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A review for discovering hepatoprotective herbal drugs with least side effects on kidney

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ABSTRACT

The liver is a vital organ which plays a major role in the metabolism and excretion of xenobiotics from the body, and liver disease is a worldwide health problem. The currently available synthetic drugs to treat liver disorders cause further damage to the liver and kidney so it is imperative to find new drugs with least side effects. There are a number of treatment combinations which are derived from medicinal plants and commonly administered as tonic for the liver. In this review, we have introduced most important medicinal plants that are used in liver disorders and have least side effects on kidney. In this regards, we have focused on their active constituents, effects and trial studies, mechanisms of action, pharmacokinetic characteristics, dosages, and toxicity. *Amaranthus spinosus* L., *Glycyrrhiza glabra*, *Cichorium inthybus* L., Phyllanthus species (*amarus*, *niruri, emblica*), *Picrorhiza kurroa*, and *Silybum marianum* have been extensively administered for the treatment of liver disorders. The introduced medicinal plants can be used for production of new drugs via antioxidant-related properties, hepatoprotective activities and least side effects on kidney for the prevention and treatment of liver disorders.

Implication for health policy/practice/research/medical education:
Most drugs that are used in treatment of liver disorders are not effective. Also they have various side effects on kidney. Phytochemicals of medicinal plants introduced in this review can be used for production of more effective hepatoprotective drugs. Also, they can prevent and treat liver disorders without significant side effects on kidney.

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Review

Introduction

The liver is one of the human body's key organs that regulates metabolism and has secretion, storage, and detoxification functions. The bile it releases significantly contributes to digestion. The liver is the first destination of toxins from the intestinal tract. Its cell injuries brought about by different toxic agents, including some chemotherapeutic agents, thioacetamide, carbon tetrachloride ($CC1_4$), peroxidized oil, chlorinated hydrocarbons, aflatoxin, chronic consumption of alcohol, microbes and viral infections (e.g. hepatitis A, B, C, D, etc.), have been extensively studied (1). Hepatotoxin-associated liver injury makes excretion of bile defective and is reflected in increase in toxins' serum levels (2). Concentrations of aspartate transaminase (AST) and alanine transaminase (ALT) in cytoplasm and mitochondria of the damaged liver cells also increase. The leakage of plasma causes an increase in serum hepatospecific enzymes, leading to cellular leakage and disturbance of functional integrity of the liver cell membrane. In addition, high bilirubin concentration in serum is a manifestation of an increase in erythrocyte degeneration rate.

On the other hand, a majority of the hepatotoxic chemicals damage liver cells and subsequently kidney mostly through lipid peroxidation or other oxidative forms. As in the presence of free radicals, lipids peroxidize more rapidly, the free radicals scavenging mechanism obviously playing an important role in inhibition of lipid peroxidation chain reaction (3). Since it is known that the overproduction of reactive oxygen species

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(ROS) reinforces oxidative stress, resulting in an injury mechanism associated with the common clinical diseases, such as heart disease, kidney and liver injury, diabetes, cancer, etc. (4), maintaining the balance between ROS and antioxidant enzymes, particularly superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) is crucial in preventing oxidative stress damages (5). The enzymatic antioxidant defense systems, such as Cu–Zn, Mn–SOD, CAT and GSH reductase, which are natural lipid peroxidation protectors, function by direct or sequential ROS removal, thus terminating or diminishing this process (6). In order to avoid lipid peroxidation, it is very important to maintain the level of GSH, an important antioxidant in cytosol involved in detoxification and excretion of xenobiotics (7). Out of the xenobiotics, $CC1_4$ is considered to be a major cause of acute liver cell injury via bioactivation trichloromethyl free radicals (8). Compounds that increase activity of glutathione S-transferase (GST), which metabolizes toxic to non-toxic compounds, have an increasingly protective mechanism in the liver.

Natural products including medicinal plants and their compounds reported to prevent and treat a lot of diseases due to fewer side effects on body systems (9-14). Herbal extracts could significantly contribute to recovery processes of the intoxicated liver and kidney. A huge number of plant species have already been examined for efficacy against a spectrum of liver diseases (15). From our previous studies, we have already reported 26 medicinal plants from Iran which have been used for liver disorders, as recorded in available ethnobotanical documents (16), and we have completely reviewed and introduced twelve plant species that are used in Iran's traditional medicine for prevention and treatment of liver disorders (17). In this review, we aimed to introduce six medicinal plant species used worldwide for prevention and treatment of liver disorders that have least side effects on kidney, with a focus on their active constituents, their efficacy, mechanism of action, pharmacokinetic characteristics, dosages, and toxicity. It should also remember that, many hepatoprotective herbal drugs, have nephroprotective efficacy. Therefore knowledge on medicinal plants with liver protective effects lead to a better understanding of their possible nephroprotective efficacy.

Materials and Methods

For this study, online databases including Web of Science, PubMed, Scopus, and Science Direct were searched for papers published from January 1970 to June 2016. Search terms were as follows, used either alone or in combination: medicinal plants, traditional medicine, folk medicine, hepatoprotective, Iran, liver, renal injury, therapeutic uses, antioxidant, compounds, $CC1_4$, hepatitis, nephrotoxicity, anti-hepatotoxic, and anti-inflammatory.

Results

Amaranthus spinosus L.

Amaranthus spinosus L. from the Amaranthaceae family, commonly called pigweed, is an annual herb found in many tropical countries (18). The whole plant is used for the treatment of jaundice in Iranian traditional medicine (19). It has a high concentration of antioxidant components (20,21) and a high nutritive value due to its high content of fibers, proteins and essential amino acids, particularly lysine (22). Also, it is used as an antimalarial and antimicrobial agent and has anti-inflammatory effects in hepatic disorders (23,24).

Active constituents

Amaranthus spinosus have many important constituents, such as flavonoids, phenolic acids, alkaloids, glycosides, steroids, amino acids, terpenoids, lipids, saponins, betalains, b-sitosterol, stigmasterol, linoleic acid, rutin, catechuic tannins and carotenoids (2). Phytochemical analysis of the plant revealed presence of spinoside, a new coumaroyl flavone glycoside, as well as xylofuranosyl uracil, hydroxycinnamates, quercetin, kaempferol glycoside, betalains, betaxanthin, betacyanin, phenolic compounds, amaranthine and isoamaranthine, b -sitosterolglycoside, campesterol, while hentriacontane, α-spinasterol, linoleic acid, rutin and betacarotene, detected in the leaves and stems as the prime constituents (18). The betalains identified in the stem bark of *A. spinosus* were amaranthine, isoamaranthine, hydroxycinnamates, quercetin and kaempferol glycosides (24). It also contains amaranthoside, a lignan glycoside, amaricin, a coumaroyl adenosine along with stigmasterol glycoside, and betaine such as glycinebetaine and trigonelline (2).

Effect and trial researches

In studies, the whole plant of *A. spinosus* was evaluated for effects against liver disorders, and results indicated that serum enzymatic levels of glutamate pyruvate transaminase, glutamate oxaloacetate transaminase, alkaline phosphatase (ALP) and total bilirubin were decreased by *A. spinosus* extract (ASE) treatments (2). Hepatoprotective activity of the 50% ethanol extract of the whole plant showed effective against d-galactosamine/lipopolysaccharide (dGalN/LPS) and against carbon tetrachloride (CCL_4) induced liver injury in rats (2). dGalN/LPS-induced hepatic damage was manifested by increasing in the activities of enzymes such as ALP, gamma glutamyl transferase, ALT, AST, and lactate dehydrogenase and by decreasing in bilirubin level of serum. Pretreatment (400 mg/kg) of rats with ASE significantly reversed these altered parameters to normal compared to the intoxicated group (25).

Mechanism of action

Activity against CCL_4 may be due to the presence compounds such as of flavonoids and phenolics in the ASE which may have hepatoprotective activities (2). Hence, it is possible that the hepatoprotective mechanism of whole plant *A. spinosus* is due to its antioxidant activity (25).

Pharmacokinetic characteristics, dosage/toxicity

From the results it is clear that the ASE has shown a

dose dependent response in which 400 mg/kg p.o. shows greatest effects compared to the control group (2).

Cichorium intybus L.

Cichorium intybus from the Asteraceae family, is a medicinally important genus native to Europe, tropical Asia, and North Africa (26). Various health benefits have been reported in these parts of the world. Aqueous root extract is used against malaria (27), for the treatment of warts (28), against liver diseases and digestive problems (29), and as a laxative and diuretic (30,31).

Active constituents

Previous phytochemical studies revealed the presence of phenolic acids, flavonoids, anthocyanins, sterols, hydroxyl cinnamic acid derivatives, polyamines, sesquiterpene lactones, triterpenoids, norisoprenoids and coumarins in the aerial parts of Cichorium species (32,33). Also fibers such as oligosaccharide and inulin have recently been recognized in root of the plant.

Effects and trial researches

Evaluations of the biological activity of whole plant extract of *C. intybus* have revealed hepatoprotective and antidiabetic activities while the aerial parts have antimicrobial, antioxidant and anthelmintic effects (31,34,35). Aqueous and alcoholic extracts of *C. intybus* L. showed anti-inflammatory activity against formalin-induced paw edema in mice (36). The anti-hepatotoxicity, anti-inflammatory, gastroprotective properties and antioxidant activity of *C. intybus* L. suggest that *C. intybus* has useful effects on acute pancreatitis (37). The results of the total phenolic content assay on the extract, sub-extracts and fractions from the roots of *C. intybus* indicated that CH2Cl2, EtOAc and n-BuOH sub-extracts were rich in phenolic constituents with significant anti-inflammatory and antioxidant effects, possibly even contributing to the wound healing process (38). Moreover, *C. intybus* have been shown to possess a wide variety of pharmacological properties such as antimicrobial, anti-tumoral, anti-inflammatory (37,39). Comparing the hepatoprotective effects of natural root extract of *C. intybus* and its root callus extracts has been showed that root callus extract had better activity against CCL_4 hepatotoxicity (40).

Mechanism of action

Various mechanisms might be involved in the protective effects of *C. intybus*. The total extracts have many different components for which there are a wide variety of pharmacological effects. *C. intybus* root extract (its ethyl acetate extract) inhibits the expression and activity of cyclooxygenase 2 (COX-2) (41). Also *C. intybus* extract (CIE) inhibits angiotensin converting enzyme and pancreatic lipase (42). Moreover, reduced levels of malondialdehyde and increased levels of antioxidant enzymes are the main mechanisms of CIE for preventing the development of liver fibrosis induced via CCl_4 (43). Hepatoprotective, gastroprotective, anti-inflammatory actions and free radical scavenging are the major properties of *C. intybus* that are assumed to be related to its flavonoids (39).

Pharmacokinetic characteristics, dosage/toxicity

The results also indicated that root extract, especially 150 mg/kg as the highest test dose, markedly prevented necrosis in liver tissue. However, lower doses of 100 were only effective to decrease milder forms of liver injures like fatty changes and bilirubin content. In oral route, the dose of 200 mg/kg showed a significant decrease in levels of lipase (24%) and amylase (16%). The dose 200 mg/kg, i.p. had only effect on inflammatory features such as leukocyte infiltration in pancreatitis tissue.

Glycyrrhiza glabra

Glycyrrhiza glabra (licorice root) originates from the Middle East and Mediterranean. Also it has been cultivated in Europe since the 16th century (44). The root aqueous extract known for its antiviral activity, detoxifying effects and anti-allergic (45). It is said to be effective in the treatment of bronchitis and other infections mentioned above. Moreover, aqueous extract of *G. glabra* has been used to treat patients with hepatitis and is well documented in reducing liver transaminases (46).

Active constituents

Glycyrrhizin, as a conjugate of glucuronic acid and glycyrrhetinic acid, is one of the most important active constituents of *G. glabra*. Glycyrrhizin is metabolized in the liver into 3-mono-glucuronide-glycyrrhetinic acid. It is excreted in bile and further metabolized by intestinal bacteria into glycyrrhetinic acid (45). Glycyrrhizin has antioxidant, immunosuppressive and anti-inflammatory effects (46). Other constituents of *G. glabra* include coumarins (umbelliferone, herniarin), triterpenoids, flavonoids (isoliquiritin and liquiritin), isoflavonoids (glabrol, kumatakenin, isoflavonol, and licoricone), phytosterols, and chalcones (47). It also includes glycyrrhetic acid, hydroxycoumarins and sterols (46).

Effect and trial researches

It has been shown that *G. glabra* has direct hepatoprotective effects. Flavonoids of *G. glabra* provided protection to hepatocytes exposed to CCL_4 hepatotoxicity. The researchers highlighted the anti-inflammatory, free-radical quenching, anti-lipid peroxidation, and immunosuppressive properties of Glycyrrhiza. Animal studies have shown that *G. glabra* can activate P450 phase I detoxification reactions and enhance liver glucuronidation (45).

Glycyrrhiza glabra exerts antiviral activity in vitro toward a number of viruses such as hepatitis A. Also, intravenous glycyrrhizin has been shown to be effective on viral hepatitis (in particular chronic viral hepatitis) in a double-blind study. It has shown that *G. glabra* can stimulate endogenous interferon production (47).

Mechanism of action

Through in vitro studies with human hepatoma cells, Crance et al showed that glycyrrhizin inhibited penetration of hepatitis A virus likely by altering cell membrane fluidity (48). In addition, glycyrrhizin has been shown to decrease the release of AST via inhibiting the activation of phospholipase A2, as well as via prevention of changes in the hepatocyte membrane permeability. Also, glycyrrhizin was found to can suppress hepatitis B surface antigen (HBsAg) production (45).

Pharmacokinetic characteristics, dosage/toxicity

The pharmacokinetic characteristics of intravenous administration of *G. glabra* has been studied in Europe and Asian in patients that have liver diseases, and comparable results have been found (49). The drug has linear pharmacokinetics up to 200 mg, and steady state is achieved after 2 weeks of 200-mg doses administered 6 times per week (45). *G. glabra* has a well-known pseudoaldosterone effect when large doses are ingested. The symptoms of pseudoaldosterone syndrome include hypertension, hypokalemia, sodium and water retention, low plasma renin activity, and suppressed urine and serum aldosterone levels. Edema and worsening of ascites are also a result of glycyrrhizin's aldosterone-like actions. The amount of glycyrrhizin needed to produce these symptoms is variable. In one study in which fourteen healthy volunteers ingested 100-200 g of a licorice product (equivalent to approximately 10^{-4} grams of the crude herb or 0.7-1.4 g glycyrrhizinic acid), for one to four weeks, plasma rennin activity or urinary aldosterone concentrations were decreased in all subjects, revealing a significant effect of licorice root on the renin angiotensin-aldosterone axis at these doses (47).

Phyllanthus species (amarus, niruri, emblica)

The Phyllanthus has about 750-800 species found in tropical and subtropical regions worldwide (50). A substantial number of Phyllanthus species are used widely in traditional medicine for the treatment liver diseases (51,52). Among different species of Phyllanthus, *P. amarus* is highly regarded in the treatment of liver ailments and kidney stones (53,54). *P. emblica* L. is native to India and *has* been shown to possess widespread pharmacological application such as liver disorders (7,43). Also, anti-hepatotoxic components present in *P. niruri* such as hypophyllanthin and phyllanthin showed hepatoprotective activities (55).

Active constituents

Vitamin C, phyllambic compounds, phenolic compounds, and flavonoids are the effective components of Phyllanthus species that may effect on oxidative damage (56). *P. amarus* was found to contain phyllanthin and hypophyllanthin and the chemical composition analysis indicated that the protective effect of *P. urinaria* extract was primarily due to the presence of corilagin and gallic acid (57). Also fruits of *Phyllanthus* have two newly identified hydrolysable tannins, emblicanin A and B, which are vitamin C-like. (58,59).

Effect and trial researches

Phyllanthus amarus is a well-known hepatoprotective and antiviral agent (60,61). Earlier studies reported that *P. amarus* is a hypoglycemic, diuretic, and hypotensive drug for humans (54). The hepatoprotective effect of methanolic extract of the leaf of *P. amarus* against ethanol-induced oxidative damage is shown in studies using adult male Wistar albino rats. Reduced levels of CAT, GSH, and SOD in the liver were significantly enhanced by *P. amarus* treatment (62). In a similar study, the ethanolic extract of *P. urinaria* was reported to protect against an acetaminophen overdose by down-regulating hepatic cytochrome P450 CYP2E1 protein (63). The methanolic extract of *P. urinaria* has also been reported to protect against CCl_4 -induced liver toxicity via elevating the activity of reduced glutathione peroxidase (GSH-Px), attenuating the increase in serum glutamate-oxalate transaminase (GOT), (64), and increasing intracellular free Ca^{2+} concentrations in liver cells (65). Also, previous studies have shown the hepatoprotective activity of the *P. emblica* fruit extract against a variety of toxins such as CCl_4, (56,66-69). Niranthin and nirtetralin are reported to possess anti-inflammatory and hepatoprotective activities. Cytotoxic effect of these compounds on some human cancer cell lines, suggests a potential action of Phyllanthus lignans as multidrug resistance (MDR) reversing agents (70). Moreover, Thyagarajan et al have shown the antiviral properties against HBV for the whole plant extract of *P. niruri* (71).

Action mechanism

The main mechanism involved in this protection could be associated with its strong capability to reduce the intracellular level of ROS (72). Hepatoprotective activity of ethanolic extract of *P. amarus* (EEP) is due to its stimulatory effect on both enzymatic and non-enzymatic antioxidant systems, as observed in experimental mice. Consequently, the damage induced by aflatoxin B1 in the liver of mice is suppressed with the administration of EEP due to the reduction in the level of ROS, as indicated by the reduction in the level of thiobarbituric acid reactive substances (TBARS) and repair process in the liver of these mice (54).

Pharmacokinetic characteristics, dosage/toxicity

Jayaram et al, studying the effect of *P. amarus* on beta-galactosamine-induced hepatotoxicity on isolated rat hepatocytes, found that *P. amarus* by itself was not hepatotoxic and at 1 mg/mL concentration it was found to be hepatoprotective (73). *P. amarus* whole plant powder administered at a dosage of 0.66 g/kg in rats showed hepatoprotective activity against CCl_4-induced liver damage (74). In another study, both 250 and 500 mg/kg doses of *P. amarus* extract significantly reduced the ethanol-induced elevated levels of lipid hydroperoxide

(LPO). More so, the 250 mg/kg extract markedly improved the ethanol-induced reduction in GSH, SOD and CAT levels, while the 500 mg/kg extract exerted a further decrease. The restoration of oxidant/antioxidant balance is further reflected in the improved hepatic activities of transaminases and ALP. A dose dependent improvement in hepatic AST, ALT and ALP activities, with a concomitant reduction in the plasma activity of ALT and AST, was seen with co-treatment of 250 mg/kg extract with ethanol, and even more so with 500 mg/kg. (75).

Picrorhiza kurroa

Picrorhiza kurroa from the Scrophulariaceae family, as a small perennial herb, grows in northwest India on the slopes of the Himalayas (76). It is an important herb in the traditional Ayurvedic system of medicine, and has been used to treat bronchial and liver problems (49). *Picrorhiza* is poorly soluble in water and so is usually not taken as a tea. It is soluble in ethanol and it can be taken in tincture form (77).

Active constituents

The most important active constituents of *Picrorhiza* are the iridoid glycoside picrosides I, II, III, and kutkoside, known collectively as kutkin (78). Many other active constituents have been identified, including flavonoids, triterpenes, alkaloids, and coumarins such as apocynin, glycosides, nine cucurbitacin, drosin, and triterpenoid ursolic acid (79).

Effect and trial researches

Picrorhiza has been shown to protect liver cells from a wide variety of inflictions including amanita poisoning (80,81), carbon tetrachloride (82-84), galactosamine (85,86), ethanol (87), aflatoxin B1 (88), acetaminophen (89), thioacetamide (90), oxytetracyline (91), and monocrotaline (92) in both in vitro and in vivo experiments. When compared with silymarin, the hepatoprotective effect was found to be similar, or in many cases, superior to the effect of silymarin (87,90). Dwivedi et al have shown significant hepatoprotective properties of picroliv using models such as monocrotaline and CCl_4-induced liver injury in rats (86). Shukla et al compared picroliv with silymarin in animal models and found potent anticholestatic and choleretic functions (93). Chander et al also found hepatoprotective properties in *P. kurroa* (94).

Picrorhiza may be valuable in the treatment of viral hepatitis. In vitro studies have shown anti-viral activity of *P. kurroa* (95) and the existing literature suggests that *P. kurroa* is a powerful immuno-modulator rather than an antiviral drug in liver diseases (96).

Mechanism of action

It has been reported that flavonoids, triterpenes, alkaloids, and coumarins may be responsible for their antioxidant and hepatoprotective effects (97-99). Also, flavonoids are known to be antioxidants, free radical scavengers, and anti-lipoperoxidants, leading to hepatoprotection (100). In the previous reports, extracted beta-sitosterol of *P. kurroa* was found to have antioxidant (101,102), anti-inflammatory (103-105), and proliferative (106) activities. Moreover, it was found that picroside-I and kutkoside inhibited the non-enzymatic generation of O2-anions, oxidative malonaldehyde (MDA), and scavenged superoxide (O2) anions. In other words, *P. kurroa* has antioxidant activity similar to SOD, metal-ion chelators, and xanthine oxidase inhibitors (107).

Like silymarin, *P. kurroa* compounds may have an effect on liver regeneration. One study demonstrated stimulation of nucleic acid and protein synthesis in liver of rats with oral administration of *P. kurroa*. The authors stated the results were comparable to silymarin (108). Also, *P. kurroa* has been shown to protect ethynylestradiol and acetaminophen -induced cholestasis, maintaining both bile volume and flow (109).

Pharmacokinetic characteristics, dosage/toxicity

The usual adult dosage *P. kurroa* is 400 to 1500 mg/d, although daily doses as high as 3.5 g/d have been recommended for fevers (110). By comparison, the maximum dose achievable with oral ingestion of *P. kurroa* root is about 3-6 mg/kg (111). No effects on cellular and humoral immunity were reported after treatment with apocynin as an active constituent of *P. kurroa* (112,113).

Silybum marianum

The genus *Silybum* is a member of the Asteraceae family (*Compositae*) and grows in India, China, South America, Africa, and Australia, among other countries (114). *S. marianum*, from the fruits of the milk thistle, has been used as a treatment for hepatobiliary diseases since the 16th century (115). It has been shown to have clinical applications in the treatment of toxic hepatitis, alcoholic liver diseases, fatty liver, cirrhosis, viral hepatitis and liver regenerating effects (116,117). The excellent hepatoprotective activity of silymarin, besides its immunomodulatory, anti-lipid peroxidative, antifibrotic, membrane stabilizing and anti-inflammatory activities, makes it a very promising drug of natural origin (118).

Active constituents

The plant consists of approximately 60%-80% of the silymarin flavonolignans and approximately 20%-30% of a chemically undefined fraction, so comprised mostly of polymeric and oxidized polyphenolic compounds (118). Silymarin is a polyphenolic flavonoid, the most prevalent component silybin (50%-60% of silymarin), which is the most active photochemical and is largely responsible for the claimed benefit of the silymarin (119,120). Besides silybin, considerable amounts of other flavonolignans are present in the silymarin complex such as dehydrosilybin, silydianin, silychristin, isosilybin, and a few taxifolin. The seeds also contain essential fatty acids, trimethylglycine, and betaine, that may contribute to silymarin's anti-inflammatory and hepatoprotective effects (121-124).

Effects and trial researches

Hepatoprotective effects of silymarin on carbon tetrachloride (125,126), phenylhydrazine (127,128), tert-Butyl hydroperoxide (129), thioacetamide (130,131), galactosamine (129,132), paracetamol (133), erythromycin estolate (134,135), microcystin (136) and amanita phalloids toxin (137) have been shown. Numerous studies have suggested that silymarin has significant anti-inflammatory effects on hepatic tissue and that it regulates inflammatory mediators such as tumor necrosis factor (TNF) (120), TNF-alpha (138), interleukin-6, nitrous oxide, and interleukin-1 receptor antagonist (139). Silybin [4-10 mol/L concentration] was found to reduce the proliferation of freshly isolated hepatic cells by about 75%. It also reduced the conversion of stellate cells into myofibroblasts and down-regulated the gene expression of extracellular matrix components necessary for fibrosis (140).

Mechanism of action

Silymarin has been found to inhibit the formation of leukotrienes via its inhibition of the lipoxygenase. These leukotrienes are known as the most damaging chemicals found to man (141). Studies also demonstrated that silymarin stabilized mast cells (142), decreased the activity of tumor promoters (143,144), shows anti-inflammatory (145) modulated immune functions (146) and is anti-fibrotic (117). One of the mechanisms to explain the ability of silymarin to stimulate the regeneration of hepatic tissue is the increase in protein synthesis in damaged livers. Silymarin led to increase in protein and mRNA of phases of cell cycle. Expression of TGFα, TGFβ1, and HGF was also enhanced (147,148). Finally, silymarin may inhibit the activity of uridine diphosphoglucuronosyl transferase and cytochrome P450 3A4 in human hepatocytes, so inhibiting the metabolism of certain drugs (148,149). Theoretically, silymarin may decrease the clearance of drugs that undergo glucuronidation and increase the clearance of estrogen by inhibiting glucuronidase (150).

Pharmacokinetic characteristics, dosage/toxicity

Silymarin has been proven to be as a non-toxic drug when administered for short periods of time at high doses, and the active components of silymarin had protective effects against hepatotoxic actions of drugs (151). Human studies have shown that silymarin is generally without side-effects. for is 240- 900 mg/d in two or three doses are the typical adult dosage. Nausea and meteorism can be seen in patients treated with 360 mg/day (152). At higher doses, 240 mg/d, silymarin may produce a laxative effect due to increased bile flow and secretion. Also stomach upset, heartburn and transient headaches were reported (153). Other symptoms have included nausea, epigastric discomfort, urticaria and arthralgia (154).

Implications and mechanisms

Most of hepatotoxic damage is mainly due to lipid peroxidation and other oxidative damages. Scavenging of free radicals is one of the main anti-oxidative mechanisms to inhibit the chain reaction of lipid peroxidation. Many studies have demonstrated that overproduction of ROS can further aggravate the oxidative stress and the result is a unifying mechanism of injury that occurs in development of many clinical disease processes, such as heart disease, diabetes, liver injury, cancer, aging, etc. (155-159). Maintaining the balance between ROS and antioxidant enzymes, especially SOD, CAT and GPx, is crucial and could serve in preventing damage by oxidative stress (160-162). In hepatic cells, enzymatic antioxidant systems act by removal of ROS, thereby terminating their activities (163,164).

The plants reviewed in this article mainly contain phenolic and flavonoid compounds which are known to be antioxidants, anti-lipoperoxidants and free radical scavengers, leading to hepatoprotection. For example, picrorhiza main constituents, picroside-I and kutkoside, inhibit the non-enzymatic generation of O2-anions and scavenge superoxide (O2) anions and level of GSH, SOD, and CAT in the liver. Also Phyllanthus species, through their strong capability to reduce the intracellular level of ROS via the reduction in the level of TBARS and the induction of recovery and repair process in the liver, can be beneficial for prevention and treatment of liver disorders. Cichoric acid as a main compound of *C. intybus* reduced the intracellular ROS. Also hydroxycinnamic acids and flavonoids are among the dominating compounds of CIE, and can significantly attenuate ROS induction. They can have a significant antioxidant effect on low density lipoprotein (165).

CCl_4, as another of the most common hepatotoxins, is biotransformed to trichloromethyl radical under the action of cytochrome P450 in the microsomal compartment of the liver (166). Glycyrrhiza flavonoids provided protection to hepatocytes exposed to carbon tetrachloride-induced hepatotoxicity by enhancing hepatic glucuronidation and activating P450 phase I detoxification reactions. Hepatoprotective activity of the 50% ethanol extract of *A. spinosus* was identified against D-galactosamine/lipopolysaccharide (DGalN/LPS) and against CCl_4 (2). Moreover, hepatoprotective activity of silymarin against toxicity caused by CCl_4, phalloiride, acetaminophen, ethanol, and D-galactosamine has been demonstrated. Stimulation of polymerase I and rRNA transcription, and protecting the cell membrane from radical-induced damage, were mechanisms of action of silymarin. Furthermore, flavonoid compounds of *C. intybus* could prevent the development of liver fibrosis induced by CCl_4 via increased levels of antioxidant enzymes (43).

Conclusion

Since treatment of liver disorders, especially viral hepatitis or other chronic liver diseases by available drugs is not adequate and is with side effects on kidney, it is necessary to produce new hepatoprotective drugs. The introduced medicinal plants via antioxidant-related properties and

hepatoprotective activities can be used for production of new drugs to prevent and treat liver diseases with least side effects on kidney. Therefore, we recommend further research, including clinical trials, to evaluate the effects of the introduced phytochemicals in this review, for production of more effective hepatoprotective drugs.

Authors' contribution

SHS, and MAS searched the databases and wrote the draft. MS, RR, MAS, and TL edited the draft. All authors read and approved the final version.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Conflict of interest

The authors declare no conflict of interest.

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