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Medicinal plants with hepatoprotective activity in Iranian folk medicine

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PEER REVIEW

Peer reviewer

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Comments

This is a valuable review. It introduced 15 plants which are used as hepatoprotectives in Iranian folk medicine. 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

There are a number of medicinal combinations in the Iranian traditional medicine which are commonly used as tonic for liver. In this review, we have introduced some medicinal plants that are used mainly for the treatment of liver disorders in Iranian folk medicine, with focus on their hepatoprotective effects particularly against $CC1_4$ agent. In this study, online databases including Web of Science, PubMed, Scopus, and Science Direct were searched for papers published from January 1970 to December 2013. Search terms consisted of medicinal plants, traditional medicine, folk medicine, hepatoprotective, Iran, liver, therapeutic uses, compounds, antioxidant, $CC1_4$, anti-inflammatory, and antihepatotoxic, hepatitis, alone or in combination. *Allium hirtifolium* Boiss., *Apium graveolens* L., *Cynara scolymus*, *Berberis vulgaris* L., *Calendula officinalis*, *Nigella sativa* L., *Taraxacum officinale*, *Tragopogon porrifolius*, *Prangos ferulacea* L., *Allium sativum*, *Marrubium vulgare*, *Ammi majus* L., *Citrullus lanatus* Thunb, *Agrimonia eupatoria* L. and *Prunus armeniaca* L. are some of the medicinal plants that have been used for the treatment of liver disorders in Iranian folk medicine. Out of several leads obtained from plants containing potential hepatoprotective agents, silymarin, β-sitosterol, betalain, neoandrographolide, phyllanthin, andrographolide, curcumin, picroside, hypophyllanthin, kutkoside, and glycyrrhizin have been demonstrated to have potent hepatoprotective properties. Despite encouraging data on possibility of new discoveries in the near future, the evidence on treating viral hepatitis or other chronic liver diseases by herbal medications is not adequate.

KEYWORDS
Medicinal plants, Iran, Compounds, Liver, Therapeutic uses, $CC1_4$

1. Introduction

Liver diseases which are still a global health problem may be classified as acute or chronic hepatitis (inflammatory liver diseases), hepatosis (non inflammatory diseases) and cirrhosis (degenerative disorder resulting in liver fibrosis). Unfortunately, treatments of choice for liver diseases are controversial because conventional or synthetic drugs for the treatment of these diseases are insufficient and sometimes cause serious side effects[1].

Since ancient times, mankind has made use of plants in the treatment of various ailments because their toxicity factors appear to have lower side effects[2]. Many of the currently available drugs

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were derived either directly or indirectly from medicinal plants. Recent interest in natural therapies and alternative medicines has made researchers pay attention to traditional herbal medicine. In the past decade, attention has been centered on scientific evaluation of traditional drugs with plant origin for the treatment of various diseases. Due to their effectiveness, with presumably minimal side effects in terms of treatment as well as relatively low costs, herbal drugs are widely prescribed, even when their biologically active constituents are not fully identified[3].

The utility of natural therapies for liver diseases has a long history. Despite the fact that most recommendations are not based on documented evidence, some of these combinations do have active constituents with confirmed antioxidant, anti-inflammatory, anticarcinogenic, antifibrotic, or antiviral properties. Although a large number of these plants and formulations have been investigated, the studies were mostly unsatisfactory. For instance, the therapeutic values, in most of these studies, were assessed against a few chemicals-induced subclinical levels of liver damages in rodents. The reasons that make us arrive at such a conclusion are lack of standardization of the herbal drugs, limited number of randomized placebo controlled clinical trials, and paucity of traditional toxicologic evaluations[4].

Hundreds of plants have been so far examined to be taken for a wide spectrum of liver diseases[5,6]. Natural products, including herbal extracts, could significantly contribute to recovery processes of the intoxicated liver. According to reliable scientific information obtained from the research on medicinal plants, plants such as *Silybum marianum*, *Glycyrrhiza glabra*, *Phyllanthus* species (amarus, niruri, emblica), and *Picrorhiza kurroa* have been widely and most of the time fruitfully applied for the treatment of liver disorders, exerting their effects via antioxidant-related properties[7-10].

Iranians have been using herbal medicine for the treatment of some common diseases; as a result, a large number of studies have been conducted to suggest new wild medicinal plants in different parts of Iran. Iranian traditional medicine is mostly relied on the consumption of plant materials. One of the important and well-documented utilities of plant products is their use as hepatoprotective agents. There are a number of medicinal combinations in the Iranian traditional medicine which are commonly used as tonic for liver. *Allium hirtifolium* Boiss. (*A. hirtifolium*), *Apium graveolens* L. (*A. graveolens*), *Cynara scolymus* (*C. scolymus*), *Berberis vulgaris* L. (*B. vulgaris*), *Calendula officinalis* (*C. officinalis*), *Nigella sativa* L. (*N. sativa*), *Taraxacum officinale* (*T. officinale*), *Tragopogon porrifolius* (*T. porrifolius*), *Prangos ferulacea* L. (*P. ferulacea*), *Allium sativum* L. (*A. sativum*), *Marrubium vulgare* L. (*M. vulgare*), *Ammi majus* L. (*A. majus*), *Citrullus lanatus* (*C. lanatus*), *Agrimonia eupatoria* L. (*A. eupatoria*) and *Prunus armeniaca* L. (*P. armeniaca*) are some of medicinal plants that have been used mainly for the treatment of liver disorders in Iranian folk medicine.

2. Medicinal plants

2.1. A. hirtifolium

A. hirtifolium from Alliaceae family, commonly known as Persian shallot (moosir in Persian) is endemic to Iran[11]. Based on available pharmaceutical investigations, antioxidant and hepatoprotective effects of *A. hirtifolium* have been also demonstrated. In addition, *A. hirtifolium* extracts had antioxidant properties comparable to or slightly higher than garlic extracts[12].

The commonly known phytochemical compounds identified in *A. hirtifolium* are saponins, sapogenins, sulphur containing compounds (*e.g.* thiosulfinates) and flavonoids including shallomin, quercetin and kaempferol[12]. Alliin, alliinase, allicin, s-allyl-cysteine, diallyl disulphide, diallyltrisulphide, and methylallyltrisulphide are the most important biological secondary metabolites of *A. hirtifolium*[13]. Disulphide and trisulfide compounds are among the most important compounds existing in *A. hirtifolium*[14]. Researches have shown that both the corn and the flower of shallot contain a high density of glycosidic flavonols. Linolenic, linoleic, palmitic, palmitoleic, stearic, and oleic acids have been identified in *A. hirtifolium* oil, as well[15].

Treating rats with hydroalcoholic extract of *A. hirtifolium* could protect liver cells against oxidant effects of alloxan, and consequently caused a significant reduction in serum concentration of alkaline phosphatase (ALP), alanine transaminase (ALT), and aspartate transaminase (AST). Biochemical results have confirmed the usefulness of *A. hirtifolium* extract in decreasing the destructive effects of alloxan on liver tissue, and consequently decreasing the enzymes' leakage into cytosol, which is possibly achieved by herbal antioxidant compounds including flavonoids[12]. It was also reported that consumption of *A. hirtifolium* caused a reduction in AST level compared to the group with a hypercholesterolemic diet[16]. A research on the effect of hydroalcoholic *A. hirtifolium* extract on the level of liver enzymes in streptozotocin-induced diabetic rats indicated that hydroalcoholic extract of *A. hirtifolium* could significantly decrease serum levels of liver enzymes [AST, ALT, ALP and (lactate dehydrogenase) LDH] in a dose-dependent manner. Antioxidant micronutrients in the extract of *A. hirtifolium* may also restore liver damages. Shallomin and other active constituents of *A. hirtifolium* did not produce any adverse effect on the organs such as liver and kidney[17].

2.2. A. graveolens

A. graveolens, commonly known as celery, is an edible plant of the Umbelliferae family that grows mostly in the Mediterranean areas. It has been considered as a medicinal plant for a long time[18,19]. Data obtained from literature reveal that *A. graveolens* has many pharmacological properties such as antifungal, antihypertensive, antihyperlipidemic, diuretic, and anticancer[20-23]. This plant has also been shown to have some other medicinal features including

hyperlipidemic effects as well as antioxidative and hepatoprotective activities[20].

The active constituents are isoimperatorin, isoquercitrin, linoleic acid, coumarins (seselin, osthenol, apigravin, and celerin), furanocoumarins (including bergapten), flavonoids (apigenin, apiin), phenolic compounds, choline, and unidentified alkaloids[21]. *A. graveolens* is full of betacarotene, folic acid, vitamin C, sodium, magnesium, silica, potassium, chlorophyll, and fiber. The essential oil contains deltalimonene and various sesquiterpene[21,22].

Seeds of *A. graveolens* are used in Iranian medicine for liver ailments and disorders, have effects on liver, and exhibit hepatoprotective activities. Examining the antihepatotoxic effect of *A. graveolens* seeds' methanolic extracts on rats' liver showed a significant hepatoprotective activity[21]. The roots open obstruction of the liver and spleen, and help in dropsy and jaundice treatment[23]. Due to apigenin-related anti-inflammatory and antioxidant properties, *A. graveolens* seeds could counteract the pro-oxidant effect of 2-acetylaminofluorine through scavenging superoxide radicals, consequently declining hepatic glutathione-S-transferase (GST) and decreasing release of γ-glutamyl transpeptidase in serum; as a result, *A. graveolens* could be assumed as a potent plant against experimentally induced hepatocarcinogenesis in rats[24]. In addition, different extracts of the plant were examined for their hepatoprotective activity against $CC1_4$-induced hepatotoxicity in albino rats. The methanolic extracts, comparable to silymarin as a conventional drug, exhibited a higher hepatoprotective activity[25]. Another study indicated that the extracts of *A. graveolens* root significantly decreased $CC1_4$-induced acute hepatic injury, increasing the activities of AST and ALT and preventing $CC1_4$-induced acute liver injury[26]. Crude ethanol extract of the whole plant was indicative of anti-inflammatory effects in rats. Furthermore, topical anti-inflammatory effects of *A. graveolens* leaves' extract have been demonstrated by Mencherini *et al*[27]. Significant anti-inflammatory effect of the aqueous and hexane extracts of *A. graveolens* was shown at all doses (100-500 mg/kg body weight). Both extracts presented remarkable anti-inflammatory effect, which confirmed the traditional use of *A. graveolens* in inflammation-associated diseases[28].

2.3. C. scolymus

C. scolymus (artichoke) from Apiaceae family, a species of perennial thistle and with a Mediterranean origin, is traditionally used for the treatment of digestive disorders, moderate hyperlipidemia, and liver and bile diseases. The leaf extract of *C. scolymus* has been used for its hepatoprotective effects[29]. Also, *C. scolymus* extract could yield nutritional supplements with antioxidant and antimicrobial effects[30]. In *C. scolymus* leaf extract, there are compounds such as cynarin, luteolin, chlorogenic acid, and caffeic acid, other flavonoids, and polyphenol compounds, some of which have antioxidant properties. *C. scolymus* leaf extract also positively affected the changes in rat serum liver enzyme induced by $CC1_4$ and histopathological damage to liver tissue[31]. In rats pretreated with artichoke extract, plasma transaminase activities significantly decreased and histopathological changes in the liver ameliorated[32]. *C. scolymus* can be conducive to the reduction in phosphatidate phosphohydrolase activity and liver triglyceride. *C. scolymus* has benefits for controlling of hyperlipidemia, oxidative stress in hyperlipidemic regimes, and abnormalities in lipid profiles[33]. In the rabbits intoxicated with $CC1_4$, *C. scolymus* leaf extract counteracted the toxic effect of $CC1_4$, blood sugar, cholesterol, triglycerides, leukocytes, and a number of erythrocytes[34]. In other studies, *C. scolymus* was significant in keeping the normal liver function parameters, maintained the hepatic redox status as it is manifested by significant increase in antioxidant enzyme activities and reduction in glutathione accompanied by inhibition of lipid peroxidation (LPO) and protein oxidation, decreased nitric oxide and tumor necrosis factor alpha, and stabilized membrane in the untreated paracetamol-intoxicated rats[35].

2.4. B. vulgaris

B. vulgaris (barberry), a well known medicinal plant in Iran and also a food, belongs to Berberidaceae family. As a shrub with 1 to 3 meters in height, *B. vulgaris* grows in many regions of the world, including Iran (especially Khorasan)[36]. Fruit, leaves, and stem have medical usages including hepatoprotection. *B. vulgaris* fruit extract contains various flavonoids that act as antioxidant[37]. Berberine, oxyacanthine, and other alkaloids such as berbamine, palmatine, columbamine, malic acid, jatrorrhizine, and berberrubine comprise some other compounds[38]. Stigmasterol, terpenoids lupeol, oleanolic acid, stigmasterol glucoside and polyphenols were also identified in this plant[39]. Berberine, an isoquinoline alkaloid with a long medicinal history, exists in roots, rhizomes, and stem bark of the plant. Berberine inhibits potassium and calcium currents in isolated rat hepatocytes. It has hepatoprotective effects, both preventive and curative, on $CC1_4$-induced liver injury through scavenging the peroxidative products. $CC1_4$ significantly increased the serum alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase levels in rats. Treatment with the methanolic extract of *B. vulgaris* fruit significantly helped these changes reach to an almost normal level. In addition, the extract could prevent $CC1_4$-induced liver oxidative damage in rats[40]. Domitrović's study was indicative of berberine's effect on protecting the liver from $CC1_4$-induced injury. The hepatoprotective mechanisms of berberine could be attributed to the free radical scavenging, decline in oxidative/nitrosative stress, and the inhibition of inflammatory response in the liver[41]. In addition, *B. vulgaris* extract/β-cyclodextrin exhibited better hepatoprotective effects than free extract on oral administration possibly due to greater bioavailability. Formulated extract could be used as an economical phytotherapeutical supplement that is helpful for chronic or acute conditions or a support for routine therapies

of serious hepatic disorders. In Hermenean's study, pre-treatment with formulated or non formulated extract prevented the increase in ALT, AST, and malondialdehyde (MDA) levels, and helped the level of antioxidant enzymes return to normal values. According to histopathological and electron-microscopic examination, in both pre-treated groups, more moderate damage in liver was observed with a more pronounced protective effect after administration of the formulated extract[42].

2.5. C. officinalis

C. officinalis (marigold), from Asteraceae family, is a medicinal plant and cosmetic herb popularly known in Europe and the USA. The dried flower heads or the dried ligulate flowers of this plant are used for pharmaceutical and/or cosmetic purposes[43]. Antibacterial, anti-inflammatory, antiviral, and antioxidant activities have been already noted for *C. officinalis*[44]. It has been taken in order to treat fevers and jaundice and to promote menstruation. Extracts, tinctures, balms, and salves of *C. officinalis* have been applied directly to heal wounds and soothe inflamed and injured skin. *C. officinalis* compounds, which are potentially active chemical constituents, are monoterpenes, such as α-thujene and T-muurolol, sesquiterpene and flavonol glycosides, triterpene alcohols, triterpenoid saponins, flavonoids, carotenoides, xanthophylls, phenolic acids, mucilage, bitters, phytosterols, tocophrrols, calendulin, resin, and volatile oil[45,46]. The anti-inflammatory features of *C. officinalis* flowers, according to *in vivo* pharmacological tests, have been associated with the triterpenoid fatty acid esters[43]. In Singh's study, 80% effect of methanolic extract of leaves (500 mg/kg orally, four doses at 12 hours interval) of *C. officinalis* was investigated against acetaminophen-induced hepatic damage in albino rats. The potential hepatoprotective effects of *C. officinalis* extracts against $CC1_4$-induced oxidative stress and cytotoxicity in isolated primary rat hepatocytes were detected[46], confirmed by significant improvement in cell viability and enzymes leakages (ALT, AST, and LDH). Also, the reduction of hepatocytolysis and steatosis, and return to normal values of various enzymes activity could be attributed to hepatoprotective effects[47]. *C. officinalis* plant extracts significantly improved cell survival, contributing greatly to preserving the cellular membranes integrity against $CC1_4$. Moreover, plant extracts of *C. officinalis* protect the intracellular antioxidant defense system, indicated by preserving GST and inhibiting LPO[48]. Protective role of the flower extract of *C. officinalis* against $CC1_4$- induced acute hepatotoxicity and cisplatin-induced nephrotoxicity has been shown[49]. Possible mechanism of action of the flower extract may be due to its antioxidant activity and reduction of oxygen radicals[50].

2.6. N. sativa

N. sativa is an aromatic plant of Ranunculaceae family, traditionally used by the Middle East nations for asthma, cough, bronchitis, headache, rheumatism, fever, influenza, and eczema. Several biological activities, including antioxidant activity and resolution of hepato-renal toxicity have been reported for *N. sativa* seeds[51]. *N. sativa* contains more than 30 fixed oils. The volatile oil has been proved to contain thymoquinone and many monoterpenes such as p-cymene and α-pinene. The $CC1_4$ treatment increased the LPO and liver enzymes, and decreased the antioxidant enzyme levels. *N. sativa* treatment helped the elevated LPO and liver enzyme levels decrease and the reduced antioxidant enzyme levels increase[52]. The levels of liver enzymes and total oxidative status, oxidative stress index, and myeloperoxidase in treated mice were significantly lower, and total antioxidant capacity in liver tissue was significantly higher compared to the controls[53]. *N. sativa* is useful in the treatment of rheumatism and related inflammatory diseases and the anti-inflammatory effect was confirmed in rats[54]. Also, the aqueous extract of *N. sativa* has an anti-inflammatory effect demonstrated by its inhibitory effects on carrageenan-induced paw edema[51]. Pretreatment of mice with 12.5 mg/kg thymoquinone (an *N. sativa* derived-compound) significantly reduced the elevated levels of serum enzymes as well as hepatic MDA content and significantly increased hepatic nonprotein sulfhydryl(-SH)[55]. *N. sativa* contributes to inhibition of enzymes present in the neoglucogenesis pathway in the liver[56].

2.7. T. officinale

T. officinale (from Asteraceae family), commonly known as dandelion, grows almost everywhere in the world[57]. With a long history of traditional use in the treatment of hepatobiliary problems, its root has been shown to have sesquiterpene lactones, triterpenes, carbohydrates, fatty acids (myristic), carotenoids (lutein), flavanoids (apigenin and luteolin), minerals, taraxalisin, coumarins, and cichoriin. Aesculin has been reported from the leaf. Germacrane- and guaiane-type sesquiterpene lactones including taraxinic acid derivatives were obtained from the roots of this plant[58]. Also, several flavonoids, *e.g.* caffeic acid, chlorogenic acid, luteolin, and luteolin 7-glucoside, have been isolated from the dandelion[59]. Ethanolic extract of *T. officinale* was effective on decrease in serum ALT levels[58]. Hydroalcoholic acid extract of the root enhanced levels of superoxide dismutase (SOD), catalase (CAT), GST, and LPO[60]. Oral administration of extracts of the *T. officinale* roots has proved to increase bile flow[1]. Another study distinguished that treatment with root extract of *T. officinale* was effective on reduction of serum ALT and ALP levels in rats[61]. Root extract reduces serum AST, ALT, ALP, and LDH activities and increases hepatic antioxidant activities such as CAT, GST, glutathione reductase, glutathione peroxidase, and glutathione. Thus, aqueous extract of *T. officinale* root protects against alcohol-induced toxicity in the liver by elevating antioxidativity and decreasing LPO. Sesquiterpene lactones in the plant have a protective effect against acute hepatotoxicity induced by the administration of $CC1_4$ in mice, which was indicated by reduced

levels of hepatic enzyme markers, such as serum transaminase (ALT, AST), ALP, and total bilirubin[62].

2.8. T. porrifolius

T. porrifolius, belonging to Asteraceae family and known as purple salsify, is grown up for its edible root and shoot[63]. It has bioactive compounds which prevent cancer or other free radical-associated illnesses. The nutritional value of this plant is derived from monounsaturated and essential fatty acids, polyphenols, vitamins, and fructo-oligosaccharides, having probiotic effects on the intestinal microflora. The most abundant compounds of this plant include 4-vinyl guaiacol (19.0%), hexadecanoic acid (17.9%), hexahydrofarnesylacetone (15.8%), and hentriacontane (10.7%)[64,65]. *T. porrifolius* has apparently yielded the hepatogenic/hepatoprotective effects against liver diseases or hepatotoxicity induced by a variety of hepatotoxic agents such as chemicals, drugs, pollutants, and infection with parasites, bacteria, or viruses (hepatitis A, B, and C). These beneficial effects of plants are related to the polyphenolic compounds. The study of antioxidant activity of the methanolic extract of the aerial part of *T. porrifolius* as well as its protection against $CC1_4$-induced hepatotoxicity in rats showed a dose-dependent increase in the activity of liver antioxidant enzymes. About 250 mg/kg body weight dose increased the activity of CAT, SOD, and GST. Also, substantial hepatoprotective capacity against $CC1_4$-induced hepatic injury has been shown, attributable to restoring the activity of AST, ALT, and LDH to normal levels[63,66]. Investigation of the effects of water extract of *T. porrifolius* shoot on lipemia, glycemia, inflammation, oxidative stress, hepatotoxicity, and gastric ulcer using a rat model showed that after one month of *T. porrifolius* water extract intake, a significant decrease in the levels of serum cholesterol, triglyceride, glucose, and liver enzyme (ALP, ALT, and LDH) was observed. Pretreating rats with *T. porrifolius* extract demonstrated considerable anti-inflammatory effects in both acute and chronic inflammation caused by carrageenan and formalin. In addition, *T. porrifolius* revealed effective antioxidant capability owing to its remarkable scavenging activity[67].

2.9. P. ferulacea

P. ferulacea from Apiaceae family grows in Southern Iran and is used in Iranian herbal medicine mainly for gastrointestinal disorders. The genus of *Prangos* with the common Persian name of Jashir includes 15 species, occurring widely in many regions of the country. In addition to Iran, other species of this genus are distributed in East Europe to Turkey, Caucasia, and Central Asia. *P. ferulacea* has been used in folk medicine as carminative, emollient, and tonic for gastrointestinal disorders, antiflatulent, sedative, anti-inflamatory, anti-viral, antihelminthic, antifungal, and antibacterial. Monoterpenes, sesquiterpenes, coumarines, flavonoids, alkaloids, tannins, saponins, and terpenoids are some important compounds identified in this plant. *P. ferulacea* was shown that the oils (both fruit and leaf essential oils) were rich in monoterpenes, specially α-pinene, and β-pinene. Some of these components have an antioxidant effect against oxidative stress. In a study, the protective and antioxidant effects of *P. ferulacea* are reported to be higher compared to α-tocopherol (vitamin E) and the effect of GST has been demonstrated. The study of effects of *P. ferulacea* hydroalcoholic extract on changes in rats´ liver structure and serum activities of ALT and AST after alloxan injection indicated that in diabetic rats, the serum ALT and AST significantly increased. Moreover, necrosis of hepatocytes, cytoplasmic vacuolations, and lymphocytic inflammation were observed. Diabetic rats treated by root extract of *P. ferulacea* in contrast to the diabetic group exhibited a significant decrease in these enzymes. Also, root hydroalcoholic extract of *P. ferulacea* was shown to affect changes in aminotransferases and to prevent the histopathological changes of liver related to alloxan-induced diabetes in rats[68-71].

2.10. A. sativum

A. sativum (garlic) is one of the world's most known medicines that have been used for flavouring and as a medical herb mainly due to its prophylactic and therapeutic capacities. Garlic from Alliaceae family has known nutritional properties, particularly for its bioactive components, and is used as antidiabetic, anti-inflammatory, antihypertension, antimicrobial, antiatherosclerotic, and hepatoprotective in different diet-oriented therapeutical regimes to heal various lifestyle-associated disorders[72]. Garlic and its supplements are taken in many cultures for their hypolipidemic, antiplatelet, and procirculatory effects. In Iran, it is known for being useful for gastrointestinal disorders. In addition, some garlic combinations may be immune-enhancing and chemopreventive. Some combinations could be antioxidative while others may stimulate oxidation. Sapogenins, saponins, sulphuric compounds, and flavonoids have been detected in different species of *Allium* genus[12]. Additional biological effects attributed to garlic extract may be due to S-allylcysteine, S-allylmercaptocysteine, and N (alpha)-fructosyl arginine that are formed throughout the extraction[72]. Most garlic's beneficial effects are due to organosulphate molecule allicin[73]. The hepatoprotective effect of garlic extracts on Cd-induced oxidative damage in rats has been reported. *A. sativum* extract decreased hepatic activities of ALT, AST, and alkaline phosphatase and simultaneously increased the plasma activities of ALT and AST. Cd-induced oxidative damage in rat liver is predisposed to decreasing by moderate dose of *A. sativum* extracts probably through reduced LPO and improved antioxidant defense system that could not prevent and protect Cd-induced hepatotoxicity[74]. *A. sativum* chemical compounds have curative effects on iron liver excess[75]. In another study, the hepatoprotective effects by *A. sativum*, ginger (*Zingiber officinale*), and vitamin E against $CC1_4$-induced liver damage were examined in male Wistar albino rats. Serum alanine amino transferase, aspartate amino transferase, and alkaline phosphatase levels decreased significantly

24 h after $CC1_4$ administration in rats pretreated with garlic, ginger, vitamin E, and various mixtures of garlic and ginger compared to the rats treated with only $CC1_4$. LPO expressed by serum MDA was assayed to assess the severity of liver damage by $CC1_4$, including the extent of hepatoprotection by garlic, ginger, and vitamin E. MDA concentration was significantly decreased in rats pretreated with garlic, ginger, vitamin E, and various mixtures of garlic and ginger compared to the rats administered by $CC1_4$ alone. Histological examination of the liver was indicative of severe infiltration of inflammatory cells in rats treated with $CC1_4$ alone although the change in the normal architecture of the hepatic cells decreased considerably in pre-treated rats[76]. The hepatoprotective activity of *A. sativum* extract at a dose of 300 mg/kg body weight, administered intraperitoneally for 14 d before the induction of D-galactosamine and lipopolysaccharide (DGalN/LPS) was investigated against DGalN/LPS-induced hepatitis in rats. Pretreatment with aqueous *A. sativum* extract helped the altered parameters (ALT , AST, ALP, LDH, gamma glutamyl transferase, bilirubin, LPO, tumor necrosis factor, and myeloperoxidase activity level, total cholesterol, triglycerides, free fatty acids, and antioxidant enzyme activities) reach to nearly normal control values. Aqueous *A. sativum* extract could afford a significant protection in the DGalN/LPS-induced hepatic damage easing[77]. An investigation of chemopreventive effects of *A. sativum* extract and silymarin on N-nitrosodiethylamine and $CC1_4$-induced hepatotoxicity in male albino rats indicated synergistic effect of silymarin and *A. sativum*, and their hepatoprotective features against hepatotoxicity[78].

The main part of therapeutic effect of *A. sativum* is attributed to antioxidant compounds, probably associated with its phenolic compounds and flavonoid substances. *A. sativum* (irrespective of the processes such as baking) has phenolic, flavonoid, and flavenol compounds as well as allicin[79]. The effect of fresh *A. sativum* on inhibiting the oxidation was higher compared to three-month *A. sativum*. Phenolic compounds of the fresh *A. sativum* were higher than the three-month *A. sativum*. The amount of allicin was 15 μg/mL and 8 μg/mL in fresh and three-month dated aqueous *A. sativum* extract, respectively.

A. sativum could play a crucial role in prevention and control of some cancers. The phenolic compounds and antioxidant activity of *A. sativum* aerial parts are less in comparison to *A. sativum* itself; however, higher doses might have anticancer features. Also, *A. sativum* had anticancer activity against WEHI-164 tumor cells, and some processes such as heating reduced the effect noticeably. The anticancer activities of different kinds of *A. sativum* may be related to the level of allicin, flavonoids, and phenolic components. Therefore, fresh *A. sativum* has bioactive components and hence anticancer efficacy[80].

2.11. M. vulgare

M. vulgare, from Lamiaceae family, commonly known as ''horehound'', is a commonplace Mediterranean plant traditionally used to treat various diseases. The plant possesses antihypertensive, analgesic, anti-inflammatory, and hypoglycemic effect, antidyslipidemic activity, and antioxidant properties[2,81]. Antimicrobial activity against Gram positive bacteria, analgesic properties, and antihypertensive, antidiabetic, and antioxidant properties were noted, particularly related to diterpenes, sterols, phenylpropanoids, and flavonoids. Totally 46 compounds, comprising 96.3% of the oil, were detected. The main components of the oil were (E)-caryophyllene, germacrene D, and bicyclogermacrene. Evaluation of the antihepatotoxic and antioxidant properties of the extract against $CC1_4$-induced hepatic damage in rats showed a significant antihepatotoxic effect via significantly reducing AST, ALT, and LDH[82]. In another study, aqueous extract of the whole plant was examined for antihepatotoxic activity against $CC1_4$-induced hepatic damage in male Wistar rats. The extract at 500 mg/kg body weight dose for 7 d was compared with the standard drug silymarin at 10 mg/kg body weight dose. The aqueous extract had significant antihepatotoxic activity and reduced the elevated levels of serum enzymes such as serum glutamic-oxaloacetic transaminase, serum glutamic pyruvic transaminase, and ALP and increasing total protein[83]. Some studies also reported the antioxidant effect of free radical scavengers in the extract thanks to flavonoid content[2,82].

2.12. A. majus

A. majus from Apiaceae family was originated from Asia and is a 0.30 to 0.60 meter high, annual plant with ascending branches and leaves that are finely dissected into filiform segments. The inflorescence is umbellate with small white flowers. The involucels are of different linear bracts and the involucral bracts are pinnately parted. The main toxins are the furocoumarins. All parts of the plants, in particular the seeds, could be phototoxic to cattle, sheep, fowl, and humans after ingestion or skin contact and subsequent exposure to sunlight. *A. majus* is a local medicinal plant with fruits that are contraindicated in nursing, pregnancy, tuberculosis, liver and kidney diseases, human immunodeficiency virus, and other autoimmune diseases. It is commonly used for skin disorders such as psoriasis and vitiligo. *A. majus* is contraindicated in diseases associated with photosensitivity, cataract, invasive squamous-cell cancer, known sensitivity to xanthotoxin, and in children under the age of 12[84]. *A. majus* concomitantly accumulates various 7-O-prenylated umbelliferones as the predominant coumarines[85]. It is considered as a source of 6-hydroxy-7-methoxy coumarine which is known as the major coumarin. *A. majus* with confirmed antioxidant effect could be used in diabetic nephropathy and myocardial injury thanks to different active compounds such as quercetine, kaempferol, and marmesinin that inhibit cytochrome P450 such as xanthotoxin bergapten, imperatorin, and isoimpinellin. Treatment of rats with different doses of *A. majus* seeds' extract could cause hepatoprotective effects against $CC1_4$-induced liver damage, in a dose-dependent fashion[86].

2.13. C. lanatus

C. lanatus (from Cucurbitaceae family) is used in traditional herbal medicine. Its fruits are eaten as a febrifuge when fully ripe or almost putrid. The fruit is also diuretic and helpful for the treatment of dropsy and renal stones. The rind of the fruit is prescribed for alcoholic poisoning and diabetes. *C. lanatus* contains bioactive compounds including cucurbitacin, triterpenes, anthraquinones, sterols, alkaloids, flavanoids, saponins, tannins, flavones aglycone, and simple phenols[87]. The aqueous extract of *C. lanatus* is believed to be a good source of glucose, fibre, vitamin C, lycopene, and beta carotene. Epidemiologically, antioxidant may reduce or inhibit the effect of oxidative stress in tissues. Watermelon juice at 120 g/70 kg body weight of rats decreased SOD activity and low density lipoprotein-cholesterol, and increased CAT and high density lipoprotein-cholesterol, which could indicate its antioxidant effects[88]. The majority of cucurbitacin has cytoprotective activity on $HepG_2$ cells. Cucurbitacin was demonstrated to have high potential as liver anti-fibrosis agent[89]. Studies have been done to investigate the effect of *C. lanatus* juice on LPO in rat's liver, kidney, and brain. *In vivo* administration of $CC1_4$ once a week for 28 d caused a significant increase in serum markers of liver damage, AST, ALT, and total bilirubin, and decline in albumin compared to the control group. However, administration of $CC1_4$ with watermelon juice or ursodeoxycolic acid attenuated these changes significantly. LPO level increased in the liver, kidney, and brain tissues after $CC1_4$ administration. However, watermelon juice and ursodeoxycolic acid treatment prevented increase in LPO. According to the results, watermelon juice protects the liver, kidney, and brain tissues from *in vitro* $CC1_4$ toxicity in rats probably thanks to the antioxidant activity and inhibition of lipid peroxide formation. Together, biological evidence supports watermelon juice usefulness in the treatment of chemical-induced hepatotoxicity[90].

2.14. A. eupatoria

A. eupatoria (from Rosaceae family) is 35-120 cm high, semiorbicular, and rather thick, with densely hirsute stems, herbaceous stipules, coarsely acutely serrated or lobed margins, and pilose and pubescent petiole. The leaf blade is interrupted imparipinnate with 3-5 pairs of leaflets[91]. *A. eupatoria* grows on clay soils. In popular medicine, it is employed for the treatment of several disorders, *e.g.* inflammations. The aqueous extract of *A. eupatoria* is full of several phenolic compounds and its ethyl acetate fraction has exhibited antioxidant activity and lower toxicity[92]. *A. eupatoria* is rich in coumarins, flavonoids, tannins, terpenoids, and phenolic compounds including protocatechuic acid, coumaric acid, chlorogenic acid, quercitrin, and gallic acid[93]. *A. eupatoria*, a medicinal herb, caused effects on the liver cells in a preliminary study. However, the active components and the biologic effect of *A. eupatoria* on liver tumor remain to be fully elucidated. The hepatoprotective effects of *A. eupatoria* on hepatocarcinogenesis induced by diethylnitrosamine and $CC1_4$ were studied in the *in vivo* models. There is evidence on the biologic actions of *A. eupatoria* and its benefits for liver tumor therapy. The hepatoprotective effects of *A. eupatoria* water extract against ethanol-induced liver injury have been already shown. Animals were treated orally with *A. eupatoria* extract at 10, 30, 100, and 300 mg/kg/day doses. After ethanol chronic consumption, serum aminotransferase activities and proinflammatory cytokines pronouncedly increased, although attenuated by *A. eupatoria* extract. The cytochrome P450 activity and LPO also increased after ethanol consumption while glutathione concentration decreased. *A. eupatoria* extract ameliorates chronic ethanol-induced liver injury, and protection likely relates to the suppression of oxidative stress and toll-like receptor-mediated inflammatory signaling[94]. Hepatoprotective effects of aqueous extract of *A. eupatoria* were investigated in experimental liver-damaged models. Hepatoprotective effects of the plant were monitored by reducing serum AST and ALT levels[95].

2.15. P. armeniaca

The *P. armeniaca* (commonly called apricot) belongs to the Rosaceae family, with many medicinal properties. It has organic acids, salicylic acid, tannins and potassium salts, pcoumaric acid, and protocatechuic, ferulic, and diferulic acids. The plant is used as antitussive and antiasthmatic, with hepatoprotective effects[96]. The plant has two new flavonoid glycosides, 4', 5, 7-trihydroxy flavone-7-O-[β-D-mannopyranosyl (1'''→2'')]-β-D-allopyranoside and 3, 4', 5, 7-tetrahydroxy-3, 5'-di-methoxy flavone 3-O-[α-Lrhamnopyranosyl (1'''→6'')]-β-D-galactopyranoside[97]. Fruit of the plant is rich in carotenoids, flavonoids, and phenols. Hepatoprotective effect of ground apricot kernel (GAK) (0.5,1 and 1.5 mg/kg/body weight/rat) was examined in rats injected with 10 mg/kg dimethylnitrosamine, demonstrating that the GAK-supplemented diet resulted in improving liver function, liver CAT, SOD, and GST and hence reducing AST, ALT, and MDA, which was confirmed by liver histology. Hierarchically high levels of GAK (1.5 mg/kg/body weight/rat) yielded the best results compared to other tested levels[98]. Animal studies have shown that *P. armeniaca* administration to rats with chronic ethanol feeding decreases the levels of ALT and AST in the serum, which reduces oxidative stress and LPO in the liver by increasing the levels of antioxidant enzymes. Studies showed that supplementation of β-carotene prevented ethanol-induced increase in the serum aminotransferases and inhibited the depletion of the antioxidant molecule GST in the liver. Additionally, *in vitro* studies on the hepatocytes isolated from the ethanol-fed rats indicated that β-carotene enhanced the cell viability, and increased CAT activity and level of GST. In mechanistic studies performed on hepatocytes isolated from the rats fed with ethanol, β-carotene ameliorated the oxidative stress, enhanced antioxidant, and decreased the expression of CYP2E1 and apoptosis. Lutein and meso-zeaxanthin present in *P. armeniaca* in small quantities are effective on treatment of alcohol-induced damage. Administering lutein and meso-zeaxanthin, compared to alcohol, reduced the serum levels of aminotransferases, alkaline phosphatase, and bilirubin to decrease the levels of LPO, conjugated diene, and hydroperoxides in rat liver. Based on histopathological studies, administering

ethanol-treated rats with lutein and meso-zeaxanthin reversed the histopathological abnormalities and reduced hydroxyproline, which is an indicator of fibrosis[99]. *P. armeniaca* fed to Wistar rats decreased oxidative stress and enhanced histological damage; its dietary intake can reduce the risk of liver steatosis caused by free radicals[100]. Examining hepatoprotective effect and antioxidant role of sun, sulphited-dried *P. armeniaca*, and its kernel against ethanol-induced oxidative stress indicated that administration of sun, sulphited-dried apricot, but not its kernel, supplementation restored the ethanol-induced imbalance between MDA and antioxidant system towards nearly normal values particularly in tissues. Altogether, apricot has a hepatoprotective effect in rats fed with ethanol, probably through the antioxidative defense systems[101]. *P. armeniaca* feeding had beneficial effects on $CC1_4$-induced liver steatosis and damage probably due to its antioxidant nutrient (beta-carotene and vitamin) contents and high radical-scavenging activity[102].

3. Conclusion

The protective effect of these plants' extract against $CC1_4$ may be related to polyphenolic compounds, terpenoids, alkaloids, coumarines, phytosterols, *etc*. Polyphenolic compounds such as flavonoids can protect the cells against emptying reduced glutathione via increasing the capability of antioxidant enzymes (such as CAT, SOD and glutathione peroxidase). Flavonoids, which act as antioxidant, free radical scavenging and antilipoperoxidant agents, are helpful for hepatoprotection. Furthermore, these compounds with antioxidant properties can counteract free radicals in the environment and therefore avoid their destructive effects. Terpenoids such as carotenoids with antihepatotoxic activity are also known as antioxidants. Ursolic acid is a triterpene, with potential hepatoprotective effects. Also, out of several leads obtained from plants containing potential hepatoprotective agents, silymarin, β-sitosterol, betalain, neoandrographolide, phyllanthin, andrographolide, curcumin, picroside, hypophyllanthin, kutkoside, and glycyrrhizin have been demonstrated to have potent hepatoprotective properties. Silymarin and glycyrrhizin were significantly effective on treatment of hepatitis, alcohol-associated liver disease, and cirrhosis. β-sitosterol showed anti-inflammatory, antioxidant, angiogenic, and proliferative effects. Betalain-containing species are used as common medicines for various diseases (*e.g.* hepatic disorders, malaria, jaundice and scanty urine). Betalains can act as antioxidant, anticancer, antiviral, and antiparasitosis.

Despite encouraging data on possibility of new discoveries in the near future, evidence on treatment of viral hepatitis or other chronic liver diseases by herbal medications is not adequate. Therefore, herbal medications should be recommended within the setting of more finely-conducted clinical trials. Better training of both patients and physicians about herbal preparations seems necessary.

Conflict of interest statement

The authors declare no conflict of interest.

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Comments

Background

The human liver is one of the most important organs in the body. It has a wide range of functions, including detoxification, protein synthesis, and production of biochemicals necessary for digestion. Because of wrong lifestyle and dietary habits, food/drinking contamination, and chemical drug abuse, the incidence of liver diseases and/or liver function abnormalities is increasing in the world. Therefore, there is need of new hepatoprotective remedies, including herbal/folk medicines.

Research frontiers

The present manuscript reviewed the plants which have hepatoprotection or antihepatotoxicity, liver tonic, in Iranian folk medicine.

Related reports

In this study, online databases including Web of Science, PubMed, Scopus, and Science Direct were searched for papers published from January 1970 to December 2013.

Innovations and breakthroughs

It is well known that there are many plants/herbs that have hepatoprotective action in the world. In the present study, authors have reviewed the hepatoprotective activity of folk medicines in Iran.

Applications

From the literature survey, it has been found that Iranian folk medicine may be used as an adjuvant for the treatment and prevention of liver injury.

Peer review

This is a valuable review. It introduced 15 plants which are used as hepatoprotectives in Iranian folk medicine. 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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