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Liver tonics: review of plants used in Iranian traditional medicine

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PEER REVIEW

Peer reviewer

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Comments

This is a valuable review. It introduced plants which have been traditionally used as liver tonics in Iran. This paper will promote the utilization of natural and traditional resources for contemporary health care. Herbal medicines have an extremely valuable, rich, lengthy and extensive practical history.
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ABSTRACT

Considering the fact that liver is one of the most important organs in our body, it deserves special attention and protection. Among various recommended supplements, complementary and alternative medicines particularly herbal remedies have received much attention owing to their truly healing properties. This review profits from Iranian traditional medicine and presents advantageous herbal guide directions for liver protection. According to credible Iranian medical literature such as Al Qanun Fil Tibb, Al-Havi and Makhzan-al-Aadvia, a wide spectrum of plants have been found to be useful for cleansing and protecting the liver. Some herbs such as ghafes (*Agrimonia eupatoria*), kasni (*Cichorium intybus*), anar (*Punica granatum*), darchin (*Cinnamomum zeylanicum*), za'feran (*Crocus sativus*), gole-sorkh (*Rosa damascena*) and zereshk (*Berberis vulgaris*) appeared to get strong consideration and were well documented as outstanding liver tonics. We conducted a comprehensive review of available Iranian medical resources such as scientific information database and medical sciences databases which cover all *in vitro* and *in vivo* studies of medicinal plants as liver tonics and hepatoprotective candidates. Literature survey was accomplished using multiple databases including PubMed, ISI web of knowledge, and Google Scholar.

KEYWORDS

Iranian traditional medicine, Liver tonic, Hepatoprotective agents, Herbal medicine

1. Introduction

The use of medicinal properties of plants in the prevention and treatment of diseases goes back to thousands years ago, and recently, it has received lots of attention due to the available scientific evidences[1]. Now, traditional medicine systems continue to play a fundamental role in health care. It should not be forgotten that about 80% of the world's population relies mainly on complementary and alternative medicines especially herbal therapies for their primary health care[2-4]. From antiquity to now, nature has been the center

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of attention as it is the richest source of medicinal agents. It has provided important opportunities for the scrutinized recognition of diseases and the related preventions[5]. In this regard, isolation and identification of herbal active ingredients have been common strategies in traditional medicine[1,6].

Liver is one of the most important organs which plays a crucial role in the daily functions of our body[7-11]. It is the main site for carbohydrates, proteins and lipid metabolism, synthesis of essential materials, and detoxifying harmful substances. Furthermore, expulsion of waste metabolites, detoxification, blood coagulation, homeostatic activities, storage of vitamins, finally excretion of bile, hormones, and drugs are other significant functions of liver.

Iranian traditional medicine (ITM) includes a wide range of medical experiences used in the prevention, diagnosis, and treatment of diseases based on the humor theory of temperament in which liver is one of the most important organs in the body. Persian scientists such as Sina[12] and Razi[13] believed that liver is one of the three essential organs (liver, heart and brain) in the body. In canon of medicine, the liver was described as a blood factory, refinery and distributor[12]. It was supposed that the liver receives all blood coming from stomach and bowel through portal vein, manufactures nutrients, and then distributes them to the rest of the body.

ITM believes that proper liver function can improve other organs performance and liver failure would lead to the inefficiency of other organs which causes various diseases such as uterine and ovarian diseases, loss of mental ability, chronic fatigue syndrome, *etc*. At this juncture, ITM has focused not only on liver diseases and treatments but also special attention to liver protection.

Liver tonics include principles of liver health protection, nutraceuticals, medications with nutritional implication and effective drugs. According to ITM, the most important principle to keep the liver healthy is to avoid eating different kinds of foods together or immediately after each other. Also, drinking too much water along with a meal, eating different incompatible foods with liver, eating large amount of sweets, and drinking cold water especially during or after exercise are important reasons leading to liver failure.

Functions of liver from both ITM and modern medicine points of view prove that a healthy liver is central to maintaining a healthy body. Liver impairment is one of the serious threats to general health around the world[14]. It is mainly caused by some toxicants such as chemotherapeutic agents (some antibiotics, large doses of acetaminophen, carbon tetrachloride, thioacetamide, peroxidised oil, aflatoxin, *etc*.), chronic consumption of alcohol, infections, and autoimmune disorders[15]. It seems that strengthening the liver against the aforementioned factors is one of the most reliable ways to prevent liver damage. For this purpose, various liver tonics have been designed and developed. Because of the increasing demand for the efficient liver tonics and hepatoprotective agents with minimal side effects[16-19], complementary and alternative therapies including nontoxic, natural and inexpensive products have attracted lots of consideration. Herein, in order to emphasize on the efficacy of ITM, we introduced a well-documented collection of therapeutic herbs acting as liver tonics.

2. Methodology

In this study, related information was obtained from available ancient sources such as Al Qanun Fil Tibb, Al-Havi, and Makhzan-al-Aadvia. Accordingly, a wide spectrum of plants was found to be useful for cleansing and protecting the liver. Finally, the obtained data was compared with those of reported in modern medicinal databases covering all *in vitro* and *in vivo* hepatoprotective investigations. In the present paper, the literature review was performed by using PubMed, ISI web of knowledge, scientific information database and Google Scholar focusing on the following keywords: “liver tonic” and “hepatoprotective”.

3. Modern proofs for the efficacy of medicinal plants used as liver tonics in ITM

3.1. Agrimonia eupatoria (A. eupatoria)

A. eupatoria known as ghafes in ITM has been repeatedly utilized in order to strengthen the liver[12,20]. The study of Yoon *et al*. showed that *A. eupatoria* decreased the toxic effects of chronic ethanol consumption on rat liver, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels[21]. In addition, oral ingestion of aqueous extract of aerial parts of *A. eupatoria* in the experimental animals which were treated by tetrachloride carbon (CCl_4) decreased AST and ALT levels[22] (Table 1).

3.2. Vitis vinifera L. (V. vinifera)

The fruits of *V. vinifera* known as maveez munaqqa in ITM have been widely used as liver tonic[12]. The hepatoprotective effects of ethanolic extract of *V. vinifera* leaves were investigated against CCl_4-induced acute hepatotoxicity in rats. The AST and ALT levels were reduced in rats pretreated by *V. vinifera* leaves extract[23]. Effects of *V. vinifera* leaf extract on alcohol-induced oxidative stress in rats were investigated by Pari and Suresh. Grape leaf extract at a dose of 100 mg/kg was highly effective than 25 and 50 mg/kg body weight. In addition, it significantly reduced the levels of lipid peroxidation level and restored the enzymatic and non-enzymatic antioxidants level in liver and kidney of alcohol administration rats[24]. In another study reported by Liu *et al*., the hepatoprotective effect of total triterpenoids (VTT) and total flavonoids (VTF) from *V. vinifera* against immunological liver injury (ILI) in mice was investigated. The hepatoprotective effects of *Vitis* VTT and VTF from *V. vinifera* were evaluated in bacille-Calmette-Guérin (BCG) plus lipopolysaccharide (LPS)-induced ILI in mice. Moreover, the increased Bax/Bcl-2 ratio was significantly down which was regulated by VTT and VTF in liver tissue of ILI mice. These results

Table 1
Plants used in ITM as liver tonics.

Iranian name	Species	Family	Part (s) used	Type of assay/hepatotoxic agent	References
Ghafes	*A. eupatoria*	Rosaceae	Aerial part	*In vivo*/ethanol	[21]
				In vivo/CCl_4	[22]
Maveez	*V. vinifera*	Vitaceae	Leaves	*In vivo*/CCl_4	[23]
				In vivo/ethanol	[24]
			Fruit	*In vivo*/BCG-LPS	[25]
			Grape seed	*In vivo*/ethanol	[26]
			Root	*In vivo*/CCl_4	[27]
Za'feran	*C. sativus*	Iridaceae	Stigma	*In vivo*/RIF	[28]
				In vivo/cisplatin	[29]
				In vivo/vitamin A	[30]
				In vivo/streptozotocin	[31]
Afsantin	*A. absinthium*	Asteraceae	Flowering aerial parts	*In vivo*/CCl_4 and BCG-LPS	[32]
				In vivo/CCl_4 and acetaminophen	[33]
Anar	*P. granatum*	Lythraceae	Edible portion (seedcoats and juice)	*In vivo*/INH and rifampin RIF	[34]
			Peel	*In vivo*/acetaminophen	[35]
			Leaves	*In vivo*/CCl_4	[36]
			Flower infusion	*In vivo*/trichloroacetic acid	[37]
Rivande chini	*R. palmatum*	Polygonaceae	Aerial part	*In vivo*/CCl_4	[38]
			Dried roots and rhizome	*In vivo*/CCl_4	[39]
			Rhizome	*In vivo*/CCl_4	[40]
Karafs	*A. graveolens*	Apiaceae	Seeds	*In vivo*/-	[41]
				In vivo/CCl_4	[42]
			Roots and leaves	*In vitro* and *in vivo*/CCl_4	[43]
			Seeds	*In vivo*/DEN	[44]
				In vivo/acetaminophen/thioacetamide	[45]
			Leaves	*In vivo*/acetaminophen	[46]
Basbaseh	*M. fragnans*	Myristicaceae	Mace	*In vivo*/LPS/D-galactosamine	[47]
				In vivo/-	[49]
				In vivo/-	[50]
				In vitro/*t*-BHP	[51]
Mastaki	*P. lentiscus*	Anacardiaceae	Gums	*In vivo*/CCl_4	[52]
			Leaves	*In vivo*/CCl_4	[53]
Zereshk	*B. vulgaris*	Berberidaceae	Bark	*In vivo*/CCl_4	[55]
			Whole plant	*In vitro* and *in vivo*/*t*-BHP	[56]
			Root	*In vivo*/CCl_4	[57]
			Fruit	*In vivo*/CCl_4	[58]
Shahtareh	*F. parviflora*	Papaveraceae	Aerial parts	*In vivo*/acetaminophen	[59]
				In vivo/CCl_4	[60]
				In vivo/CCl_4	[61]
			Whole plant	*In vitro*/nimesulide	[62]
Darchin	*C. zeylanicum*	Lauraceae	Inner bark	*in vivo*/CCl_4	[64,65]
				In vivo/gamma irradiation	[66]
Gole-sorkh	*R. damascena*	Rosaceae	Flower	*In vivo*/acetaminophen	[67]
				In vivo/CCl_4	[68]
Kadooye shirin	*C. maxima*	Cucurbitaceae	Aerial parts	*In vivo*/CCl_4	[69]
			Seeds	*In vivo*/acetaminophen	[71]
Ameleh	*P. emblica*	Phyllanthaceae	Fruits	*In vivo*/acetaminophen	[72]
				In vivo/DEN	[73]
			Stem and fruit	*In vivo*/RIF, INH and pyrazinamide	[74]
			Fruits	*In vivo*/ethanol	[75]
				In vivo/thioacetamide	[76]
Barhang	*P. major*	Plantaginaceae	Seeds	*In vivo*/CCl_4	[77]
				In vivo/CCl_4	[78]
			Not mentioned	*In vivo*/7,12-dimethylbenz(a)anthracene	[80]
Salikheh	*C. cassia*	Lauraceae	Bark	*In vivo*/dimethylnitrosamine	[84]
				In vivo/alcohol	[86]
Balasan	*C. opobalsamum*	Burseraceae	Aerial parts	*In vivo*/CCl_4	[87]
Kasni	*C. intybus*	Asteraceae	Leaves	*In vivo*/CCl_4	[88]
			Aerial parts	*In vivo*/CCl_4	[89]
			Seeds	*In vivo*/CCl_4	[90]
				In vivo/thioacetamide	[91]

Table 1, continued

Plants used in ITM as liver tonics.

Iranian name	Species	Family	Part (s) used	Type of assay/hepatotoxic agent	References
			Leaves	*In vivo*/acetaminophen	[92]
				In vivo/nimesulide	[93]
Annab	*Z. vulgaris*	Rhamnaceae	Aerial parts	*In vivo*/CCl_4	[94]
Fandogh	*C. avellana*	Betulaceae	Leaves	*In vivo*/CCl_4 and acetaminophen	[95]
Foloos	*C. fistula*	Fabaceae	Leaves	*In vivo*/DEN	[97]
				In vivo/DEN	[99]
			Fruit pulp	*In vivo*/CCl_4	[101]
Zanjabil	*Z. officinale*	Zingiberaceae	Rhizomes	*In vivo*/acetaminophen	[102,103]
				In vivo/CCl_4 and acetaminophen	[104]
				In vivo/ADR	[106]
				In vivo/atorvastatin	[107]
				In vivo/Hg, Pb and Cd	[108]

C. sativus: Crocus sativus; A. absinthium: Artemisia absinthium; P. granatum: Punica granatum; R. palmatum: Rheum palmatum; A. graveolens: Apium graveolens; M. fragnans: Myristica fragnans; P. lentiscus: Pistacia lentiscus ; B. vulgaris: Berberis vulgaris; F. parviflora: Fumaria parviflora; C. zeylanicum: Cinnamomum zeylanicum; R. damascena: Rosa damascena; C. maxima: Cucurbita maxima; P. emblica: Phyllanthus emblica; P. major: Plantago major; C. cassia: *Cinnamomum cassia; C. opobalsamum: Commiphora opobalsamum; C. intybus: Cichorium intybus; Z. vulgaris: Zyziphus vulgaris; C. avellana: Corylus avellana; C. fistula: Cassia fistula; Z. officinale: Zingiber officinale.* RIF: Rifampin; INH: Isoniazid; DEN: Diethylnitrosamine; *t*-BHP: *Tert*-butyl hydroperoxide; ADR: Adriamycin.

are comparable to those of biphenyl dicarboxylate (distributed data base, the reference hepatoprotective agent) and suggest that VTT and VTF play a protective role against ILI, which may have important implications for our understanding of the immunoregulatory mechanisms of this plant[25]. In the next study by Dogan and Celik, hepatoprotective and antioxidant activities of grape seeds against ethanol-induced oxidative stress in rats were evaluated. The results indicated that grape seeds could be as important as diet-derived antioxidants in preventing oxidative damage in the tissues by reducing the lipid oxidation or inhibiting the production of ethanol-induced free radicals in rats[26]. Sharma *et al*. studied the ethanolic extract of the root of *V. vinifera* for its hepatoprotective activity in rats with liver damage induced by CCl_4[27]. The activity of extract was also comparable to that of silymarin, a known hepatoprotective drug.

3.3. C. sativus

Stigma of *C. sativus* known as Za'feran in ITM is another natural product used as liver tonic[12,13]. Hepatoprotective effects of *C. sativus* stigma against RIF in compare with silymarin have been investigated by Mohajeri *et al*. The results demonstrated that ethanolic extract of *C. sativus* has the same protection as silymarin[28]. In addition, hepatoprotective effects of saffron stigma against cisplatin hepatotoxicity were evaluated by the same group[29]. In the work of Mokhtari *et al*., the protective and antioxidant effects of hydro-alcoholic extract of saffron on liver enzymes following vitamin A toxicity were investigated[29]. It was found that saffron extracts protected hepatocytes against oxidative stress which was caused by hyper-vitaminosis A[30]. Also, protective effects of ethanolic extract of *C. sativus* on hepatic tissue damage in streptozocin-induced diabetic rats was investigated by Rahbani *et al*. It was depicted that saffron had beneficial effects on antioxidant defense system of diabetic rats[31].

3.4. A. absinthium

A. absinthium known as Afsantin in ITM has been traditionally used as liver tonic in Iran[12]. Amat *et al*. evaluated *in vivo* hepatoprotective activity of the aqueous extract of *A. absinthium*. It was demonstrated that the pretreatment with *A. absinthium* dose-dependently chemically or immunologically induced increase in serum levels of hepatic enzymes. Furthermore, it has significantly reduced the lipid peroxidation in the liver tissue[32]. Effect of hydro alcoholic extract of *A. absinthium* against acetaminophen and CCl_4-induced hepatic damage was investigated by Gilani *et al*. This study indicated that the crude extract of *A. absinthium* exhibited hepatoprotective property and confirmed the traditional use of plant in hepatic damage[33].

3.5. P. granatum

P. granatum known as anar in ITM is a famous fruit in all around the world. This amazing fruit has been traditionally consumed in Iran as liver tonic[12]. Antihepatotoxic effects of acetone extract of *P. granatum* agains INH and RIF and induced hepatotoxicity in rats were studied by Yogeeta *et al*. In addition, its hepatoprotective property on tissue defense systems in rat was well established[34]. The hepatoprotective activity of *P. granatum* aqueous extract has been evaluated by Khalil. The acute elevation of AST, ALT, lactate dehydrogenase, and liver damage reduced in pretreated group by pomegranate mix with acetaminophen[35]. In another report by Rao and Dama, hepatoprotective activity of aqueous and alcoholic extract of *P. granatum* leaves using CCl_4-induced liver damage in rats was

proved. It was revealed that biochemical changes produced by CCl_4 were restored to normal by aqueous and alcoholic extracts of *P. granatum* leaves[36]. Celik *et al*. investigated the hepatoprotective and antioxidant effects of *P. granatum* beverage against trichloroacetic acid-exposure in rats[37].

3.6. R. palmatum

R. palmatum known as Rivande chini in ITM has been widely used as liver protectant by Persians[12]. Investigations of Guo *et al*. revealed that rhein could protect hepatocyte from injury and prevent the progress of hepatic fibrosis in rats. It may be associated with the fact that rhein plays a vital role in antioxidation and anti-inflammation, inhibiting the expression of transforming growth factor-beta1, and suppressing the activation of hepatic stellate cells. Also it can inhibit liver fibrosis induced by CCl_4/ethanol in rats[38]. Wang *et al*. investigated the protective effect of *R. palmatum* on CCl_4-treated rats. The curative effect of administering the two lowest dosages of *R. palmatum* to CCl_4-treated rats was mainly expressed as a decrease in the extent of cellular injury. The hepatoprotective mechanism of *R. palmatum* might be related to its antioxidant effect that the antagonism of the free radical damage to hepatocytes caused by CCl_4. By contrast, the liver damage induced by *R. palmatum* was mainly expressed as a significant increase in the amount of fibrosis in both normal rats at all dosage levels and CCl_4-treated rats at the two highest dosage levels[39]. Tseng *et al*. detailed prevention of hepatic oxidative injury by *R. palmatum* in combination with some other herbal medicines. The results suggested that this formulation has noteworthy antioxidant activity and hepatic protection potential[40].

3.7. A. graveolens

Various products from *A. graveolens* known as Karafs in ITM have been used to relieve some of liver dysfunctions in Persian traditional therapies[19]. The effect of volatile oil of *A. graveolens* seeds on some hepatic enzymes including ALT, AST and alkaline phosphatase (ALP) in rats was examined. The results demonstrated that the active ingredients of *A. graveolens* may act as an antioxidant or to decrease the production of free radicals, causing stabilization of hepatocyte membrane and decreasing the release of enzymes into the blood[41]. In the study of Ahmed *et al*., various extracts of *A. graveolens* seeds were tested for their hepatoprotective activity against CCl_4-induced hepatotoxicity in albino rats. Treatment of rats using different extracts of *A. graveolens* at dose of 250 mg/kg markedly prevented CCl_4-induced elevation of serum glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT) and ALP, and increased the level of total protein and albumin[42]. Efficacy of *A. graveolens* leaves and roots extracts as antioxidant in CCl_4-treated rats was examined by Popović *et al*. It was concluded that the examined extracts showed promising protective effects. All the *n*-butanol extracts exhibited the highest protective effect[43]. The chemopreventive activity of methanolic extract of *A. graveolens* seeds was investigated against Solt-Farber protocol of hepatocarcinogenesis, oxidative stress, and induction of gamma-glutamyl transpeptidase-positive foci in the liver of Wistar rats by Sultana *et al*. According to their results, *A. graveolens* is a potent plant against experimentally induced hepatocarcinogenesis in Wistar rats[44]. The antihepatotoxic effects of methanolic extract of *A. graveolens* seeds was studied by Singh and Handa on rat liver damage induced by a single dose of acetaminophen or thioacetamide by monitoring several liver function tests. This study confirmed remarkable hepatoprotective activity of the methanolic extract of celery[45]. The hepatoprotective effects of celery leaves on acetaminophen-induced toxicity in a freshwater fish was demonstrated by Shivashri *et al*. It was clear that the abnormalities associated with acetaminophen exposure were reversed by treatment with *A. graveolens*[46].

3.8. M. fragrans

Mace of *M. fragrans* known as basbaseh in ITM has been broadly used as liver tonic in Iran[12,20]. It has been recognized as chemoprevention of chemically induced carcinogenesis[47]. Myristicin extraction from nutmeg has exhibited important hepatoprotective effects[48]. It has also been reported that the mace modulates glutathione (GSH) S-transferase activity in liver of mouse[49]. Chhabra and Rao examined the possible transfer of active principles of mace through the transmammary route and its ability to modulate hepatic xenobiotic-metabolizing enzymes in mice. Active principles which presented in the aqueous extract of mace were effective in transmammary modulation of hepatic xenobiotic-metabolizing enzymes in the liver of mouse pups[50]. Sohn *et al*. investigated the protective effect of macelignan, isolated from *M. fragrans* against *t*-BHP-induced cytotoxicity. The results showed that macelignan intensively reduced the cell growth inhibition and necrosis caused by *t*-BHP. The results strongly suggested that macelignan has significant protective ability against oxidative damage caused by reactive intermediates[51].

3.9. P. lentiscus

P. lentiscus known as Mastaki in ITM has been used as liver tonic affirmed by Sina[12]. Mavridis *et al*. investigated total extracts of *P. lentiscus* to protect liver from CCl_4-induced damage in Wistar rats. Animals treated with mastic and silimarin alone showed a decrease in AST, ALT and malondialdehyde levels either in control or in CCl_4-treated rats. The result suggested that mastic gum extracts have a strong inhibitory effect against lipid peroxidation in rat liver. The CCl_4-treated group showed a remarkable reduced GSH level but the pre-treatment with mastic gum and silimarin inhibited GSH depletion caused by CCl_4. Mastic gum increased the content of GSH in the rat liver compared to control rats. Similar results have been

observed in activities of GSH-related enzymes, superoxide dismutase and catalase. It was concluded that total extracts of mastic gum could protect liver cells from CCl_4-induced oxidative damage[52]. The hepatoprotective effect of the boiled and non-boiled aqueous extracts of *P. lentiscus*, *Phillyrea latifolia* and *Nicotiana glauca* was evaluated *in vivo* using CCl_4 intoxicated rats as an experimental model by Janakat and Al-Merie *et al*. At the end, aqueous extract of *P. lentiscus* (both boiled and non-boiled) showed satisfactory hepatotoxic activities against CCl_4 by reducing the activity of the three enzymes and the level of bilirubin. The effect of the non-boiled aqueous extract was more noticeable than that of the boiled[53].

3.10. B. vulgaris

B. vulgaris known as zereshk in ITM has been widely used as liver protectant from the past to till now in Iran[12,13,54]. The capacity of formulated *B. vulgaris* extract/β-cyclodextrin to protect liver against CCl_4-induced hepatotoxicity in mice was investigated by Hermenean *et al*. Their results showed that *B. vulgaris*/β-cyclodextrin treatment prevented hepatic injury induced by CCl_4 and could be considered for further nutraceutical studies[55]. Inhibitory effect study of berberine on *t*-BHP-induced oxidative damage in rat liver was continued by Hwang *et al*. Berberine had a dose-dependent ability to quench free radicals in diphenylpicrylhydrazyl test. Furthermore, the *in vivo* study showed that pretreatment with berberine for 5 d before a single dose of *t*-BHP significantly lowered the serum levels of hepatic enzyme markers (ALT and AST) and reduced oxidative stress in the liver. The histopathological evaluation of the liver revealed that berberine reduced the incidence of liver lesions induced by *t*-BHP. It was conceived that berberine may play a chemopreventive role via reducing oxidative stress in living systems[56]. The effects of *B. vulgaris* root extracts at the different doses in CCl_4-induced liver toxicity in rats was investigated by Huseini *et al*. *B. vulgaris* reduced the serum ALP levels significantly as compared to control group. The liver micro-vesicular steatosis was considerably inhibited as well[57]. Likewise, the efficacy of methanolic extract of *B. vulgaris* fruits in CCl_4-induced liver injury was detailed by Eidi *et al*[58].

3.11. F. parviflora

F. parviflora known as shahtareh in ITM has been traditionally used to support liver in Iran[12]. The hepatoprotective activity of aqueous and methanolic extract of *F. parviflora* was investigated against acetaminophen- and CCl_4-induced hepatic damage by Gilani *et al*. Pretreatment of rats with plant extract prevented the acetaminophen-induced rise in serum enzymes ALP, AST and ALT. Posttreatment with the extract also restricted the acetaminophen-induced hepatic damage. It is conceivable that *F. parviflora* extract exhibits protective effect against acetaminophen-induced hepatotoxicity[59]. Protective effect of hydroalcoholic extract of *F. parviflora* was determined in a CCl_4-induced hepatotoxicity model in male rats by Jamshidzadeh and Nikmahad, in which the liver function test and hystopathological observations were performed[60]. The data from this study outlined that the hydroalcoholic extract of *F. parviflora* with doses higher than 100 mg/kg prevented CCl_4-induced liver damage. In the study of Alqasoumi *et al*., the efficacy of *F. parviflora* on CCl_4- induced liver injury in rats was evaluated. The results indicated a good protection of the extracts from CCl_4 hepatotoxicity[61]. Tripathi *et al*. conducted complete studies on nimesulide (a non-steroidal anti-inflammatory drug with serious hepatotoxicity)-induced cell death in primary rat hepatocyte cultures to explicate the effect of *F. parviflora*. It was indicated that *F. parviflora* extract modulates critical events and pro- and anti-apoptotic proteins in mitochondria-dependent apoptosis which were induced by nimesulide[62]. *In vivo* studies were conducted to explore the hepatoprotective potential of *F. parviflora* extract against nimesulide-induced hepatotoxicity by the same group. Pretreatment with *F. parviflora* extract for 5 d significantly reduced the impact of nimesulide-induced toxicity as evident from the serum biomarkers of liver damage and histopathology[63].

3.12. C. zeylanicum

C. zeylanicum known as darchin in ITM has been frequently consumed in Iran as liver tonic[12,20]. Hepatoprotective effect of cinnamon extracts against CCl_4-induced oxidative stress and liver injury in rats was demonstrated by Moselhy and Ali[64]. Similary, Eidi *et al*. evaluated the protective effect of cinnamon bark extract against CCl_4-induced liver damage in male Wistar rats, which was reported as a potent hepatoprotective[65]. Rezk studied the protective effects of cinnamon against tissue injuries which were induced by gamma irradiation. It was found that taking adequate amount of aqueous extract of cinnamon would protect hepatic and cardiac tissues from gamma radiation-induced damage for a long time[66].

3.13. R. damascena

Aqueous extract of *R. damascena* known as gole-sorkh in ITM has been well known and popular in Iran[19]. Saxena *et al*. confirmed hepatoprotective activity of the aqueous extract of *R. damascena* flowers at different oral dose levels (250, 500, and 1000 mg/kg body weight) on acetaminophen-induced toxicity in rats[67]. It was assumed that it is likely to be mediated through its antioxidant activities. Achuthan *et al*. evaluated the antioxidant activity of the partially purified acetone fraction of *R. damascena*. Also it was proved that *R. damascena* protected against CCl_4-induced hepatotoxicity[68].

3.14. C. maxima

C. maxima known as kadooye-shirin in ITM was nominated as one of the liver tonics[19]. The hepatoprotective activity of *C. maxima*

against CCl_4-induced hepatotoxicity has been evaluated. It was shown that methanol extract of aerial parts of *C. maxima* possessed significant hepatoprotective activity[69,70]. In another study conducted by Nidhi and Pathak, methanolic extract of *C. maxima* seeds showed strong hepatoprotective activity against acetaminophen toxicity[71].

3.15. Emblica officinalis (E. officinalis) or P. emblica

P. emblica known as ameleh in ITM has been used as liver tonic in Iran[19]. The efficacy of the *P. emblica* for the prevention of acetaminophen-induced hepatotoxicity in rats was studied by Malar and Bai. The results clearly confirmed the hepatoprotective effect of aqueous extract of *P. emblica* fruits[72]. Jeena *et al*. demonstrated that extract of *E. officinalis* inhibited hepatocarcinogenesis induced by DEN in a dose-dependent manner[73]. The hepatoprotective effects of two medicinal plants (*Tinospora cordifolia* and *P. emblica)* and their combination were investigated in a rat model of INH, RIF and pyrazinamide-induced hepatic damage by Panchabhai *et al*. This study proved the synergistic protective effects which were exerted by the combination of *Tinospora cordifolia* and *P. emblica* when co-administered with mentioned drugs[74]. The protective effects of *P. emblica* extract on ethanol-induced rat hepatic injury were reported by Pramyothin *et al*. The results which were confirmed by histopathological studies showed that the treatment of rats with *P. emblica* with ethanol enhanced liver cell recovery by bringing the levels of AST, ALT and interleukin-1beta back to normal[75]. Sultana *et al*. found that *E. officinalis* fruit extracts inhibit thioacetamide-induced oxidative stress and hyper-proliferation in rat liver[76].

3.16. P. major

P. major known as barhang in ITM have been extensively applied as liver tonic in Iran[12,20]. Türel *et al*. studied hepatoprotective effect of *P. major* in CCl_4-induced hepatotoxic rats. The results showed that *P. major* has a considerable hepatoprotective activity[77]. In a similar study by Atta *et al*., methanol extract of *P. major* was evaluated for its potential hepatoprotective effect against CCl_4-induced hepatic damage. The applied treatment significantly decreased the elevated AST and gamma-glutamyl transpeptidase activities and blood triglyceride level. The effect was nearly similar to that of silymarin[78]. Mello *et al*. indicated that *P. major* was able to prevent oxidative mitochondrial damage, which contributed to the understanding of its hepatoprotective action against reactive oxygen species-mediated toxicity[79]. The results in the work of Oto *et al*., suggested that the preventive effects of *P. major* on 7,12-dimethylbenz(a)anthracene-induced oxidative damage in Wistar albino rats might be due to the decrease of free radical generation. The antioxidant activity of this plant was established by Oto *et al*. as well[80]. It was also proved that some flavonoids which derived from *P. major* possessed hepatoprotective effects of baicalein against CCl_4-induced liver injury in rats[81,82]. Furthermore, aucubin was found to be potential antidote for poisonous amanita mushrooms in mice to protect against liver damage induced by amanitin[83].

3.17. C. cassia

The bark of *C. cassia* known as salikheh in ITM has been well-known as liver tonic in Iran[12,13]. The protective effects of *C. cassia* in the fibrogenesis of activated hepatic stellate cells-T6 cells and dimethylnitrosamine-induced acute liver injury in rats were successfully demonstrated by Lim *et al*. The results were significantly protected by *C. cassia* powder in the serum total protein, albumin, total bilirubin, direct-reacting bilirubin, GOT, GPT, and ALP[84]. Bansode reported that *C. cassia* inhibited fibrogenesis, followed by hepatic stellate cells-T6 cell activation, and increased restoration of liver function, which ultimately resulted in acute liver injury[85]. According to the results reported by Kanuri *et al*., cinnamon extract protects against acute alcohol-induced liver steatosis in mice[86].

3.18. C. opobalsamum

Fruits of *C. opobalsamum* known as balasan in ITM have been the focus of Iranians[20]. Its applications as an efficient liver tonic were frequently emphasized by Sina[12]. Al-Howiriny *et al*. investigated the hepatoprotective activity of the ethanolic extract of *C. opobalsamum* in rats by inducing hepatotoxicity with CCl_4. This extract has been shown to possess significant protective effect by lowering serum transaminase levels of GOT, GPT, ALP and bilirubin. This study suggested that the plant *C. opobalsamum* may act as an antioxidant agent as it possessed hepatoprotective effect[87].

3.19. C. intybus

C. intybus known as kasni in ITM is one of the most important liver tonics[12]. Hepatoprotective activity of *C. intybus* leaves extract against CCl_4-induced toxicity was investigated by Jamshidzadeh *et al*. It was worth to mention that high concentration of the plant extract was hepatotoxic[88]. In a similar study, the hepatoprotective activity of hydroalcholic extract of *C. intybus* was investigated on CCl_4-induced liver injury in rats. The results confirmed the hepatoprotective activity effects of the hydroalcholic extract of *C. intybus*[89]. Different fractions of alcoholic extract and phenolic compound from *C. intybus* seeds were screened for their antihepatotoxic activity on CCl_4-induced liver damage in albino rats by Ahmed *et al*. The histopathological study of the liver was also carried out, and the results showed almost complete normalization of the tissues as neither fatty accumulation nor necrosis[90]. In another study by Madani *et al*., the protective effects of polyphenolic extracts of *Silybum marianum* (*S. marianum*) and *C. intybus* on thioacethamide-induced hepatotoxicity in rat were investigated.

Treatment with the polyphenolic extracts of *S. marianum* and *C. intybus* reduced the level of enzymes activities (ALT, AST and ALP) as well as total bilirubin, when comparing with thioacetamide group[91]. Butt *et al*. evaluated the hepatoprotective potential of *C. intybus* leaf extract on acetaminophen-induced liver damage in albino rats. Extract at a dose of 400 mg/kg body weight exhibited remarkable anti-hepatotoxic activity[92]. The phytochemical and hepatoprotective activities of hydroalcoholic extract of *C. intybus* leaves against nimesulide intoxicated albino rats was conducted by Mushtaq *et al*. It was ascertained that the leaves extracts of *C. intybus* possessed significant hepatoprotective activity[93].

3.20. *Z. vulgaris*

Z. vulgaris known as annab in ITM has been extensively used by Iranian scholars[20]. The protective effect of ethanolic extract of *Z. vulgaris* against hepatic injury induced by CCl_4 in rats has been investigated. Results revealed that although there was a significant decrease in liver enzymes of the treated groups, there were insignificant differences in protein and albumin concentrations between experimental groups. In addition, *Z. vulgaris* treatment reduced hepatic necrosis and portal inflammation compared with the control group. According to both serological and pathological investigations, *Z. vulgaris* showed hepatoprotective impact against CCl_4-induced liver injury[94].

3.21. *C. avellana*

C. avellana known as fandogh in ITM has been endorsed by Sina as an efficient liver tonic[12]. Effects of *C. avellana* in acetaminophen- and CCl_4-induced toxicosis have been investigated by Rusu *et al*. *C. avellana* extract had some beneficial effects in CCl_4 toxicosis: it reduced hepatocytolysis as well as histological lesions and returned the activity of some enzymes to normal values[95,96].

3.22. *C. fistula*

C. fistula known as foloos in ITM was frequently utilized by Persians[12,13,20]. Pradeep *et al*. evaluated the hepatoprotective and antioxidant effect of *C. fistula* leaf extract on DEN-induced liver injury. It was observed that *C. fistula* protected the liver against DEN-induced hepatic injury in rats[97,98]. Bhakta *et al*. investigated the hepatoprotective activity of the *n*-heptane extract of *C. fistula* leaves. The extract at a dose of 400 mg/kg body weight exhibited significant protective effect by lowering serum levels of AST, ALT, bilirubin and ALP. The protective effect was comparable to that of a standard hepatoprotective agent[99,100]. Evaluation of hepatoprotective activity of aqueous extract of *C. fistula* fruit pulp against CCl_4-induced liver damage in albino rats was investigated by Das *et al*. Aqueous extract of fruit pulp of *C. fistula* possessed significant hepatoprotective activity[101].

3.23. *Z. officinale*

Z. officinale known as zanjabil in ITM has been widely used in ancient Iranian medicine[12,20]. The protective effects of the ethanolic extract of *Z. officinale* rhizome on acute hepatotoxicity induced by acetaminophen were studied in plasma and hepatic tissue samples. It showed protective effect against acetaminophen-induced hepatotoxicity. The most satisfactory results were obtained with high doses of plant extract[102,103]. In another study, the effect of ethanolic extract of *Z. officinale* rhizome was tested against CCl_4- and acetaminophen-induced liver toxicities in rats. It was indicated that the rhizome oil of *Z. officinale* could be useful in preventing chemically induced acute liver injury[104,105]. The effect of ginger (*Z. officinale)* upon hepatotoxicity induced by the anticancer drug and ADR in albino rats, was studied by Sakr *et al*. The results depicted that ginger had protective effect against liver damage induced by ADR due to its antioxidant activities[106]. The combination therapy of atorvastatin and *Z. officinale* in rat liver was studied by Heeba and Abd-Elghany. Combination regimens containing *Z. officinale* and low dose of statins could be advantageous in treating hypercholesterolemia patients who are susceptible to liver failure[107]. The protective ability of *Z. officinale* against Hg, Pb and Cd accumulation in liver was examined. It was conceived that *Z. officinale* could affect the bioavailability, elimination and uptake of these metals in a time-dependent way with the highest beneficial reducing effect to Cd followed by Hg and the least protection to Pb in the liver[108].

4. Discussion

Despite the fact that people pay much more attention to their health, they have been involved in controversial health issues in today's society. Considering the fact that liver plays a crucial role in the body, liver failure is now the most common health issue. If it does not work properly, the whole body may encounter severe problems. Viral, autoimmune and metabolic diseases, wrong life style and dietary, cancers, drugs and herbal supplements abuse are some of the common causes of liver injuries. It seems that protecting and strengthening the liver against the above mentioned factors is essential. Meanwhile, finding effectual liver tonics has been emerged as a main issue.

ITM has offered efficient natural healing herbs with successful clinical trials for several diseases. In this review, a wide range of plants frequently used in ITM were presented as liver tonics which could make an immense impact on the preventive strategies in liver protection. It should be noted that all of them have shown satisfactory *in vitro* and *in vivo* hepatoprotective. Although the mechanisms of action have been understood to some extent, thoroughgoing studies would be more advantageous in discovery of drugs with low toxicity. Among various reported herbs in this review, ghafes (*A. eupatoria*), kasni (*C. intybus*), anar (*P. granatum*), darchin

(*C. zeylanicum*), za'feran (*C. sativus*), gole-sorkh (*R. damascena*), and zereshk (*B. vulgaris*) were found to be much more useful and extensively recommended in Persian medical literature.

In spite the fact that ITM possess a valuable source in medicine, current marketed hepatoprotective agents such as milk thistle (*S. marianum*) and general antioxidant supplements, are still prescribed by Iranian physicians. Recently, Iranian scientists have paid more attention to herbal remedies evolved from ITM to develop novel therapeutic agents in their drug discovery researches. In this context, there are various plants such as Gharanfal, Faranjamashk, Kholanjan, Kashoos, Zaranb, Oshnah, Gole-nasrin, Narmeshk, Poodineh koohi, *etc*. which have been traditionally used as liver tonics by Persians, but any investigation has not yet been conducted. We intend to investigate the therapeutic efficacy of these plants and hope to publish the results in our next research articles.

Conflict of interest statement

We declare that we have no conflict of interest.

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Comments

Background

Human liver is one of the most important organs in our body. It has a wide range of functions, including detoxification, protein synthesis, and production of biochemicals which are necessary for digestion. Because of wrong lifestyle and dietary habits, food/drinking contamination, chemical drug abuse, the incidence of liver diseases and/or liver function abnormalities are increasing in the world. Therefore, new hepatoprotective remedies derived from plants are urgent.

Research frontiers

The present manuscript reviewed the plants which have hepatoprotection or antihepatotoxicity ability as liver tonic in Iran.

Related reports

In the current study, authors conducted a comprehensive review of scientific information database and medical sciences databases covering all *in vitro* and *in vivo* studies of medicinal plants as liver tonics and hepatoprotective candidates.

Applications

From the literature survey, it has been found that plants used in Iran are safe to humans. They may be used as an adjuvant for the treatment and prevention of liver injury.

Peer review

This is a valuable review. It introduced plants which have been traditionally used as liver tonics in Iran. This paper will promote the utilization of natural and traditional resources for contemporary health care. Herbal medicines have an extremely valuable, rich, lengthy and extensive practical history.

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