



A REVIEW OF THE PROTECTIVE EFFECTS OF NATURAL COMPOUNDS AGAINST CHEMICAL-INDUCED HEPATOTOXICITY

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ABSTRACT

Globally, liver injuries are a serious public health problem for people. Recent investigations have demonstrated that plants and their important active ingredients exert protective effects against toxic agents that may cause liver injuries, such as pollutants, drugs, and alcohol, which consequently develop into the liver failure, cirrhosis, fibrosis, hepatitis, fatty liver, and even carcinoma. Several natural products and their bioactive compounds are protective against liver injuries. The underlying mechanisms mainly include lipid metabolism regulation, DNA damage repair, anti-necrosis, anti-apoptosis, anti-inflammation, and anti-oxidation. In this review, the protective effects and especially mechanism of action of natural products and bioactive components on liver damages caused by chemicals has been summarized. This current information will aid in the prevention and treatment of liver-related diseases, especially those induced by chemicals.

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Introduction

Oxidative stress is a biochemical condition that occurs in the body, producing several types of reactive species, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) [1]. ROS are very reactive against macromolecules such as DNA, proteins, and membrane lipids in living cells. Oxidative stress-induced changes play a key role in the etiology and pathogenesis of many diseases, such as hepatotoxicity, nephrotoxicity, diabetes mellitus, and cancers [2]. A variety of risk factors, such as drugs, alcohol, irradiation, and environmental pollutants, can induce oxidative stress in the liver and result in the development of severe liver diseases [3].

Liver is the largest internal organ in the human body that plays a significant role in the metabolism and detoxification of various chemicals, drugs, and other toxic compounds [4]. Liver diseases caused by oxidative stress facilitate the pathogenesis of hepatic fibrosis, liver cirrhosis, and even hepatocellular carcinoma [5,6]. Oxidative stress is regarded as one of the pathological mechanisms that cause the initiation and progression of liver damage through inducing irreversible alterations in lipid membranes, proteins, and DNA and, more importantly, through modulating pathways that control biological function [7,8].

The human body has natural defense mechanisms that protect against free radicals and oxidative damage. These mechanisms are both enzymatic, such as reactions catalyzed by catalase (CAT), superoxide dismutase (SOD), and the glutathione system (glutathione (GSH), glutathione reductase, peroxidase, and transferase), and non-enzymatic, such as the pathways driven by low molecular weight antioxidants such as vitamins A, E, and C [9,10]. However, the need for antioxidant supplements to combat oxidative damage becomes essential if the balance between antioxidant defense system and free radicals is compromised [11].

Antioxidants are free radical scavengers that can neutralize free radicals before attacking cells, preventing damage to proteins, enzymes, lipids, carbohydrates, and DNA [12]. For treating liver toxicity, A wide range of antioxidants from natural and synthetic sources have been proposed [13]. The good candidates to protect against toxicities-induced by

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chemicals are natural compounds that inhibit enzymes that activate free radicals. In this review, we summarized *in vivo* and *in vitro* investigations related to the hepatoprotective effects of plants and their active ingredients against toxic chemical agents.

Liver Diseases

Liver disorders are among the major global health problems and are the 5th most prevalent cause of death worldwide [14,15]. Changes in liver anatomy or liver function are characterized as liver disease. Liver diseases may be classified as cirrhosis (degenerative disorder leading to liver fibrosis), chronic or acute hepatitis (inflammatory liver diseases), and hepatosis (noninflammatory diseases). Additionally, the liver is the first organ involved in counteracting the effects of toxic compounds and metabolites capable of inducing damage, namely, cellular necrosis, GSH depletion, and increased lipid peroxidation associated with increased liver markers, including bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) [16].

After chronic liver injury, liver disorders lead to various pathological changes like fatty liver, increased ROS or oxidative stress, liver cell necrosis, hepatitis, steatosis, cholestasis, veno-occlusive diseases vascular lesions, granuloma, and, increased inflammatory markers, cirrhosis, fibrosis, and hepatocellular carcinoma, which further promote portal hypertension and organ failure [17]. Exposure to xenobiotics and several environmental pollutants, including acetaminophen (or N-acetyl-para-aminophenol, APAP), antibiotics, chemotherapeutic agents, carbon tetrachloride (CCl₄), thioacetamide (TAA), and chronic alcoholism, is responsible for the progression of liver disorders, as liver damage is caused by elevated levels of ROS in liver tissues [18,19]. Unfortunately, since the conventional or synthetic drugs used to treat these diseases are insufficient and sometimes cause serious side effects, the preferred treatments for liver diseases are controversial [20].

Recent investigations have focused on drugs derived from medicinal plants due to high levels of flavonoid and polyphenolic compounds and presumably minimal treatment side effects as well as relatively low cost; the protection provided by medicinal plant-based drugs against various drug- and chemical-induced hepatotoxicity has been extensively studied *in vivo* and *in vitro*, and this research is urgently needed [21,22]. To date, hundreds of plants have been examined in a wide spectrum of liver diseases [23,24].

Protection against CCl₄-induced hepatotoxicity

CCl₄ is a hepatotoxic agent that is extensively used in animal models to induce chronic and acute liver injury [25] and to evaluate the effectiveness of many hepatoprotective drugs [6]. CCl₄ is known to cause liver damage and hepatocyte apoptosis/necrosis *in vitro* and *in vivo* [26-29]. The damage responses induced by injection of CCl₄ in a rat model are similar to human liver cirrhosis [30]. CCl₄ is converted by hepatic cytochrome P450 2E1 (cytochrome P450, family 2, subfamily E, polypeptide 1; CYP2E1) into highly reactive radicals, such as trichloromethyl (CCl₃•) free radical and trichloromethyl peroxy radical (CCl₃OO•) [31]. Then, these radicals attack cellular macromolecules and cause lipid peroxidation, protein degradation, and DNA damage. The process is followed by the release of hepatic inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β), which subsequently leads to damage, including hepatocellular necrosis [26, 27, 31].

In numerous studies, the results have revealed that, by inhibiting lipid peroxidation and enhancing antioxidant enzyme activity, plant extracts with antioxidant activities protect against CCl₄-induced hepatotoxicity [15, 32-38]. *In vitro* and *in vivo* experimental animal model studies suggested that a variety of natural product extracts or their bioactive components exert potent hepatoprotective activities against CCl₄-induced hepatotoxicity (Table 1).

Protection against Acetaminophen-Induced Hepatotoxicity

Acetaminophen (APAP), which is also known as paracetamol, is a well-known antipyretic and analgesic drug worldwide [39]. APAP overdose leads to severe centrilobular hepatic necrosis in experimental animals and humans [40]. The metabolic activation of APAP produces N-acetyl-p-benzoquinone imine (NAPQI) and ROS. NAPQI can bind to sulfhydryl groups, spontaneously reacting with GSH and binding to hepatic proteins, leading to the critical event that initiates cell death in APAP-induced liver injury and GSH depletion [41]. However, due to the prolonged activation of cJun-N-terminal kinase (JNK), mitochondrial dysfunction, hepatocyte necrosis, and hepatotoxicity occur with APAP overdose or GSH shortage [42,43]. A recent study demonstrated that PARP1 is involved in this process by activating PXR and promoting toxic P450 enzymes [44].

Several investigations have demonstrated that medicinal plants can enhance liver function against paracetamol-induced toxicity. In *in-vivo* and *in vitro* studies, results have revealed that the plasma concentrations of NAPQI in rats significantly enhanced the absorption of paracetamol and was reduced by chrysin, a plant flavonoid, which may be due to inhibition of CYP2E1 and other cytochrome p450 (CYP) enzymes (CYP3A4 and CYP1A2). Additionally, chrysin significantly reduced hepatic injury markers such as serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), ALP, total protein (TP) and total bilirubin (TBL); ameliorated histopathological alterations; reduced oxidative stress damage; and inhibited microscopic changes in liver tissue with paracetamol-induced oxidative stress [45]. Table 2 shows the phytochemicals derived from different plant sources and their hepatoprotective activity against APAP-induced hepatotoxicity.

Protection against D-Galactosamine and Lipopolysaccharide-Induced Hepatotoxicity

D-galactosamine, as an amino sugar, is a selective hepatotoxin that induces liver damage resembling viral hepatitis [46]. D-galactosamine causes necrotic and apoptotic cell death in the liver by inducing oxidative stress. The increase in plasma ALT in rats and induction of both oncotic necrosis and hepatocellular caspase-dependent apoptosis can be caused by a single high dose of D-galactosamine [47]. D-galactosamine is metabolized exclusively in the liver through the galactose pathway, leading to the deoxynucleotidyl transferase-mediated depletion of the uracil nucleotide 2'-deoxyuridine 5'-triphosphate (dUTP), thus inhibiting hepatic transcription [48].

Numerous reports indicate that, by using free radical scavengers and/or naturally occurring antioxidants, such as spirulina platensis [49], pentoxifylline and caffeic acid phenethyl ester [50], catechin [51], biochanin A [52], *p*-coumaric acid and kaempferol [53], and quercetin [54], D-galactosamine-induced liver damage is attenuated.

An *in vivo* study showed that the treatment of ICR mice with flavonoid and phenolic acid fractions isolated from *Lolium multiflorum* Lam. reduced the D-galactosamine-induced increases in serum ALP, AST, ALT, and lactate dehydrogenase (LDH) levels [55]. The combined treatment of phenolic acid and flavonoid fractions isolated from *L. multiflorum* Lam. inhibited the D-galactosamine-mediated increases in histological damage, serum enzyme levels, and hepatic malondialdehyde (MDA) levels, while restoring the activities of hepatic antioxidant enzymes to control levels and augmenting the D-galactosamine-induced expression of nuclear factor erythroid-2-related factor 2 (Nrf2) and Heme oxygenase 1 (HO-1) in the liver [55].

A recent study demonstrated that a nanoformulation of ganoderic acid (bioactive component in *Ganoderma lucidum*) significantly attenuated markers of hepatic damage in rats with D-galactosamine-induced hepatotoxicity [56]. Also, a methanolic extract of *Flacourtia sepiaria* exhibited significant hepatoprotective activity and afforded protection from galactosamine-induced liver damage, which could be at least partly attributed to the free radical scavenging activity of the tannins and antioxidants in the extract [57].

Lipopolysaccharide (LPS), a key cell wall component in gram-negative bacteria, can induce severe inflammation leading to hepatic injury [58]. D-galactosamine suppresses the synthesis of different RNAs and increases susceptibility to LPS-induced hepatotoxicity [59]. TNF- α is the main mediator during GalN/LPS-evoked apoptotic liver injury [60]. Also, excess ROS and hepatic GSH depletion are involved in the pathogenesis of GalN/LPS-induced apoptotic liver injury [61].

Amygdalin (D-mandelonitrile- β -D-glucoside-6- β -D-glucoside), also known as laetrile or vitamin B17, is distributed universally in the seeds of almonds, peaches, apricots, and other rosaceous stone fruits and exhibited a protective effect against LPS/GalN-induced acute liver injury that may be associated with the suppression of inflammatory cytokine production, the inhibition of the NLRP3 inflammasome and nuclear factor kappa B (NF- κ B) activation, and the upregulation of the Nrf2/quinone oxidoreductase (NQO1) signaling pathway [62].

Also, rosmarinic acid, extracted from *Rosmarinus officinalis* Linn, can protect C57BL/6 mice from LPS/D-GalN-induced acute liver injury, as indicated not only by the decrease in serum AST and ALT but also in the amelioration of increases in NF- κ B and extracellular signal-regulated kinase (ERK1/2) phosphorylation, p38 protein expression and tissue myeloperoxidase (MPO) content. Moreover, rosmarinic acid can increase the glutathione-dependent peroxidase (GPX) level. Furthermore, rosmarinic acid promoted the Nrf2 transport into the nucleus and then upregulated HO-1, glutamate-cysteine ligase catalytic subunit (GCLC), glutamate-cysteine ligase modifier (GCLM), and NQO1 [63].

Recently, forsythiaside (major active component in *Forsythia suspense*) supplementation alleviated the inflammatory response induced by *Escherichia coli*-derived LPS in broiler chickens by inhibiting the production of TP, NO, LITAF, IL-1 β , IL-17, and IL-6 and by downregulating the mRNA expression of pro-inflammatory cytokines and inducible nitric oxide synthase (iNOS) [64].

Geraniol (GOH) is acyclic monoterpene alcohol isolated from the essential oils of orange, ginger, rose, or lemon [65, 66]. The results showed that LPS/D-GalN-induced fulminant hepatic failure was protected effectively by GOH, as evidenced by the attenuation of pathological liver injury, MPO activity, MDA level, and serum AST and ALT levels. GOH reduced liver TNF- α and IL-1 β levels by inhibiting the activation of the NF- κ B signaling pathway [67]. Furthermore, GOH increased PPAR γ expression in fulminant hepatic failure induced by LPS/D-GalN. This study demonstrated that GOH protects against LPS/D-GalN-induced fulminant hepatic failure by inhibiting the inflammatory response and increasing PPAR γ expression [67].

Tectorigenin, a component of *Belamcanda adams*, has antioxidant, anti-inflammatory, and antiproliferation activities [68]. *In vivo* and *in vitro* studies concluded that pretreatment with tectorigenin ameliorated liver injury, attenuated hepatic inflammation, and decreased mortality in mice with fulminant hepatic failure by inhibiting inflammation through the TLR4/mitogen-activated protein kinase (MAPK) and TLR4/NF- κ B pathways and promoting autophagy [69].

Protection against Thioacetamide-Induced Hepatotoxicity

TAA is an organosulfur, white crystalline compound with liver damage and carcinogenic activity caused by cytomegaly [70]. After the oxidative bioactivation of TAA by CYP enzymes and flavin adenine dinucleotide-containing monooxygenase, TAA metabolites react to cellular proteins and amine lipids, preventing hepatocyte dysfunction and cytotoxicity [71] in addition to dramatically increasing ROS production [72], increasing serum transaminase levels, and remarkably decreasing hepatic GSH levels [73].

Dendropanax morbifera significantly prevents hepatic fibrosis by TGF- β 1/Smads signaling pathways and inhibiting oxidative stress in rats treated with TAA [74]. The administration of an ethanol extract of *Andrographis paniculata* at different doses of (200 and 250 mg/kg bw) to albino rats with TAA-induced hepatotoxicity significantly decreased the levels of serum bilirubin, ALP, SGPT, and SGOT but increased the level of protein in the liver [75].

Protection against Alcohol-Induced Hepatotoxicity

Alcoholic liver disease is a major global health problem. The alcoholic liver disease typically progresses through the stages of alcoholic steatosis, hepatitis, and cirrhosis [76, 77]. Frequent and excessive alcohol consumption leads to about 2.5 million deaths annually [78]. A previous research report linked chronic alcohol consumption to various pathological conditions from simple intoxication to severe life-threatening pathological states [79]. The pathological condition of alcohol-induced liver disease is characterized by a range of morphological changes from minimal injury to advanced liver damage [80]. Chronic ethanol ingestion causes fibrosis, inflammation, hepatomegaly, fatty liver, and cirrhosis, stimulates hepatic oxygen consumption, and induces free radical production.

Fatty liver is present in more than 90% of people with chronic alcoholism, while approximately 10–20% of people who drink heavily progress to alcoholic hepatitis and cirrhosis, indicating that factors such as viral infection (HBV), nutrition, genetic background, and chronic exposure to/intake of xenobiotics, heavy metals, aflatoxins, and paracetamol interact to influence the progression of liver disease [81].

Chronic alcohol consumption has been reported to induce oxidative stress via multiple mechanisms [82, 83]. 3 mechanisms suggested to cause alcoholic liver injury include: (1) acetaldehyde toxicity [84]; (2) exposure to oxidative stress or metabolic generation of ROS [85-88]; and (3) promotion of an immune response that causes oxidative stress in hepatocytes [89-91].

Ethanol is primarily metabolized by alcohol dehydrogenase and aldehyde dehydrogenase enzyme systems that generate acetaldehyde and acetate as products [87]. Acetaldehyde forms adducts with the vital biomolecules DNA and proteins and these adducts are responsible for the impaired structure and function of the liver. Another metabolic pathway that plays a significant role in alcohol toxicity is the CYP2E1 pathway, which comprises a microsomal ethanol oxidation system [83] that is involved in the generation of ROS [92-94].

ROS formation leads to collagen generation in hematopoietic stem cells (HSCs) as acetaldehyde directly upregulates collagen I transcription and indirectly upregulates the synthesis of TGF- β 1 through initiating phagocytosis by macrophages [95]; thus, this process sensitizes hepatocytes to TGF- β -induced apoptosis [96]. In a defensive mechanism, Kupffer cells, along with infiltrating neutrophils and macrophages, potentiate the release of several pro-inflammatory cytokines, including TNF- α , IL-1 β , and IL-6 [97].

Herbal drugs play a role in the treatment and management of various liver disorders [98]. The oral administration of 250 and 500mg/kg of an aqueous extract of *Boswellia serrata* offered significant ($P < 0.01$) dose-dependent protection against hepatotoxicity induced by ethanol [99]. In animal models, by decreasing CYP2E1 activity quercetin, increasing GSH levels, and inducing antioxidant enzymes, the quercetin ameliorated lipid metabolism and ethanol-induced liver damage [87,100]. The activity and expression of CYP2E1 in human hepatocytes is also inhibited by Quercetin [87, 101]. Concerning hepatoprotective effects, *in vitro* investigations have reported that quercetin ameliorated and AST and LDH release from hepatocytes, GSH depletion, lipid peroxidation, and ethanol-induced liver cell injury, while upregulating hemoxygenase-1 via the MAPK/Nrf2 pathways in human hepatocytes [102, 103]. Notably, the induction of HO-1 expression utilizing natural compounds helps protect liver in different experimental models. Quercetin was found to induce HO-1 in the livers of normal ICR mice [104, 105].

Following ethanol intoxication, treatment with quercetin also reversed the ethanol-induced increases in serum aminotransferase levels and liver tissue lipid peroxides and hydroperoxides levels and restored the levels of GSH, SOD, GPX, and GR in rats [106]. The antioxidant effect of quercetin is due to the presence of a rich source of OH groups and conjugating π bond orbital that act as potent H₂O₂ scavengers and proton or electron donors [107].

Silymarin, a traditional herbal medicine extracted from milk thistle fruit (*Silybum marianum* L. Gaertn), is used to protect the liver [108]. Concerning hepatoprotective effects, silymarin has been shown to possess protective effects in both acute and chronic models of ethanol toxicity [109-111]. Tea extract is rich in catechins that can reduce the CYP2E1 expression and hepatic lesions induced by paracetamol injection [112]; moreover, a diet that contained epigallocatechin gallate (EGCG) improved hepatic injury but did not reduce hepatic CYP2E1 levels [113]. Catechins have previously been reported to stimulate the 63 kDa laminin receptor [114-117], which may initiate ROS production [118]. The development of an ethanol-induced acute gastric lesion was prevented by the ingestion of a strawberry extract rich in anthocyanins before ethanol treatment via the induction of gastric antioxidant enzymes [119].

Pretreatment with Changkil saponins extracted from the root of *Platycodon grandiflorum* before ethanol administration significantly decreases hepatic triglyceride level, hepatic lipid peroxidation, hepatic TNF- α level, serum and ALT activity [120]. The liver histopathological studies have indicated that changkil saponins prevents ethanol-induced necrosis and steatosis. Additionally, Changkil saponins are protected against depletion of hepatic GSH levels induced by ethanol. CYP2E1 can contribute to ethanol-induced oxidative stress and liver injury. The concurrent administration of Changkil saponins more efficaciously abrogated CYP2E1 induction and the CYP2E1-dependent hydroxylation of aniline than the administration of individual treatments at high doses.

Curcumin has been reported to be the principal active component of *Cucuma longa*; several recent studies showed the strong antioxidant action of curcumin [121]. Molecular investigations have proven that the administration of curcumin to rats with alcohol-induced liver disease suppresses the expression of iNOS, cyclooxygenase (COX)-2, chemokines, and cytokines in Kupffer cells of the liver and prevents the activation of NF- κ B [122]. Previous studies have shown the protective impact of curcumin against alcohol-induced hepatotoxicity; curcumin mitigates oxidative stress and prevents liver cell damage in experimental animals [123-125]. *In vitro* studies with liver slice culture, the results have shown that lipid peroxidation was decreased by curcumin. Curcumin reduced the release of LDH, and attenuated the antioxidant enzymes GPX, CAT, and SOD [123].

A recent study demonstrated that alcohol-induced hepatic damage in rats was effectively prevented by the extracts of *Radix fici* Hirtae. Moreover, the possible mechanisms of this hepatoprotective effect may be attributed to free radical scavenging and decreased lipid peroxidation [126]. Also, triterpenoids, major components of *G. lucidum*, protected from alcohol-induced liver injury by inhibiting lipid peroxidation, increasing antioxidant enzyme activities, and suppressing apoptosis and the immune-inflammatory response [127].

Protection against Rifampicin- and Isoniazid-Induced Hepatotoxicity

Tuberculosis (TB) has recently become a major health risk along with the increasing HIV epidemic [128]. Isoniazid (INH) and rifampicin (RIF) are the first-line antituberculosis drugs recommended by the World Health Organization. These two drugs are metabolized in the liver, and both INH and RIF cause hepatotoxicity [129]. The mechanism behind RIF- and INH-induced toxicity is a drug-drug interaction in which the induction of hepatic microsomal enzymes by RIF results in the increased production of a hepatotoxic metabolic product of INH [130]. Irreversible damage, including steatosis, inflammation, cell necrosis, and liver failure can be caused by INH/RIF [131-133], which are mainly associated with oxidative stress [134]; Via oxidative stress, INH induces apoptosis and prevents Nrf2 translocation into the nucleus, thereby inhibiting the cytoprotective effect of Nrf2 [135].

By suppressing hepatocyte apoptosis and oxidative stress, plant extracts alleviate liver injury [136]. The naphthoquinones lawsone (2-hydroxy-1,4-naphthoquinone) is the major bioactive component found in the leaves of the henna plant, *Lawsonia inermis* L. (Lythraceae). Lawsone at very low concentrations, significantly restores the cells' viability (7.5 μ M), reduces transaminase secretion, and decreases MDA levels in RIF-INH-treated HepG2 cells [137]. Additionally, the administration of lawsone to the RIF-INH-treated animals significantly decreases the levels of serum transaminases, improves albumin/globulin ratio, and decreases the level of bilirubin [137].

A fruit pulp extract of *Telfairia occidentalis* significantly ($P < 0.001$) reduced the elevated biochemical enzyme markers (ALP, ALT, and AST), lipid profile, and MDA in RIF- and INH-induced oxidative stress and improved the antioxidant potential in rats [138]. A recent study demonstrated that a hot aqueous leaf extract of *Lasianthera africana* attenuated RIF- and INH-induced hepatotoxicity and the major mechanisms of action responsible for this hepatoprotective effect of *L. africana* depend on antioxidant effects [139]. *Tamarix gallica* leaf extract possesses promising hepatoprotective activity against RIF- and INH-induced liver injury in experimental rats [140].

Protection against Non-Steroidal Anti-Inflammatory Drugs (Nsaids)-Induced Hepatotoxicity

10% of the total cases of drug-induced hepatotoxicity are caused by Non-steroidal anti-inflammatory drugs (NSAIDs) [141]. NSAIDs induce liver damage due to ROS production and increase lipid peroxidation by decreasing the GSH levels that induce hepatotoxicity due to the generation of free radicals [142, 143]. Several enzymes found in the cytosol are released into the blood in response to the disturbance of hepatocyte transport function, resulting in increased enzyme levels in the blood serum, which indicate hepatocellular damage [144].

Diclofenac is an extensively circulated drug used for the treatment of pain, musculoskeletal diseases, and inflammation in animals and humans due to anti-inflammatory, analgesic, and antipyretic properties; however, severe pathologic conditions like renal papillary necrosis, hepatotoxicity, gastrointestinal bleeding, peptic ulceration, and renal failure could be as a result of long-term administration of this drug [145-148]. Diclofenac was found to cause a rare but fatal hepatotoxic disorder that may be related to the formation of reactive metabolites (5-hydroxy diclofenac and N,5-dihydroxy diclofenac) [149-151] that may act as ROS/RNS, further increasing the accumulation of endogenous ROS and promoting oxidative stress in animal tissues, which consequently leads lipids, protein, and nucleic acid oxidation [152].

A recent study concluded that ethanol extraction of moringa leaves exhibited *in vivo* antioxidant activity, suggesting a beneficial effect against the oxidative liver damage induced by diclofenac sodium. Also, the bioactive phenolics in ethanol extracts of moringa leaves protected the plasma membrane and increased the reparative and regenerative capacity of the liver [153]. Compared with the control, pretreatment of diclofenac-intoxicated rats with an aqueous ethanol extract of *Dialium guineense* leaf significantly ($p < 0.01$) reduced the levels of ALT, AST, gamma-glutamyl transferase (GGT), MDA, creatinine, and urea and significantly ($p < 0.01$) increased the levels of SOD, CAT, GPX, glutathione S-transferase (GST), GSH, and glucose 6-phosphatase (G6Pase) [154].

Protection against Chemotherapeutic Agent-Induced Hepatotoxicity

Carboplatin is a second-generation platinum group-based chemotherapeutic drug [155] that is commonly used for ovarian, head-neck, and small cell lung cancer and is preferred over other platinum (cisplatin, etc.) group-based drugs due to few

adverse effects and high tolerance [156, 157]. It interacts with nucleophilic molecules including RNA and DNA as it does with all other members of the platinum group when entering the cell and causes various lesions on the purine base after binding to DNA [158].

Cisplatin, as a chemotherapeutic drug, is used to treat different types of malignancies, including head, neck, ovarian, and testicular cancers [158]. Despite the well-documented efficacy of cisplatin in the treatment of a variety of tumors, the clinical use of cisplatin is often limited because of cellular resistance and severe side effects in normal tissues [159-161]. Also, the non-specific action of cisplatin is detrimental to the morphology and functions of vital tissues, which primarily occur in kidneys [162,163], testes [164-166], and liver [167,168]. The exact biochemical and molecular mechanism of cisplatin-induced tissue injury has not been well defined, although many hypotheses propose that cisplatin toxicity is related to the generation of RNS and ROS, which results in cell injury and mitochondrial dysfunction [169, 170]. The key mechanisms involved in cisplatin toxicity include inflammation, oxidative stress, and apoptosis in tissue [171,172].

Pro-apoptotic proteins are activated to induce BCL2-associated X (Bax) translocation to the mitochondrial outer membrane, which causes the release of cytochrome c into the cytosol when cisplatin induces ROS generation [173]. Caspase-9 is initiated and activates downstream caspase-3, which causes apoptosis upon receiving an apoptosis signal from Bax [174]. Also, numerous studies have shown that activated NF- κ B may activate many pro-inflammatory cytokines, such as IL-1 β and TNF- α , and induce inflammatory mediators, such as COX-2 and iNOS [175,176].

Medicinal plants have been recognized as a major source of dietary phytochemicals with strong antioxidant activity, which, when coadministered with chemotherapeutic agents, provide better efficacy than chemotherapeutic drugs alone and attenuate vital tissue toxicity [177-179]. Three limonoids, deacetoxy-7R-hydroxygedunin, 7-deacetoxy-7-oxogedunin, and 17-epi-methyl-6-hydroxyangolensate, were isolated from *Khaya grandifoliola* and found to protect the normal human liver cell line L-02 against cisplatin-induced hepatotoxicity mainly through the induction of mitogen-activated protein kinase phosphatase-1, an endogenous inhibitor of JNK phosphorylation, and through the nuclear translocation of Nrf2 [180]. *Nigella sativa*, known as black cumin, has been used as a traditional medicine to prevent a wide range of diseases in different parts of the world, particularly in Arab countries. A recent study has shown that *N. sativa* seed oil has a hepatoprotective effect that decreases the oxidative stress markers and histological damage in the liver tissue of carboplatin-treated rats [181]. Several plant extracts have hepatoprotective effects against cisplatin-induced hepatotoxicity (Table 3).

Protection against Lead-Induced Hepatotoxicity

Heavy metals (lead, arsenic, mercury, etc.) are severe menaces to human health due to their toxic effects on various vital organs, including the liver. Lead is a potential environmental pollutant that is toxic to most body organs, including organs in the nervous, digestive, and cardiovascular systems as well as the bone, kidney, liver, and blood [182-184]. Long-term exposure to lead even at a low concentrations has been reported to be a potential factor that induces nephrotoxicity, hepatotoxicity, behavioral dysfunction, reproductive dysfunctions, and so on [185-187]. In the organs of animals and humans affected with lead poisoning, the liver is considered the second most common organ for lead storage, followed by the kidney [188]. Also, some research has shown that lead causes liver lipid peroxidation [189,190], GSH reduction [191], and antioxidant defense system destruction [192], which is the main reason for lead-induced liver injury [193, 194].

C. longa (turmeric), native to tropical South Asia, belongs to the *Zingiberaceae* family [195]. Investigations have reported that the liver was protected against lead acetate by *C. longa* at a dose of 500mg/kg body weight [196] and curcumin or nano curcumin at doses of 15mg/kg through decreasing lipid peroxidation, liver enzymes, and oxidative stress, while increasing antioxidant content, such as SOD [197]. Salidroside is a secondary metabolite of *Rhodiola rosea* L. can decrease the lead content in the body, inhibit oxidative stress, increase antioxidant activity, and inhibit liver CYP2E1/NOX2 expression, thus improving the liver tissue structure [198].

Conclusion

Due to universal alcohol overconsumption, medicine administration, and unavoidable environmental pollutants that exist worldwide, chemical-induced liver injuries are very common. The cascades of pathological processes can be initiated by liver injuries, which goes beyond the liver and worsen overall health. Many natural products have been investigated, and their potent hepatoprotective effects have been demonstrated through mechanisms that reduce oxidative stress, decrease inflammation, inhibit apoptosis, ameliorate necrosis, repair DNA damage, and modulate lipid metabolism. These capabilities to restore the structure and function of hepatocytes enable natural products to be considered promising alternatives in the selection of a healthy diet and potential candidates for the development of functional pharmaceuticals and foods. As most of the current evidence is derived from animal-based studies, human trials are needed in the future, and the bioavailability of natural products should be taken into consideration. Moreover, additional natural products should be evaluated for hepatoprotective effects, and the active components of natural products need to be identified and isolated to describe additional active chemicals. Various mechanisms must also be further explored and clarified. This review provides current information regarding the use of natural products in the treatment and prevention of chemical-induced liver injuries. Using this review, people can be advised by physicians and nutritionists to consume some foods and also, medicinal herbs to protect themselves against alcohol, drugs, and environmental pollutants which cause liver injuries.

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Table 1: Natural Products that Display Hepatoprotective Effects against Carbon Tetrachloride Toxicity

| Experimental Model | Natural Products | Reference |
|--------------------|------------------------------------------------------------------|-----------|
| Rats | Matricaria chamomilla L. extract | [199] |
| Rats | Olive oil and N. sativa oil | [200] |
| Rats | Fresh juice of the bark from tender stems of Azadirachta indica | [201] |
| Rats | Extracts of Zapoteca portoricensis leaves | [202] |
| Mice | Apple polyphenols (AP, Appjfnol) | [203] |
| Mice | Rosmarinic acid | [204] |
| Rats | Aerial and root extracts of Gentiana asclepiadea L. | [205] |
| Mice | Oleuropein (leaves and fruits of olive, Olea europaea L.) | [206] |
| Rats | Methanol extract of Solanum xanthocarpum leaves | [207] |
| Rats | Methanol extracts of different parts of Tamarindus indica Linn. | [208] |
| Rats | Citrullus lanatus extract | [209] |
| Mice | Ethanol extracts of Lophatherum gracile leaves | [210] |
| Rats | Extract of Vetiveria zizanioides roots | [211] |
| Rats | Ethyl acetate fraction of L. inermis fruit extract | [212] |
| Rats | Silene villosa (Caryophyllaceae) methanol extract (aerial parts) | [213] |
| Rabbits | Parthenium hysterophorus crude extract | [214] |
| Mice | Ethyl acetate fraction of Dracocephalum rupestre Hance | [215] |
| Mice | Ethanol extract of Syringa oblata Lindl. leaves | [216] |
| Mice | Spondias mombin leaf and stem extracts | [217] |
| Rats | Hydroalcoholic extract of Urena lobata leaves | [218] |
| Rats | Whole plant methanol extracts of Sauropus bacciformis | [219] |
| Mice | Capparis spinosa seeds (extracted with methanol) | [220] |
| Rats | Olea europaea L. dry leaf extract | [221] |
| Rats | Methanol extract of Anacardium occidentale bark | [222] |
| Rats | Aqueous extract of Allium cepa | [223] |
| Rabbits | Aqueous extract of Argyrolobium roseum (whole plant) | [224] |
| Rats | Methanol extract of Kyllinga brevifolia (whole plant) | [225] |
| Rats | Origanum majorana root extract | [226] |
| Rats | Ethanol extract of Nerium indicum Mill. leaves | [227] |
| Rats | Black mulberry (Morus nigra) extract | [228] |
| Rats | Aqueous extract of Atriplex halimus leaves | [229] |
| Rats | Methanol extract of Syzygium samarangense leaves | [230] |
| Rats | Hydroethanolic extract of the stem bark of Oroxylum indicum | [231] |
| Rats | Linum grandiflorum Desf Seed oil. | [232] |
| Rats | Hydroalcoholic extract of Cichorium intybus leaves | [233] |
| Rats | Ethanol extract of Mentha arvensis Leaves | [234] |
| Rats | Aqueous-methanol extract of Cichorium intybus seeds | [235] |
| Rats | Mentha piperita L. essential oil | [236] |
| Rats | Rumex tingitanus leaf extracts | [237] |
| Rats | S. marianum or milk thistle seed extract | [238] |

Table 2: Plants That Have Hepatoprotective Effects against Apap-Induced Hepatotoxicity

| Experimental Model | Natural Products | Reference |
|--------------------|------------------------------------------------------------------------|-----------|
| Rats | <i>Curcuma xanthorrhiza</i> Roxb extracts | [239] |
| Rats | <i>Psidium guajava</i> (guava) fruit polysaccharide | [240] |
| Rats | <i>Opuntia robusta</i> and <i>Opuntia streptacantha</i> fruit extracts | [241] |
| Mice | Methanol extract of <i>Costus Speciosus</i> (Koen. ex. Retz.) | [242] |
| Rats | Aqueous extract of <i>Casuarina equisetifolia</i> | [243] |
| Rats | Chloroform extract of <i>Indigofera barberi</i> (whole plant) | [244] |
| Rats | Leaf extract of <i>Aegle marmelos</i> (L.) Corrêa, Rutaceae | [245] |
| Rats | Aqueous extract of <i>Celosia argentea</i> L. | [246] |
| Rats | Ethanol extract of <i>Pavetta indica</i> Linn leaves | [247] |
| Mice | Ethanol and ethyl acetate extracts of <i>Copaifera multijuga</i> bark | [248] |
| Mice | Polysaccharides isolated from <i>Dendrobium officinale</i> | [249] |
| Rats | Ethanol extract of <i>Centella asiatica</i> Linn. | [250] |
| Rats | Saponarin, isolated from <i>Gypsophila trichotoma</i> Wend. | [251] |
| Rats | <i>N. sativa</i> Linn. oil | [252] |
| Rabbit | Aqueous ethanol extract of <i>Alhagi maurorum</i> Boiss. | [253] |
| Rats | Ethanol extract of <i>Moringa oleifera</i> bark | [254] |
| Rats | Ethanol extract of <i>Trichosanthes lobata</i> | [255] |
| Rats | Leaf extract of <i>Eclipta alba</i> (L.) Hassk. | [256] |
| Rats | Aqueous and ethanolic extracts of <i>Helicanthus elastica</i> | [257] |
| Rats | Zerumbone isolated from the rhizomes of <i>Zingiber zerumbet</i> | [258] |
| Rats | Ethanol and aqueous extracts of <i>Aloe vera</i> Linn. stems | [259] |
| Rats | Ethanolic root extract of <i>Taraxacum syriacum</i> Boiss | [260] |
| Rats | Leaf extract of <i>Pterospermum acerifolium</i> | [261] |
| Mice | Diallyl sulfide (DAS) | [262] |
| Rats | <i>Myristica fragrans</i> (nutmeg) kernel extract | [263] |

Table 3: Plants that Have Hepatoprotective Effects against Cisplatin-Induced Hepatotoxicity

| Experimental Model | Natural Products | Reference |
|--------------------|---------------------------------------------------|-----------|
| Mice | Methanol extract of <i>Capparis spinosa</i> seeds | [220] |
| Mice | <i>N. sativa</i> | [264] |
| Mice | <i>Cuminum cyminum</i> | [264] |
| Rats | Hydro-methanol extract of <i>Cornus mas</i> fruit | [265] |
| Rats | <i>Aegle marmelos</i> fruit | [266] |

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