçya papatyası, Krizantem in Turkish)

Chrysanthemum cinerariaefolium is used as a natural pesticide; in particular, the 3 natural pyrethrin derivatives of the plant, i.e., deltamethrin, permethrin, and alphacypermethrin, are widely used as insecticides [50, 51]. Chrustek et al. [52] reported deltamethrin to have potential liver injury effects by increasing ALT and AST activity and decreasing lipid peroxidation concentration in animals. Although pyrethroids are

admitted to be safe and nontoxic, there exist various life-threatening cases related to the use of *C. cinerariaefolium*, and as a widely used plant, further research is required into its potential hepatic effects [52].

***Crocus sativus:* Saffron** (Safran in Turkish)

Crocus sativus flowers and stalks are used for nervous system stimulation, appetizing, and menstrual and digestive disorders [17, 28]. Although it has been evaluated as useful for liver diseases through its antioxidant, antiapoptotic, and anti-inflammatory effects and is accepted as a candidate for treatment of hepatocellular carcinoma, Byeon et al. [16] reported that saffron is among the plants that probably cause liver damage [53-55]. Further research about saffron will be valuable in understanding its effects on the liver.

***Datura stramonium* L.** (Tatula Boru Çiçeği in Turkish)

Leaves, flowers, and seeds of *Datura stramonium* are used for pain relief and shortness of breath [28]. In a recent experimental study, Ogunmoyole et al. [56] reported *D. stramonium* to increase the ALT, AST, malondialdehyde (MDA), and alkaline phosphatase (ALP) levels in serum. Although the hepatotoxic molecular mechanism of *D. stramonium* seems to be unclear, there exist cases with "highly probable" causality assessments in Turkey, and there is a need for detailed study about its hepatotoxic effects [57, 58].

Ecballium elaterium (Acı Dülek, Eşek Hıyarı in Turkish)

The fruits, seeds, and roots of *Ecballium elaterium* are used externally in chronic skin diseases and rheumatic pain, and the juice of the fruit is widely applied through inhalation in sinusitis [24, 59]. Although in an experimental study, El Naggar et al. [60] showed *E. elaterium* juice to have hepatoprotective and anti-inflammatory effects, a case of a patient with cholestatic hepatitis with hyperbilirubinemia, increased ALP, and normal transaminase levels after consumption of *E. elaterium* has been reported in Tunisia [61].

Epimedium sp (Azgın Teke Otu, Keşişkülahı in Turkish)

Epimedium plant leaves have antidiabetic and antiosteoporotic properties and are widely used as an aphrodisiac [17, 62-64]. The main components of Epimedium are 2-O-rhamnosyl icariside II, baohuoside-I, and baohuoside-II, which are thought to have hepatotoxic potential. Zhang et al., [62] in an *in-vitro* study, determined baohuoside-I to be the main hepatotoxic component, which increased oxidative stress and induced apoptosis.

***Ginkgo biloba* L.** (Mabet Ağacı, Ginkgo in Turkish)

Apart from its ability to enhance mental concentration, *Ginkgo biloba* leaves are used for the treatment of Alzheimer's disease, dizziness, and cardiovascular problems [25, 28, 65]. Antioxidant, anti-inflammatory, and antitumor benefits of the plant had led to its widespread use among the population [65]. There are several studies about its hepatoprotective effects [66, 67]; however, there also exist contradictory results. *G. biloba* has been observed to increase hepatocellular carcinoma in mice, and its leaf extract has been classified as a possible group 2B human carcinogen by the International Agency for Research on Cancer in the recent times [68].

Ginkgolic acids (GAs) are the major components of *G. biloba* extracts. GAs (15:1) have been reported to increase the ALT and AST levels, increase glutathione-S-transferase and xanthine oxidase activity, cause severe oxidative stress, and induce liver damage [69]. Qing-Qing et al. [70] showed that GA (17:1) causes hepatotoxicity through CYP1A- and CYP3A-mediated metabolism. Furthermore, *G. biloba* induces CYP2C19 pathways in the liver. Hence, the use of *G. biloba* could be a potential risk factor for drug interactions [26, 71].

***Gymnema sylvestre* (Retz.) Schult.** (Cinnema otu, Gimneya in Turkish)

Gymnema sylvestre mainly grows in South-East Asia and is widely used for its sugar masking, antidiabetic, and hypolipidemic effects [28, 72, 73]. Although the studies about *G. sylvestre* are generally about the curative effects of the plant, a case of a patient with diabetes with acute hepatic toxicity was reported by Shiyovich et al. [74]. An *in-vitro* study with rat liver microsomes by Vaghela et al. [75] showed gymnemic acids to inhibit CYP450 activity (CYP3A4-mediated testosterone 6-hydroxylation and CYP2C9-mediated flurbiprofen 4-hydroxylation) strongly in a dose-dependent manner. In addition, Rammohan et al. [76] determined that *G. sylvestre* extracts inhibit CYP450 1A2, 3A4, and 2C9 activity, and these effects of *G. sylvestre* are thought to be a potential factor for herb-drug interactions.

***Hypericum perforatum* L.: St John's wort** (Binbirdelikotu, sarı kantaron, kan otu, mayasıl otu in Turkish)

Flowers and branches of *Hypericum perforatum* are used worldwide because of their antiviral, antibacterial, anti-inflammatory, antirheumatic, sedative, antidepressive, and anxiolytic efficacy [17, 18, 24, 26, 28, 77]. However, St John's wort has also been detected to have widespread side effects, including gastrointestinal symptoms, dizziness, confusion, fatigue, and allergic skin reactions. Although there is no report about its hepatotoxic effect when used alone, there are many studies about St John's wort's induction of the CYP450 family and reducing the effect of plasma concentra-

tions or efficacy of conventional drugs [16, 26, 77-80]. Piccolo et al. [77] reported a 61-year-old woman with a 20-fold increase in aminotransferase levels after using St John's wort. The study by Piccolo et al. [77] reports the Roussel Uclaf Causality Assessment Method score of St John's wort to be "probable," especially for drug-plant and plant-plant interactions [78-80].

Ilex paraguariensis (Mate in Turkish)

The leaves and branches of *Ilex paraguariensis* are widely used for mental and physical fatigue, headache, and rheumatic pain [17, 24, 25]. No hepatotoxic effect of *I. paraguariensis* has been determined yet; however, Rodriguez et al. [81] reported mate-intake-related acute hepatitis in a 21-year-old with increase in the bilirubin (32.9 mg/dL), ALT (2,685 U/L), AST (1,842 U/L), and ALP (129 U/L) levels and a "highly probable" causality score.

***Mentha piperita* L.** (Nane in Turkish)**:**

Leaves and oil of *Mentha piperita* are widely used for their analgesic, carminative, spasmolytic, and antibacterial activities [17, 18, 24]. Its main component is menthol, and there is no report about any adverse hepatic effects of menthol. However, an experimental study on pulegone, which is found in low concentrations in the oil extracts of the plant, found it to be hepatotoxic. Moreover, Douros et al. [79] reported the causality score of liver injury as "possible" in a Berlin case-control surveillance study of *M. piperita*.

Momordica charantia (Kudret Narı in Turkish)

Momordica charantia is widely used in diabetes, hyperlipidemia, stomach disorders (especially ulcers), menstrual problems, and vaginal disorders [17, 28]. Although there are studies about the positive effects of its antioxidant capacity on the liver [82, 83], Byeon et al. [16] reported the plant to cause liver injury. Further detailed research into the hepatic effects of *M. charantia* will be valuable to understand its safety.

Panax pseudoginseng: Panax ginseng (Ginseng in Turkish)

Panax ginseng is used for its anticarcinogenic effect [18]. Although there are several studies about its hepatoprotective effects [84, 85], Byeon et al., [16] in their detailed systematic review, reported it to cause more than 10 cases of liver injury. Multidisciplinary studies about the plant's effect on the liver would be important to determine its usage modalities.

***Ranunculus ficaria* L.** (Basurotu in Turkish)**:**

Seeds, flowers, leave, and roots of *Ranunculus ficaria* are used specifically in hemorrhoid treatment [17, 18]. Yılmaz et al. [19] reported a 36-year-old patient with hepatocellular injury with a 5-fold increase in transaminase levels and no other hepatic disease history, which rapidly improved after the discontinuation of *R. ficaria* and was considered to have "probable" causality according to the CIOMS scale.

***Ricinus communis* L.** (Hint Yağı Bitkisi, Kene Otu in Turkish)

Ricinus communis is used for its laxative effect [17, 18]; however, Kumar et al. [86] showed ricin (a glycoprotein of *R. communis*) to have serious hepatotoxic potential with an increase in the hepatic markers in an experimental study. In addition, Palatnick and Tenenbein [87] reported a case of reversible *R. communis* hepatotoxicity in a 20-month-old child with a "possible" causality assessment.

***Rosmarinus officinalis* L.** (Biberiye, Kuş Dili in Turkish)

Rosmarinus officinalis leaves have anticancer, antiadipogenic, anti-inflammatory, antiseptic, spasmolytic, and diuretic effects. They are also used widely for arrhythmia and migraine [17, 18, 24, 28, 88]. Several studies exist about the hepatoprotective effects of *R. officinalis* [89, 90]; however, Dickmann et al. [88] reported that carnosic acid in the plant causes hepatotoxicity in human hepatocytes. In their study, they showed carnosic acid to inhibit CYP2C9- and CYP3A4- catalyzed reactions and induce CYP2B6 and CYP3A4 mRNA and enzyme activity in a dose-dependent manner. Hence, this plant needs to be studied for its potential hepatic adverse effects.

***Salvia officinalis* L.** (Adaçayı in Turkish)

Leaves, flowers, and roots of *Salvia officinalis* are widely used in upper and lower respiratory tract infections, inflammatory wounds, epilepsy, indigestion, and abdominal pain in Turkey [17, 18, 24]. There are numerous studies about the hepatoprotective effects of *S. officinalis* [91, 92]. However, in an experimental study, Lima et al. [93] showed that *S. officinalis* increased CCl_4-induced hepatotoxicity in mice and may have an indirect liver injury effect by herb-drug interactions.

Teucrium polium (Acı yavşan in Turkish)**:**

Teucrium polium (mount germander) leaves are used for convulsions, digestive system diseases, chronic bronchitis, gout, asthma, diabetes, and rheumatic pain [17, 28]. In Turkey, *T. polium* is widely used during pregnancy and lactation for gastrointestinal complaints relieving and increasing breast milk [21]. Although there are studies about its hepatoprotective effects, it has also been stated to cause severe injury cases [16, 26, 27, 94]. In Turkey, Dağ et al. [21] reported

3 different patients with severe hepatotoxicity, which was related to the use of *T. polium* during pregnancy and lactation and had increased the transaminase (30–60-fold), ALP (2–5-fold), ¬glutamine transferase (GGT) (2–3-fold), and bilirubin (12–20-fold) levels. In the study, they pointed out that postpartum physiological changes may play a role in liver injury. In another study, Dağ et al. [95] indicated that *T. polium* was the "highly probable" cause of 7/10 HILI cases.

Trigonella foenum: **Fenugreek** (Çemenotu, Boyotu in Turkish)

Trigonella foenum is known for its antibacterial and hypoglycemic effects, and it is also used in the treatment of acne and constipation [17, 18]. The therapeutic potential of fenugreek polysaccharides has been shown by various studies; however, Byeon et al. [16] reported liver injury related to its use [96, 97]. Therefore, there is a need for further studies about the plant's hepatotoxic effects.

Valeriana officinalis **L.** (Kedi Otu in Turkish)

Roots and rhizomes of *Valeriana officinalis* are widely used for their sedative, tranquilizing, hypnotic, hypotensive, antispasmodic, and carminative effects [17, 18, 24]. Vassiliadis et al. [98] reported a 50-year-old patient with acute hepatotoxicity with increased AST (344 IU/L), ALT (564 IU/L), and GGT (72 IU/L) levels and mild fibrosis. The hepatic effect was thought to be related to the inhibition of P450 isoforms CYP3A4, CYP2D6, and CYP2C19 by the use of *V. officinalis*. Furthermore, there exist various reports about the plant's hepatotoxic potential, and the causality score of the plant is considered "possible" [16, 71, 99].

In conclusion, similar to many of the cultures, the use of plants as an alternative and complementary treatment method is very common in Turkey. However, herbal modalities are generally used without professional health assistance, and this situation has the potential to cause morbidity and mortality [6]. This review aimed to reveal the adverse hepatic effects of the commonly used plants in Turkey. We compiled a list of plants according to herbalists' studies, and the research into each plant was thoroughly evaluated [17, 24-26]. Normally, in the literature, there exist more than 60 plants (Chaparral, *C. yanhusuo*, Jin Bu Huan, *P. multiflorum*, *P. corylifolia*, *R. officinale*, Syo Saiko, and so on) with HILI potential [16, 18, 27, 100]. However, at the end of our search, adverse hepatic effects of 27 plants were determined, and they have been discussed in this review according to the results that we obtained. Other plants with HILI potential were carefully looked for in the obtained list of "the plants used in Turkey"; however, because they were not found in the herbalists' studies, they were not included in our study. In addition, case reports about the adverse hepatic effects of some other plants in Turkey, such as *Papaver rhoeas* (Gelincik in Turkish), great fennel (Büyük Rezene in Turkish), and *Teucrium chamaedrys* or Germander (Dalak Otu in Turkish) were determined while scanning the databases [20, 101, 102]. This could be owing to the regional herbal medicine approaches in different parts of the country and/or use of the plants by directly gathering from the nature. Hence, further advanced research into the usage culture of plants in the Turkish population would be valuable to obtain a more detailed result.

When the herb and liver interactions were studied, different topics, such as direct liver injury, hepatotoxic effects, cholestatic effects, and drug interactions, confronted the researchers. Many plants used for therapeutic purposes interact with other substances, such as nutrients and drugs, and change the effectiveness of the drugs used, and the liver plays an important role in these interactions [26, 42, 71, 76]. In this review, the hepatic effects of the plants have been evaluated without differentiating the mechanisms mentioned earlier.

Studies show that some plants such as *T. polium*, Aloe vera, *C. sativa*, *A. calamus*, and Cassia sp. have been reported to cause direct hepatic injury, hepatotoxicity, and/or cholestatic effects [21, 22, 32, 37, 38, 40, 47]. Another important finding of our study was that potential adverse hepatic effects of many plants, such as *A. calamus*, Aloe vera, *E. elaterium*, *G. biloba*, and *R. officinalis*, which had been reported to have hepatoprotective activity in various studies, were highlighted [27, 32, 35, 61, 68, 88].

One limitation of this study is that there are only experimental studies about some of the included plants, such as *A. calamus*, *C. cinerariaefolium*, Epimedium, *R. officinalis*, and *S. officinalis* [31, 52, 62, 88, 93]. Furthermore, there are only a few reports about the adverse hepatic effects of some plants [19, 40, 44, 61, 87].

As mentioned in different parts of this review, the active ingredients, metabolism, and potential interactions of many of the plants used for herbal treatment modalities are yet to be determined. Some of the mentioned studies were experimental and some included human cases. Further and detailed multidisciplinary studies about these plants would be valuable to understand the contradictory results and evaluate the role of plants and hepatotoxicity in treatment modalities.

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