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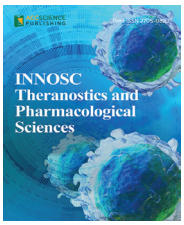

REVIEW ARTICLE

Effects of Medicinal Plants on Carbon Tetrachloride-Induced Liver Injury: A Review

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Abstract:

The liver is the primary organ for metabolizing and eliminating foreign chemicals. When liver cells are exposed to large concentrations of dangerous substances, hepatocyte malfunction, membrane damage, and degradation may occur. Another chemical that can harm the liver is carbon tetrachloride (CCl_4). CCl_4 is converted into trichloromethyl radical $[CCl_3]^-$ by several cytochrome P450 isoforms. $[CCl_3]^-$ subsequently reacts with oxygen to generate trichloromethyl peroxyl radical $[CCl_3OO]^-$ and induce lipid peroxidation in cell membranes. In this study, the mechanism by which a variety of recently identified medicinal plants display hepatoprotective activity against CCl_4-induced liver injury is investigated. We find that animal models have been used in investigations of plant extracts. Herbal plants largely protect against CCl_4-induced hepatotoxicity because their phytochemicals have an inhibitory nature. The antioxidant properties of phytochemicals can halt lipid oxidation and restrict the production of free radicals by inhibiting microsomal enzymes. They can also help liver cells in their fight against CCl_4-induced inflammation by strengthening and fortifying them. The effectiveness of various herbs that are hepatoprotective and are thus plausible candidates for use in medicine must be confirmed. Experiments using entire plant extracts should be replaced with tests that pinpoint the active ingredients and assess the extracts' effect on a variety of liver cell lines.

Keywords: Liver, Hepatocytes, Carbon tetrachloride, Medicinal plants, Hepatoprotective, Inflammation

1. Introduction

Toxicology is the study of how substances adversely affect living things. The toxicological effects of a substance may have significant impact on various aspects, including commercial items, medications, product requirements, waste disposal, enforcement activities, legal disputes, and broader governmental issues. Given the rising importance of these concerns, it is crucial to be aware of the ethical, legal, and cultural ramifications of toxicological research as well as to assess the impact of chemical toxicity on the society. There are several ethical issues in toxicology that need to be addressed. First, the need for extremely well-defined ideals of human, animal, and ecological safety has been highlighted as a result of experiences and current developments in biological sciences. Second, the negative effects of lead, asbestos, and tobacco exposure on human health have led to several legal, administrative, and policy-making initiatives. Third, our framework for analyzing ethical and societal issues has improved. Fourth, all human and animal research must be conducted following ethical and responsible standards. In addition, in view of the inherent uncertainty and biological

variability in biological sciences, a decision must be made with little or no understanding [1].

The liver is the main organ for metabolizing and excreting foreign substances. Organ dysfunction, membrane damage, and liver degeneration invariably follow as a result of liver cell exposure to high quantities of hazardous compounds. The different cell types and functions of the liver allow it to respond to both short-term and long-term injuries in different ways. Understanding the fundamental liver functions, the morphology of the liver, the processes involved in hepatic excretory function, and the causes of cell and organ damage are necessary to identify possible hepatic cell dysfunction and injury. The liver is responsible for the damage caused by chemicals, medicines, drugs, or environmental pollutants despite having a significant ability for regeneration [2]. The liver also plays a critical role in detoxification and metabolism.

Trichloromethyl radical, $[CCl_3]^-$, is formed when cytochromes (CYP)2E1, CYP2B1, or CYP3A activate carbon tetrachloride (CCl_4). Since this radical may attach to lipids, proteins, and nucleic acids, it can impair cellular processes, including lipid metabolism. It has been hypothesized that the formation of adducts between this radical and deoxyribonucleic acid (DNA) is what causes liver cancer. Moreover, this radical may interact with oxygen to form trichloromethyl peroxyl radical, $[CCl_3OO]^-$. The chain reaction of lipid peroxidation, which is initiated by the radical $[CCl_3OO]^-$, attacks, and destroys polyunsaturated fatty acids, especially those linked to phospholipids [3].

Due to the numerous side effects caused by contemporary drugs in allopathic medical practices, many medicinal herbs and their preparations are widely used as effective therapies for liver disorders in indigenous medicinal strategies and classical systems of medicine in Asia, Africa, and other countries [4]. These drugs contain phytochemicals, such as polyphenols, flavonoids, alkaloids, sterols, and xanthenes, that largely contribute to their hepatoprotective effect [5]. Nearly 80% of the world's population, or four billion people, use herbal remedies to cure a range of diseases, and the use of herbal treatment has lately grown across the globe [6-8].

Hence, in this review, an attempt is taken to consolidate the effects of some recently reported medicinal plants against CCl_4-induced liver toxicity.

2. Hepatic functions and artifacts

Due to its ideal location in the body, between the digestive system and the rest of the body, the liver is well suited to perform its fundamental function of promoting metabolic equilibrium in the body. The portal vein transports venous blood from the stomach and intestines to the liver, where it passes via the liver and joins the systemic circulation. Ingested minerals, vitamins, metals, drugs, contaminants, and microbial end products first interact with hepatic cells before reaching the portal blood. These ingested substances are eliminated from the circulation through catabolism, storage, and/or excretion into the bile through efficient scavenging or absorption processes [9]. The basic functioning of the liver may be affected by toxins (**Table 1**).

Toxicants can interfere with or clog the liver's production and transport processes, which may lead to dysfunction without causing significant cell damage. Loss of function may also occur when a large number of cells perish as a result of exposure to dangerous chemicals or when a scar tissue that is incapable of regenerating the original cell mass forms as a result of protracted exposure.

2.1. Types of toxicant-induced liver injury

Liver sensitivity to chemical assaults is substantially influenced by the degree of injury, the volume of cells affected, and whether the contamination is immediate or chronic. The types of toxicants that cause liver injury are shown in **Table 2** [10].

2.2. Liver cell death

The manner of death for liver cells can be either apoptosis or necrosis, depending on their structural makeup. Cell expansion, leakage, nuclear disintegration (karyolysis), and an inflow of inflammatory cells are characteristics of necrosis. When hepatocytes die, the cellular membranes that are leaking can be detected biochemically by examining liver cytosol-derived enzymes such as gamma-glutamyl transpeptidase and alanine or aspartate aminotransferases. Apoptosis, on the other hand, is characterized by cell shrinkage, nuclear disintegration, the production of apoptotic bodies, and the absence of inflammation. It often affects a single cell and removes cells that are no longer essential for the proliferation of aged cells [2,3].

Table 1. Major functions of the liver and consequences of impaired hepatic functions

Type of function	Examples	Consequences of impaired functions
Nutrient homeostasis	Glucose storage and synthesis Cholesterol uptake	Hypoglycemia and confusion Hypercholesterolemia
Filtration of particulates	Products of intestinal bacteria (e.g., endotoxin)	Endotoxemia
Protein synthesis	Clotting factors Albumin Transport proteins	Excess bleeding Hypoalbuminemia and ascites Fatty liver
Bioactivation and detoxification	Bilirubin and ammonia	Jaundice
	Steroid hormones	Loss of secondary male sex characteristics
	Xenobiotics	Diminished drug metabolism and inadequate detoxification

Table 2. Types of toxicant-induced liver toxicity

Type of injury or damage	Representative toxins
Fatty liver	Amiodarone, CCl_4, ethanol, tamoxifen, and valproic acid
Hepatocyte death	Acetaminophen, allyl alcohol, Cu, and dimethyl formamide
Canalicular cholestasis	Chlorpromazine, cyclosporin A, 1,1-dichloroethylene, estrogen, Mn, and phalloidin
Sinusoidal disorders	Anabolic steroids, cyclophosphamide, microcystin, and pyrrolizidine alkaloids

CCl_4: Carbon tetrachloride; Cu: Copper; Mn: Manganese

3. CCl_4-induced liver damage

Trichloromethyl radical, $[CCl_3]^-$, is formed as a result of CCl_4 metabolism by cytochromes (CYP)2E1, CYP2B1, or CYP2B2, and possibly CYP3A. $[CCl_3]^-$ appears to be capable of binding to biological molecules (nucleic acid, protein, and lipid), which might affect crucial physiological processes, such as fat breakdown, and might cause fatty degeneration (steatosis). It is believed that hepatic cancer is caused by an adduct formed by $[CCl_3]^-$ and DNA. However, by combining with oxygen, this radical can produce potently oxidizing trichloromethyl peroxyl radical $[CCl_3OO]^-$. The chain reaction of lipid peroxidation triggered by $[CCl_3OO]^-$ attacks and destroys polyunsaturated fatty acids, especially those linked to phospholipids [3] (Figure 1).

As a result, the equilibrium and sequestration of cytosolic calcium are compromised, thus potentially

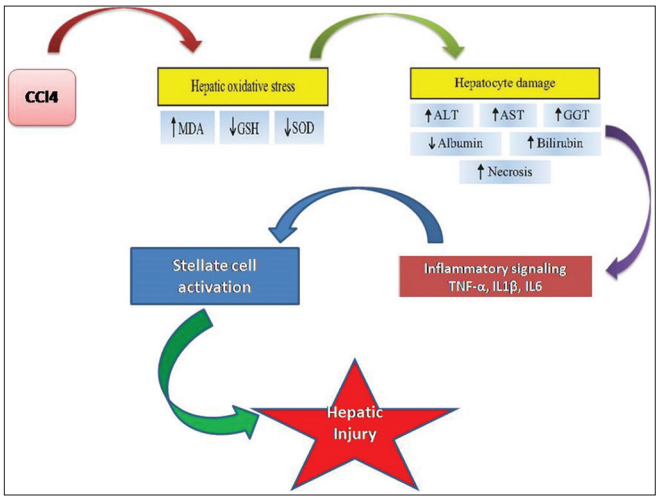

Figure 1. A schematic presentation of the mechanisms of carbon tetrachloride-induced hepatic damage.

leading to future cell injury. The permittivity of plasma, endoplasmic reticulum, and mitochondrial membranes is also affected by this. Reactive aldehydes, in particular 4-hydroxynonenal, are byproducts of fatty acid degradation that readily bind to functional protein groups and inhibit essential enzyme activities. Another consequence of CCl_4 toxicity is the hypomethylation of cellular components (proteins); in the case of ribonucleic acid (RNA), this is anticipated to decrease protein synthesis, while in the case of phospholipids, it helps to limit lipoprotein release.

At the cellular level (inside the cell), CCl_4 increases specific markers, such as tumor necrosis factor alpha (TNF-α), nitric oxide (NO), and transforming growth factor (TGF)-α and -β, as well

as actions that appear to primarily cause the cell to develop cirrhosis or fibrosis. While TNF-α induces cell death, TGFs appear to accelerate fibrosis. TNF-α induces the production of interleukin (IL)-6, which has a strong antiapoptotic effect, while IL-10 inhibits the effects of TNF-α. Therefore, both interleukins can initiate the repair process of CCl_4-damaged hepatocytes [3].

4. Medicinal plants with hepatoprotective activity in CCl_4 models

4.1. *Acalypha wilkesiana*

Many scientists are currently focusing their efforts on identifying and researching medicinal plants that might serve as a shield against any cellular or tissue injury. In a study, reno-hepatic tissue damage caused by CCl_4 in rats was investigated to determine the restorative effect of *A. wilkesiana* java white ethanol extract. All oral treatments with the extract were administered following 1 mL/kg of 50% v/v CCl_4 intravenous injection to induce tissue damage. The extract successfully prevented the abnormal development of CCl_4 reno-hepatic tissue by lowering the increased levels of alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), lactate dehydrogenase, gamma-glutamyl transferase, urea, and creatinine in the blood. Through a molecular docking analysis, the study showed that 2,6,10-trimethyldodecane, 2-bromododecane, and 3-methyltridecane had the highest binding affinity to adenomatous polyposis coli protein. Histological examination also showed regeneration of the liver and kidney cells [11]. This investigation shows that *A. wilkesiana* java white ethanol extract has restorative effects on CCl_4-induced reno-hepatic tissue dysfunctions.

4.2. *Aegle marmelos*

Methanol extracts from the leaves and fruits of *A. marmelos* (Rutaceae) were investigated to determine their efficiency in CCl_4-induced liver damage mice. Numerous biochemical tests, such as those for blood lipid profile, liver enzyme activity, and glycolytic enzyme profile, were thus carried out. In addition, lactate dehydrogenase and succinate dehydrogenase were also investigated. The results demonstrated a significant increase in lipid profiles, transaminase biomarkers, and glycolytic enzyme activity due to CCl_4-induced hepatotoxicity. The biochemical results were supported by a histopathological examination. The animals that received both *A. marmelos* extracts showed signs of improvement in both cellular and biochemical results. In light of their potential to normalize liver enzyme indicators, repair the hepatic structure, and restore the body's physiological condition against CCl_4 intoxication, it may be inferred that both extracts could be employed therapeutically [12].

4.3. *Alstonia congensis*

The hepatoprotective and *in vivo* antioxidant properties of *Alstonia congensis* stem bark extract were investigated in CCl_4-induced liver injury Wistar rats. The rats were given oral treatments containing 200 and 400 mg/kg of stem bark extract for 2 weeks. A single dose of 3 mL/kg of CCl_4 mixed with olive oil was administered intraperitoneally to induce liver damage in the rats. The rats that were administered with *A. congensis* methanol extract showed a significant increase in total protein, albumin, reduced glutathione, and superoxide dismutase activity but a significant decrease in serum ALP, ALT, AST, and bilirubin levels, as well as hepatic tissue lipid peroxidation when compared to the control group. The findings were reinforced by histopathological findings. The results demonstrate that the bark extract has dose-dependent *in vivo* antioxidant and hepatoprotective properties against CCl_4-induced liver impairment [13].

4.4. *Curcuma longa*

Conventionally, patients with hepatic dysfunction are treated with the rhizome of *C. longa* L. *C. longa* is a popular spice, coloring, flavoring, and traditional medicine that is of the ginger family and is extensively used in China, India, and Japan. In an acute CCl_4-induced liver stress model, the hepatoprotective effects of *C. longa* extract and its active component curcumin were investigated [14]. A single intraperitoneal dose of CCl_4 (0.1 mL/kg body weight) caused acute hepatic stress in rats. Three doses of *C. longa* extract (100, 200, and 300 mg/kg/day) were given orally, once daily, for 3 days, while 200 mg/kg/day of curcumin was given orally once daily. The study investigated the total lipid, triglyceride, and cholesterol levels, lipid peroxidation, and the ALT and AST

activity [14]. At 100 g *C. longa*, the curcuminoid components curcumin (901.63 ± 5.37 mg/100 g), bis-demethoxycurcumin (108.28 ± 2.89 mg/100 g), and demethoxycurcumin (234.85 ± 1.85 mg/100 g) were quantified through high-performance liquid chromatography. In CCl_4-treated rats, serum AST and ALT levels increased 2.1- and 1.2-fold compared with the control. CCl_4-induced AST but not ALT elevation was significantly alleviated in *C. longa* and curcumin-treated rats. The peroxidation of membrane lipids in the liver was prevented by *C. longa* (100, 200, and 300 mg/kg/day) on tissue lipid peroxidation assay and immunostaining with anti-4-hydroxynonenal antibody. *C. longa* extract and curcumin exhibited significant protection against liver injury by improving hepatic superoxide dismutase ($P < 0.05$), glutathione peroxidase activity, and glutathione content in the CCl_4-treated group ($P < 0.05$), leading to reduced lipid peroxidase level [14]. By reducing hepatic oxidative stress, *C. longa* extract and curcumin protected the liver from acute CCl_4-induced damage in the rat model. Therefore, curcumin and *C. longa* extract are potential therapeutic antioxidant agents for treating acute hepatotoxicity [14].

4.5. *Dicranostiga Leptodu*

The *D. Leptodu* (Maxim.) fedde poppy plant is said to offer several benefits and medicinal properties. It also has the capacity to purge and scavenge free radicals. Extracts of this plant have been shown to reduce CCl_4-induced liver failure in rats by increasing anti-oxidative enzyme activity to improve mitochondrial function. In a study, pre-treating mouse liver with the extract decreased the morphological damage and the enhanced lipid peroxidation brought on by CCl_4. The extract also improved mitochondrial function by reducing respiratory chain disruption and mitochondrial Na^+K^+-ATPase and Ca^{2+}-ATPase activity. In addition, feeding the extract boosted the levels of catalase, glutathione peroxidase, and superoxide dismutase, while maintaining the equilibrium of the redox status. These findings suggest that the extract can be used as a potential toxic defense agent for the liver against hepatotoxic agents since its protective effect against toxic on mice hepatocytes is influenced by improving mitochondrial respiratory function and maintaining the equilibrium of the redox condition [15].

4.6. *Jasminum grandiflorum*

J. grandiflorum is a medicinal plant that contains several bioactive elements. A study has investigated the effect of two of this plant's components and four different extracts on acute CCl4-induced liver abnormalities and related cellular processes. By administering 10 mL/kg of 1% CCl_4 intraperitoneally to C57BL/6 male mice at 7 weeks of age, a liver damage model was established. The two functional compounds and extracts showed varying degrees of protective effects against CCl_4-induced liver damage by lowering the increased levels of blood transaminases and the hepatic index as well as attenuating the histological alterations in mice. The plant that was extracted using petroleum ether, however, had a far more noticeable effect. The liver's oxidative stress and inflammation were both dramatically decreased by the same extract. In addition to the petroleum ether extract, the other extracts blocked the expression of cytochrome CYP2E1 to safeguard the liver tissue. These results imply that the extracts and their constituent parts may have prospective preventive properties by imposing antioxidative and anti-inflammatory effects over CCl_4-induced hepatotoxicity in mice [16].

4.7. *Maytenus robusta*

The hepatoprotective effect of a methanolic extract from *Maytenus robusta* leaves was investigated in mice and HepG2 cells. When mice were given CCl_4, as opposed to the control group, the lobular structure of their liver was severely disrupted. In addition, their blood ALT levels were noticeably raised. *M. robusta* extract reduced the histological changes in the liver and restored ALT levels to normal. The hepatocyte antioxidant effect of the extract stimulated a decrease in glutathione synthesis, an increase in the levels of superoxide dismutase, catalase, and glutathione-S-transferase, as well as a decrease in lipoperoxide levels when compared with the vehicle group. In addition, the extract decreased myeloperoxidase activity, TNF-α, and IL-6 concentrations in comparison with the control group, which decreased hepatic inflammation. HepG2 cells showed a survival of 29.56 ± 3.07% after being incubated with CCl_4; however, the extract (300 g/mL) increased survival

to 65.27 ± 8.75% and aspartate aminotransferase levels to 41.82 ± 4.41 U/L. At 2000 mg/kg, the extract had an IC_{50} of 14.44 and 3.00 g/mL for 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), respectively, and did not cause acute toxicity in mice. In general, the antioxidant properties of *M. robusta* support its hepatoprotective potential [17].

4.8. *Portulaca oleracea*

P. oleracea, one of the most popularly used dietary herbs, has a variety of bioactivities, including anti-inflammatory, antibacterial, and antioxidant effects. Several deadly hepatopathies may be facilitated by acute liver injury. CCl_4 is an example of an ecological toxin that may induce acute liver injury. Studies on rats have shown that supplementing with the extract reduced the amount of lactate dehydrogenase and serum transaminases as well as the production of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) in mice with CCl_4-induced hepatic injury. There was a significant decrease in serum transaminase activity following extract treatment in HepG2 cells. Furthermore, both *in vivo* and *in vitro* investigations have shown that the extract greatly reduced the production of pro-inflammatory indicators S100A8 and S100A9 protein on CCl_4-induced acute liver damage. Therefore, this herb may limit the flow of pro-inflammatory cytokines, plunging S100A8 and S100A9 expression, and suggesting a prospective therapeutic significance for managing the disease [18].

4.9. *Punica granatum*

As one of the healthiest fruits, due to its high nutritional value of minerals, vitamins, and protective antioxidant molecules, a study has been conducted to highlight the therapeutic benefits of pomegranate (*P. granatum*) fruits and peel in CCl_4-injected rats. Before the experiment, all of the rats were divided into seven groups ($n = 6$) and fed a basal diet for 7 days. The first group, as the control negative group, was fed only the basal diet for 28 days. The remaining rats were injected with CCl_4. Five groups were fed with varying quantities of experimental food (5%, 10%, and 15% fruits; and 5% and 10% peel), whereas one group that was diagnosed with the illness and disease was not fed the experimental diet. The results demonstrated that the total and direct bilirubin levels in the rats that were injected with $CC1_4$ to induce hepatopathy were substantially greater than those in normal rats. When taking into consideration of direct bilirubin levels, the best treatment was 5% pomegranate fruits. The levels of transaminase and ALP all reduced dramatically after consuming 5%, 10%, and 15% of the fruits and 5% and 10% of the peel compared with the control (+ve) group. A remarkable drop in transaminase and ALP levels was observed especially in the group receiving 5% of pomegranate fruits in comparison with the control (+ve) group [19].

4.10. *Rosmarinus officinalis*

There are claims that *R. officinalis* extracts protect the liver from injuries. A study that investigated the hepatoprotective effects of *R. officinalis* cold-pressed oil against CCl_4-induced liver damage in laboratory rats has been conducted. The rats in the study were given two doses of *R. officinalis* cold-pressed oil (1 mL/kg in olive oil) orally, along with $CCl_{4\,(}$1 mg/kg) for 8 weeks. After the delivery of 200 mg/kg oil, the levels of creatinine, urea, and uric acid decreased. Analyses of the components of the oil were also carried out. After 8 weeks of treatment, the levels of total lipids, total cholesterol, total triacylglycerol, low-density lipoprotein cholesterol, and very-low-density lipoprotein cholesterol all dropped. In rats fed with oil, malondialdehyde levels were lower, while glutathione levels were greater. The oil reduced renal function levels, lipid and protein profiles, as well as the elevated activity of liver transaminase and ALP. A histological examination of the liver revealed that oil therapy appeared to have reduced fatty degenerations, cytoplasmic vacuolization, and necrotic cells. Oil may have a hepatoprotective effect against CCl_4-induced damage as a result of its antioxidant properties. Being a major source of phenolics and tocopherols, which are reactive species scavengers, this oil is a potential ingredient for medications and functional food [20].

4.11. *Terminalia bellirica*

The medicinal plant *T. bellirica* (Gaertn.) Roxb. serves as a rejuvenator and all-purpose health booster in the treatment of several ailments in

traditional medical systems like Ayurveda. The fruit of this plant is one of the components of the traditional Ayurvedic medicine "Triphala." The preventive effect of the aqueous acetone extract from this fruit against CCl_4-induced liver damage and oxidative stress in an animal model has been evaluated, along with the advantages of the extract in two dosages (200 and 400 mg/kg). After treatment, the total bilirubin, total protein, albumin, globulin, and albumin-globulin ratio were evaluated, along with liver function indicators, such as ALT, AST, and ALP, as well as the hepatic oxidative assaults or protective antioxidants (superoxide dismutase, catalase, and reduced glutathione). Supplementation with the extract markedly decreased the levels of the biochemical indicators compared with the elevated levels seen in CCl_4-treated animals. The restoration of normal tissue architecture was also observed through histological examination. The results of the aqueous acetone extract of *T. bellirica* fruits (400 mg/kg) were found to be comparable across all parameters to those of the recommended drug (silymarin) [21]. The aforementioned results point to the plant's medicinal potential for reducing hepatic oxidative stress and injury, thus supporting its conventional application in this context [21].

4.12. *Tradescantia pallida*

Hepatic cirrhosis is a neglected public health issue on a global scale. Present-day medications used for therapy are still ineffective. Although *T. pallida*, a plant native to Mexico, has a lot of antioxidants, little is known about how it works. Its ethanol extract has been assessed using histopathology, along with the evaluation of functional and biochemical indicators. The efficiency of the extract (50 mg/kg) was evaluated in a Wistar rat model of chronic CCl_4-induced hepatotoxicity. When the extract was co-administered, the increased ALP, albumin, AST, and ALT levels significantly dropped. The histopathological examination findings supported the functional and biochemical findings. The extract boosted the expression of genes related to antioxidant (nuclear factor erythroid 2-related factor 2, NRF2 and NAD(P)H quinone oxidoreductase 1, NQO1) and antifibrotic (matrix metalloproteinase-2, MMP-2 and tissue inhibitor of metalloproteinase 3, TIMP-3) processes in chronically CCl_4-intoxicated rats. These findings indicate that this extract and silymarin, a popular hepatoprotective compound, both have beneficial hepatoprotective properties [22].

4.13. *Vaccinium macrocarpon*

A study has been conducted to investigate the liver-protective properties of cranberry (*V. macrocarpon*) extract against CCl_4-induced liver damage using an *in vivo* mouse model. The study investigated how well the extract (200 and 400 mg/kg) prevented liver damage brought on by CCl_4 (4 mL/kg). The results showed that there was a significant degree of hepatotoxicity in laboratory mice exposed to CCl_4 compared with the untreated group. Following oral administration of the extract, the liver transaminases and ALP significantly decreased, while the endogenous antioxidant defense was strengthened (reduced glutathione, catalase, and superoxide dismutase). In addition, plasma malonaldehyde levels were reduced in rats that were given the extract [23]. According to the collected data, the extract provides significant antioxidant defense against oxidative stress caused by free radicals and exhibits remarkable hepatoprotective potential over chemical-induced hepatotoxicity [23].

5. Mechanisms of herbs against CCl_4-induced hepatotoxicity

By reducing the oxidative burden on liver enzymes, extracts from various natural resources may be hepatoprotective against CCl_4-induced damage at varying doses. The findings of the present study show that much research has been done on how these natural substances affect CCl_4-induced toxicity in animals (**Table 3**). There would be a rise in hepatoprotective chemicals without equivalent therapeutic value if the full extract is not broken down to identify its active components. There is a pressing need for research into specific components of plant extract, particularly through the employment of animal models for experiments. Herbal plants primarily defend against CCl_4-induced hepatotoxicity in view of the inhibitory nature of their phytochemicals. By blocking microsomal enzymes, these phytochemicals can halt lipid oxidation and limit the formation of free radicals with their antioxidant capabilities. They can also promote radical scavenging, liver cell

Table 3. Hepatoprotective herbs against carbon tetrachloride-induced liver toxicity

Medicinal plants	Key findings	References
Acalypha wilkesiana	• Transaminase, ALP, lactate dehydrogenase, gamma-glutamyl transferase, urea, and creatinine levels in the blood were all significantly reduced by the extract. • According to an immunohistochemistry examination, the extract-treated liver and kidney tissues both showed reduced expression of adenomatous polyposis coli.	[11]
Aegle marmelos	• The measurements for blood lipid profile, liver enzyme activity, transaminase biomarkers, glycolytic enzyme profile, succinate dehydrogenase, and lactate dehydrogenase improved. • The body's physiological state was restored to protect it against CCl_4 toxicity, and the hepatic structure was repaired.	[12]
Alstonia congensis	• In addition to an increase in total protein, albumin, reduced glutathione, and superoxide dismutase activity, there was a notable reduction in serum ALP, ALT, AST, bilirubin, and hepatic tissue lipid peroxidation. These conclusions were supported by histopathological results.	[13]
Curcuma longa	• Serum AST and ALT levels increased by 2.1- and 1.2-fold compared with the control. CCl_4-induced elevation of AST but not ALT was significantly alleviated in *C. longa* and curcumin-treated rats. • Peroxidation of membrane lipids in the liver was significantly prevented by *C. longa* on tissue lipid peroxidation assay and immunostaining with anti-4- hydroxynonenal antibody. • *C. longa* extract and curcumin exhibited significant protection against liver injury by improving hepatic superoxide dismutase and glutathione peroxidase activity, as well as glutathione content in the CCl_4-treated group, leading to reduced lipid peroxidase level. • Curcumin and *C. longa* extract are possible therapeutic antioxidant agents for treating acute hepatotoxicity.	[14]
Dicranostiga Leptodu	• Using the extract as a pre-treatment decreased the morphological damage and increased lipid peroxidation. • The extract improved mitochondrial function by reducing respiratory chain disruption, inhibiting the effectiveness of the mitochondrial Na^+K^+-ATPase and Ca^{2+}-ATPase, and enhancing the activities of endogenous antioxidants.	[15]
Jasminum grandiflorum	• The extract attenuated histological alterations and decreased the increased serum transaminases and liver index. • TNF-α, the signal pathway, NF-κB p65, and the inflammatory molecules IL-1β and IL-6 were all markedly reduced.	[16]
Maytenus robusta	• The extract normalized the ALT levels. • The extract promoted the reduction of lipoperoxide, increased reduced glutathione levels, and improved the activity of catalase, glutathione-S-transferase, and superoxide dismutase. • The extract reduced the levels of TNF-α, IL-6, and myeloperoxidase activity, which reduced hepatic inflammation. • The extract amplified the viability of HepG2 cells.	[17]
Portulaca oleracea	• The release of the pro-inflammatory cytokines and the levels of lactate dehydrogenase and serum transaminases were all reduced when the extract was added to the diet (IL-1β, IL-6, and TNF-α). • Pro-inflammatory markers S100A8 and S100A9 protein were significantly down-regulated by the extract.	[18]
Punica granatum	• The addition of fruits or peels considerably reduced both total and direct bilirubin levels. • ALP and transaminase values all fell sharply.	[19]

(Cont'd...)

Table 3. *(Continued)*

Medicinal plants	Key findings	References
Rosmarinus officinalis	• After the delivery of 200 mg/kg oil, the levels of creatinine, urea, and uric acid decreased. • Total lipids, total cholesterol, total triacylglycerol, and low-density lipoprotein cholesterol, and very-low-density lipoprotein cholesterol all dropped. • Kidney function levels, lipid and protein profiles, liver transaminase, and ALP levels were all lowered. • A liver histological study revealed slight fatty degenerations, cytoplasmic vacuolization, and necrotic cells.	[20]
Terminalia bellirica	• ALT, AST, ALP, total bilirubin, total protein, albumin, globulin, and albumin-globulin ratio all improved after administration of the extract, as were hepatic oxidative stress or protective antioxidants (superoxide dismutase, catalase, and reduced glutathione). • The restoration of normal tissue architecture was observed through histological analysis.	[21]
Tradescantia pallida	• When the extract was co-administered, the levels of ALP, albumin, AST, and ALT were all reduced. • The extract boosted the expression of genes related to antioxidant (NRF2 and NQO1) and antifibrotic (MMP-2 and TIMP-3) processes in chronically CCl_4-intoxicated mice.	[22]
Vaccinium macrocarpon	• Liver transaminase enzymes and ALP revealed a considerable dose-dependent reduction in response to the extract, which also improved endogenous antioxidant defense and reduced plasma malonaldehyde levels.	[23]

ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate aminotransferase; CCl_4: Carbon tetrachloride; IL: Interleukin; MMP-2: Matrix metalloproteinase-2; NF-κB: Nuclear factor kappa B; NQO1: NAD (P) H quinone oxidoreductase 1; NRF2: Nuclear factor erythroid 2-related factor 2; TIMP-3: Tissue inhibitor of metalloproteinase 3; TNF: Tumor necrosis factor

regeneration, and the ability of liver cells to fend off CCl_4-induced inflammation [24,25].

Table 3 is a summary of the most current findings, along with their citations. According to the findings in **Table 3**, these plant extracts upregulate the activity of antioxidant enzymes and total protein, while downregulating serum liver marker enzymes, such as serum transaminase, ALP, total bilirubin, and malondialdehyde. In addition, medicinal plants reduce the expression of inflammatory markers in liver cells. Through histology analyses, a number of research results have verified the hepatoprotective efficacy of these medicinal plant compounds.

6. Conclusion

We deduce from this that some recently discovered medicinal plants have hepatoprotective properties against CCl_4-induced toxicity. They essentially restore the liver's structure and functionality by reducing the liver marker enzymes and boosting the liver's natural antioxidant status. In addition, inflammation plays a role in CCl_4-induced liver damage. We observe that medicinal herbs lessen the liver damage caused by CCl_4 by blocking certain pro-inflammatory signals. It is necessary to validate the efficacy of the herbs that have been suggested to be hepatoprotective and are therefore potential candidates for medicinal use. Experiments that identify active components and assess the effects of the extracts on several liver cell lines should replace those employing full plant extracts.

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Conflict of interest

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Author contributions

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