REVIEW ARTICLE

Folklore medicinal plants used in liver disease: A review

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Abstract

The liver is the largest organ of the body and the main site of essential biochemical reactions in the human body. This is useful for detoxification of toxic substances and the production of biological molecules. Therefore, liver damage leads to severe consequences. Because herbs and herbal antioxidants are used to detoxify and treat liver disorders, this review was conducted to report the most important medicinal plants affecting liver disorders and diseases. Key terms liver cancer, medicinal plants, liver disorder and medicinal plants, liver disease and medicinal plants, effect of extract and essential oil of effective medicinal plants on liver tissues in rats, mice, and laboratory mice, and effect of extract and essential oil of medicinal plants on liver disease were used to retrieve relevant publications indexed in databases IranMedex, Irandoc, ISI, PubMed, Scopus, SID, Magiran, and Google Scholar. Based on the evidence found in this review, the medicinal plants *Zingiber officinale*, *Cucurbita pepo*, *Citrus reticulate*, *Petroselinum crispum*, *Andrographis paniculata*, *Silybum marianum*, *Camellia sinensis*, *Nasturtium officinale*, *Physalis peruviana*, *Thonningia sanguinea*, *Nigella sativa*, *Cichorium intybus* L., *Terminalia catappa*, *Glycyrrhiza glabra*, *Curcuma zanthorrhiza*, *Hibiscus sabdariffa*, *Vaccinium vitis-idaea*, *Salvia miltiorrhiza*, *Kigelia africana*, *Alchornea cordifolia*, *Boerhavia diffusa*, *Schisandrae chinensis*, *Tinospora cordifolia*, *Brassica rapa* subsp. rapa, *Lygodium flexuosum*, *Carica papaya*, *Solanum fastigiatum*, and *Cheilanthes farinosa* are some of the most important medicinal plants affecting liver disorders and diseases.

Key words: Liver cancer, liver disease, liver disorder and medicinal plants, medicinal plants, medicinal plants

INTRODUCTION

The liver is the largest organ of the body and the main site of essential biochemical reactions in the human body. This is useful for detoxification of toxins and the production of biological molecules. Thus, liver damage leads to severe consequences.[1,2] The liver plays an important role in many essential physiological processes such as glucose homeostasis, the production of essential proteins, the production of lipoprotein and lipids, the production and secretion of bile acids, and vitamin storage.[3] This damage is caused by chronic alcohol abuse, viral hepatitis, or inherited metabolic disorder. Liver damage is associated with cell necrosis, fibrosis, increase in tissue lipid peroxidation, and decrease in tissue glutathione levels. Most toxic chemicals cause damage to the hepatocytes by inducing lipid peroxidation and other oxidative effects.[4] Antioxidants have also shown to reduce this toxicity.[5,6] Natural antioxidants in many compounds are classified as secondary metabolites. For example, polyphenols (phenolic acids and flavonoids) and terpenoids (carotenoids) and the consumption of foods containing these compounds in large quantities play an important role in preventing many diseases.[7,8] Remedies derived from plant extracts are increasingly used to treat

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Table 1: A number of anti-liver cancer medicinal plants and additional information

Scientific Name	Part of plant	Family name	Common name	Origin of plant	Country of study	Year	Result	Ref.
Zingiber officinale	Root (aqueous extract)	Zingiberaceae	Ginger	In Indian subcontinent to Southern Asia, Chine	Cairo, Egypt	2016 *in vitro*	*Zingiber officinale* root aqueous extract may exert hepatoprotective effects against aspartame, which may cause hepatotoxicity and oxidative stress. *Zingiber officinale* root extract exerts hepatoprotective effects against aspartame-induced hepatotoxicity and reduces liver damage markers (ALT, AST, ALP, and γ-GT), total serum protein, total albumin and bilirubin levels, serum LDH activity, α-photoprotein, and TNF, which increases the levels of antioxidant enzymes and reduces the level of MDA	[17]
Cucurbita pepo	Seeds	Cucurbitaceae	Pumpkin	North America	Cairo, Egypt	2016 *in vitro*	*Cucurbita maxima* oil plays an important role in protecting against alcohol hepatotoxicity and alcohol-induced oxidative stress. Prevention using *Cucurbita maxima* oil may have diverse hepatoprotective effects including oxidation, anti-lipid peroxidation, detoxification, and protection against glutathione removal	[17]
Citrus reticulata	Fruit	Rutaceae	Mandarin	Particularly from Japan, and in Canada, the United States, and Russia	Cairo, Egypt	2016 *in vitro*	Rutin (quercetin rutinoside) is a flavonoid glycoside. Hesperidin is a flavanone glycoside (flavonoid $C_{28}H_{34}O_{15}$), which is found abundantly in citrus fruits. Hesperidin plays an important role in preventing doxorubicin-induced hepatotoxicity by improving the activity of the liver enzymes (ALT, AST, ALP, and GGT) in addition to improving total bilirubin, albumin, and sialic acid levels. Rutin and hesperidin significantly increase the activity of liver glutathione, glutathione peroxidase, and glutathione S-transferase and peroxidase, and reduce lipid peroxidation levels. Preventive treatment with rutin and hesperidin may protect the liver against doxorubicin-induced hepatotoxicity	[17]
Petroselinum crispum	Leaves and flowers	Apiaceae	Parsley or garden parsley	Native herb of the central Mediterranean region (Southern Italy, Algeria, and Tunisia).	Cairo, Egypt	2016 *in vitro*	*Petroselinum crispum* oil plays an important role in exerting an effect on the liver function enzymes, and antioxidant and anti-lipid peroxidation effects, which increases detoxification and protects against glutathione reduction against chemical toxicity due to alcohol and oxidative stress	[17]

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Table 1: (*Continued*)

Scientific Name	Part of plant	Family name	Common name	Origin of plant	Country of study	Year	Result	Ref.
Andrographis paniculata	Aerial parts	Acanthaceae	King of bitters	Native to India and Sri Lanka. It is widely cultivated in Southern and Southeastern Asia	Cairo, Egypt	2016 *in vitro*	The plant has antidiabetic and antitumor activity. Treatment with the total extract of *Andrographis paniculata* effectively reduces the level of lipid peroxidation and increases the level of antioxidant enzymes, which is due to the presence of various flavonoids, phenols, and glycosides in various drugs and toxins in the body	[17]
Silybum marianum	Seed	Asteraceae	Milk thistle	Native in Southern Europe through to Asia, it is now found throughout the world	Cairo, Egypt	2016 *in vitro*	This plant has been used for centuries as a natural remedy for gastrointestinal and bile duct diseases. *Silybum marianum* beads also contain betaine (a hepatoprotective protein), and it has been reported that *Silybum marianum* beads protect hepatocytes against various types of toxins including acetaminophen, ethanol, and carbon tetrachloride. The mechanisms that provide *Silybum marianum* beads produce their own hepatoprotective effects including antioxidants, anti-lipoprotein, anti-peroxidation, and detoxification	(17)
Camellia sinensis	Leaves	Theaceae	Green tea	Native to East Asia, the Indian Subcontinent, and Southeast Asia	Cairo, Egypt	2016 *in vitro*	*Camellia sinensis* improves liver function by preventing the production of ROS and increasing the capacity of the antioxidant defense system. Therefore, the *Camellia sinensis* extract exerts protective effects against ethanol-induced hepatotoxicity	[17]
Nasturtium officinale	Aerial parts	Brassicaceae	Watercress	Native to Europe and Asia	Tabriz, Iran	2014 *in vivo*	The results showed that the use of *Nasturtium officinale* extract increased the activity of antioxidant enzymes and decreased the activity of liver enzymes and also decreased the concentrations of MDA and OHdG-8 in the liver. The effect of *Nasturtium officinale* extract leads to reduction in salicylic acid-induced oxidative stress and oxidative DNA damage in the liver	[18]
Physalis peruviana	Fruit	Solanaceae	Goldenberry	England, and in South Africa, and grows wild across the world in temperate and tropical regions	India	2006 *in vivo*	Extract injection increased the hepatic GSH and decreased MDA in mice. Preliminary phytochemical analysis demonstrated the presence of various beneficial hepatoprotective constituents in the unprocessed aqueous extract. The extract was found to cause no clear acute toxicity in mice, which increases the activity of the hepatic antioxidant enzymes and decreases lipid oxidation in the mouse liver	[19]

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Table 1: (*Continued*)

Scientific Name	Part of plant	Family name	Common name	Origin of plant	Country of study	Year	Result	Ref.
Thonningia sanguinea	Root	Balanophoraceae	Ground pineapple	Southern and Western Africa, and tropical regions	Japan	2000 *in vitro* and *in vivo*	The results showed that GST activity in the liver cytosol is significantly inhibited by *Thonningia sanguinea* extract *in vitro*, and its injection into the plant vitamin has no effect on the enzyme and the GSH level. GST inhibition may have a qualitative effect	[20]
Nigella sativa	Seeds	Ranunculaceae	Black cumin	Native to South and Southwest Asia	Egypt	2015 *in vivo*	*Nigella sativa* altered liver function and increased alanine transaminase, AST, and levels of LDH, decreased total protein levels, and increased superoxide dismutase and MDA by extracting APAP against (N-acetyl-P-aminophenol) at the administered dose in mice, while reduction in catalase, glutathione peroxidase, and glutathione decreased the activity. *Nigella sativa* extract is the strongest agent to reduce the toxicity of APAP and improve liver function and antioxidant capacity of the mouse.	[21]
Terminalia catappa	Leaves	Combretaceae	Malabar-almond	Asia, Africa, and Australia	Japan	2007 *in vitro* and *in vivo*	In a study, the antioxidant and protective activities of the *Terminalia catappa* leaf were observed. The *Terminalia catappa* leaf extract exhibited a strong radical disinfectant for ROS	[22]
Glycyrrhiza glabra	Root	Fabaceae	Liquorice	Native to Southern Europe and parts of Asia, such as India	China	2011 *in vitro* and *in vivo*	*Glycyrrhiza glabra* extract inhibits the activity of AST, ALP, and ALT and decreases Alb levels in liver damage. The data of this study support the chemical potential of the *Glycyrrhiza glabra* extract against oxidative damage to the liver	[23]
Curcuma zanthorrhiza	Rhizome or entire plant	Zingiberaceae	Javanese ginger	South East Asia, cultivars in China, Indochina, Barbados, India, Japan, Korea, the United States, and some countries in Europe	Taiwan	1996 *in vivo* and *in vitro*	The results clearly showed that *Curcuma xanthorrhiza* extract significantly reduced the acute increase of serum aminotransaminases induced by hepatotonic and reduced liver damage 24 h after intraperitoneal administration of hepatotoxins	[24]
Hibiscus sabdariffa	Flower	Malvaceae	Roselle	Native to West Africa	Taiwan	2005 *in vivo* and *in vitro*	*Hibiscus sabdariffa* L. extract protects the liver against CCl4-induced fibrosis. This protective effect appears to be due to the antioxidant properties of *Hibiscus sabdariffa* extract. The *Hibiscus sabdariffa* extract also significantly inhibits the activation of the liver stem cells. *Hibiscus sabdariffa* extract significantly reduced the levels of AST and ALT	[25]

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Table 1: (*Continued*)

Scientific Name	Part of plant	Family name	Common name	Origin of plant	Country of study	Year	Result	Ref.
Vaccinium vitis-idaea	Leaves	Ericaceae	Lingonberry	Northern Hemisphere from Eurasia to North America	Japan	2003 *in vivo*	The results showed that galactosamine (GalN)-induced hepatotoxicity and oxidative stress caused hepatotoxicity in mice, and the activity of serum ALT and glutathione-S-transferase (GSH), and lipid peroxidation in liver hemoglobin increased for 24 h. The *Vaccinium vitis-idaea* extract is a strong antioxidant and protects against GalN-induced hepatotoxicity	[26]
Salvia miltiorrhiza	Root	Lamiaceae	Red sage	Native to Asia and China and Japan.	Korea	2000 *in vivo*	Hepatotoxicity treatment with *Salvia miltiorrhiza* extract significantly reduced aspartate transaminase, alanine transaminase, alkaline phosphatase, and total cholesterol in mouse model of BDL. The amount of hydroxyproline in the liver in the extract-treated BDL mice was reduced to 68% of the control BDL mice. The amount of MDA in the extract-treated BDL mice was reduced to 47% of the control BDL mice	[27]
Kigelia africana	Leaves	Bignoniaceae	Lam	Africa from Eritrea and Chad South to Northern South Africa, and West to Senegal and Namibia	Nigeria	2007 *in vivo*	The effect of plant extract on the activities of superoxide dismutase, catalase, and glutathione peroxidase statistically significantly decreased liver peroxidation	[28]
Alchornea cordifolia	Leaves	Euphorbiaceae	Thonn	African	Nigeria	2007 *in vivo*	The results of a study showed that the plant can act as an antioxidant for the liver and significantly reduced the activity of superoxide dismutase, catalase, glutathione peroxidase, and aminolevulinate dehydratase	[29]
Salvia miltiorrhiza	Roots	Lamiaceae	Red sage	Native to China and Japan	China	2008 *in vivo*	This study showed that the extract of this plant had the antiviral effects of SMPS in liver immunity damage and decreased serum levels of ALT, AST, and nitrogen oxide, as well as liver hemoglobin levels of tumor necrosis factor 1 alpha and interleukin 1 beta	[29]
Schisandrae chinensis	Fructus	Schisandraceae	Chinese magnolia-vine	Northern China and the Russian Far East	China	2009 *in vivo*	Extract of *Schisandra chinensis* leaf serum ALT and AST activity decreased in rats. The effects of plant leaves and their combination on serum ALT, AST, and ALP levels, significantly change antioxidant enzymes in rat liver tissue	[30]

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Table 1: (*Continued*)

Scientific Name	Part of plant	Family name	Common name	Origin of plant	Country of study	Year	Result	Ref.
Curcuma longa	Rhizome	Zingiberaceae	Turmeric	Native to the Indian subcontinent and Southeast Asia	India	2007 *in vivo*	*Curcuma longa* showed the greatest protective activity and reduced ALP. The hepatoprotective potential of *C. longa* has been clearly demonstrated in the experimental findings of this study. Curcumin has antiviral, antiproteasic, antibacterial, anti-inflammatory, and antioxidant activities; in addition to the protective activity of this hepatoprotein, it is known to cause no complication or toxicity	[31]
Tinospora cordifolia	Leaves	Menispermaceae	Guduchi	India, Myanmar, and Sri Lanka	India	2007 *in vivo*	*Tinospora cordifolia* showed the greatest protective activity, while *Tinospora cordifolia* had also a strong immune activity. *Tinospora cordifolia* generates enzymes for the metabolism of the drug and the antioxidant system and inhibits lipid peroxidation in mice. This plant produces desirable antioxidant effects and has a good hepatoprotective potential, making the plant an ideal adjuvant for clinical cases	[31]
Lygodium flexuosum	Rhizomes, roots, and leaves	Lygodiaceae	Climbing fern	Southern China South to Northern Australasia, Kerala (South India).	India	2006 *in vivo*	In extract-treated mice, a significant hepatoprotective effect ($P \leq 0.05$) was observed after CCl4-induced liver injury, which reduced the amounts and activities of AST, ALT, LDH, and MDA. Levels of liver cholesterol increased significantly ($P \leq 0.05$), which increased with the extract treatment. n-hexane *Lygodium flexuosum* extract can lead to hepatoprotective effects	[32]
Carica papaya	Unripe and ripe fruits and leaves	Caricaceae	Papaya	Originally from Southern Mexico (particularly Chiapas and Veracruz), Central America, and Northern South America	Spain	2012 *in vitro*	Treatment of human liver cancer cells, HepG2, with papaya extract in non-cytotoxic doses (0.5–50 μg/mL) increased glutathione peroxidase activity and decreased MDA and LDH levels. Leaf extract seems to produce the greatest protective effect against cell oxidative damage in the HepG2 cells that can react with free radicals to stabilize and block the reaction of the radical chain	[33]
Solanum fastigiatum	Leaves	Solanaceae	False Jurubeba	Worldwide, in America, Asia, and Africa	Brazil	2008 *in vivo* and *in vitro*	The results indicated that the plant exerted antiseptic and protective effects on the hepatocytes and had the potential to treat liver diseases. Aqueous *Solanum fastigiatum* extracts produced desirable antioxidant effects in the hepatocytes against two oxidant proteins in all tissues. However, in the brain and the liver, it was effective against Fe2+inhibition compared to the TBARS	[34]

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Table 1: *Continued*

Scientific Name	Part of plant	Family name	Common name	Origin of plant	Country of study	Year	Result	Ref.
Cheilanthes farinosa	Leaves	Pteridaceae	Forsk or silver fern	In warm, dry, rocky regions in Southern Europe and parts of Asia, such as India and America	India	2010 *in vivo*	In that study, the aqueous extract of *Cheilanthes farinosa* significantly reduced the count of liver cancer cells, the Hep3B population. The time- and dose-dependent effects of the aqueous extract of this plant on Hep3B proliferation, according to the MTT assay, showed that in the treated cells, the dose and time dependence decreased. The most marked reduction in viability by the plant extract was obtained when the cells treated after 72 h of incubation were exposed to the extract	[35]

ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, γ-GT: Gamma-glutamyl transferase, LDH: Lactate dehydrogenase, TNF: Tumor necrosis factor, ROS: Reactive oxygen species, BDL: Bile duct ligation, SMPS: *Salvia miltiorrhiza* polysaccharide, MDA: Malondialdehyde, TBARS: Thiobarbituric acid reactive substances

various types of clinical illnesses.[9,10] More attention has recently been paid to the protective effects of natural antioxidants against the toxicity of various, especially in cases where free radicals are produced.[5,6]

Ancient societies have used herbal medicines to induce health conditions including hepatoprotection. The popularity of herbal drugs is increasing, and at least a quarter of patients with liver disease use medicinal plants.[11,12] The World Health Organization estimates that 80% of the population of some Asian and African countries currently use herbal medicines for some aspects of primary health care.

Some medicinal plants produce strong and optimal hepatoprotective effects.[13,14] Given medicinal plants and plant antioxidants are used to detoxify and treat liver disorders,[15,16] this review was conducted to report the most important medicinal plants affecting liver disorders and diseases.

MATERIALS AND METHODS

The data of this review were obtained using key terms liver cancer, medicinal plants, liver disorder and medicinal plants, liver disease and medicinal plants, effect of extract and essential oil of effective medicinal plants on liver tissues in rats, mice, and laboratory mice, and effect of extract and essential oil of medicinal plants on liver disease to retrieve relevant publications indexed in databases IranMedex, Irandoc, ISI, PubMed, Scopus, SID, Magiran, and Google Scholar.

RESULTS

Based on the evidence found in this review, the medicinal plants *Zingiber officinale*, *Cucurbita pepo*, *Citrus reticulate*, *Petroselinum crispum*, *Andrographis paniculata*, *Silybum marianum*, *Camellia sinensis*, *Nasturtium Officinale*, *Physalis peruviana*, *Thonningia sanguinea*, *Nigella sativa*, *Cichorium intybus* L., *Terminalia catappa*, *Glycyrrhiza glabra*, *Curcuma zanthorrhiza*, *Hibiscus sabdariffa*, *Vaccinium vitis-idaea*, *Salvia miltiorrhiza*, *Kigelia africana*, *Alchornea cordifolia*, *Boerhavia diffusa*, *Schisandrae chinensis*, *Tinospora cordifolia*, *Brassica rapa* subsp. Rapa, *Lygodium flexuosum*, *Carica papaya*, *Solanum fastigiatum*, and *Cheilanthes farinosa* are some of the most important medicinal plants effective on liver diseases and liver cancer [Table 1].

DISCUSSION

Plants contain various compounds by which they can confer hepatoprotection against hepatotoxic agents. The most important of these components are polyphenols, organic acids, carotenoids,

xanthines, glycosides, alkaloids, lignans, monoterpenes, coumarins, essential oils, and flavonoids.[36] From several hepatoprotective plants which have been reported till now, the most important plants were described in this review. The *Opuntia* genus has good capacity for hepatoprotection. The plants of this genus other than liver disease are usually used against dyspnea, ulcers, and glaucoma. *Opuntia ficus-indica* can be used to reduce the hepatotoxicity induced by organophosphorus chlorpyrifos.[37] Ethanol-induced hepatotoxicity in rats was reduced by prickly pear juice. Histopathological markers and lipid oxidation were also decreased. These effects were suggested to be due to the plant capability of counteracting free-radical chain reactions, as well as enhancing endogenous antioxidant capacities.[38] *Matricaria chamomilla* contains more than 100 components with biological activities. This plant influences the cytochrome P450 activity. The rats fed with this plant, decreased the activity of CYP1A2 isoform by about 40% in comparison to control group.[39] The hydroalcoholic extract of *Chamomile capitula* reduced paracetamol-induced injury in rats. *S. marianum* has also been shown a good effect in treatment or protection of liver damage.[40] Although different mechanisms have been suggested for liver protection of various plants, stabilization of cell membrane and decreasing toxin penetration to hepatocytes, stimulation of hepatocyte regeneration, increasing SOD activity, enhancement of hepatocyte protein production, reduction of lipid peroxidation, and increasing glutathione tissue concentration are the most important ones which have been reported. This prevents hepatotoxic agents from entering the hepatocytes. *S. marianum* is one of the most important of these plants which imposes a good liver protection by most of these mechanisms.[41,42] Hepatotoxicity is always associated with oxidative stress and inflammation. Antioxidant activity of plants is a general mechanism by which most of plants impose their liver protection. A lot of plants presented in this article have been shown to possess antioxidant property.[43-49] Some of the presented plants here, as well as other plants, have anti-inflammatory activities which may impact on liver toxicity of toxic agents.[50-57] Fatty liver and lipid peroxidation are also important parameters of lipid toxicity. A lot of the plants presented here and other plants have hypolipidemic activities and/or reduce lipid peroxidation.[58-60] Furthermore, medicinal plants usually have multiple effects.[53,61,62] Hence, other than hepatoprotective activity, they may have extra beneficial effects on patient.

CONCLUSION

This herbal plants as antioxidant and natural sources and they are some of the most important medicinal plants affecting liver disorders and diseases.

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