RESEARCH PAPER

Plant-Based Antioxidants in the Prevention and Treatment of Oxidative Stress–Driven Liver Injury: Mechanisms, Efficacy, and Future Perspectives

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ABSTRACT

Background

Globally, liver diseases are still a big health problem and cause a lot of sickness and death. Oxidative stress plays a central role in the pathogenesis of various hepatic disorders, including drug-induced liver injury, non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, viral hepatitis, and cirrhosis. Excessive generation of ROS (Reactive oxygen species) results in cellular redox dyshomeostasis followed by lipid peroxidation, protein oxidation, DNA damage, mitochondrial dysfunction, inflammation, and hepatocellular apoptosis.

Objective

In recent years, plant-derived antioxidants have gained significant attention as potential therapeutic agents for the prevention and control of oxidative stress–mediated liver injury. This review aims to critically analyze the molecular pathways underlying antioxidant hepatoprotection and the therapeutic potential of plant-derived antioxidants.

Mechanisms

The review identifies the molecular pathways underlying antioxidant hepatoprotection including modulation of the Nrf2/Keap1/ARE signaling pathway, inhibition of NF-κB–mediated inflammatory cascades, regulation of apoptotic markers (Bax/Bcl-2, caspases) and attenuation of pro-fibrotic mediators. Special emphasis is placed on bioactive phytoconstituents such as flavonoids, phenolic acids, alkaloids, terpenoids and saponins that possess potent free radical scavenging and cytoprotective properties.

Experimental Models and Future Directions

Experimental in vitro and in vivo models commonly used for hepatoprotective activity evaluation are also discussed. In this regard, new evidence to back the therapeutics potential of little explored medicinal plants such as Corchorus trilocularis is critically analysed with reference to their phytochemical and antioxidant potential. However, bioavailability, standardization, dose optimization, and clinical translation challenges represent significant barriers despite promising preclinical evidences.

Conclusion

Antioxidants from plants, in general, offer an integrative and mechanistically validated remedy for oxidative stress–induced hepatic injury. Future researches focusing on molecular targeting, advanced drug delivery systems, and well-designed clinical trials are essential to translate these phytopharmacological interventions into effective hepatoprotective therapies.

Keywords: Oxidative stress; Hepatoprotection; Plant-derived antioxidants; Nrf2 pathway; Reactive oxygen species; Corchorus trilocularis; Phytopharmacology.

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ABSTRACT:

Globally, liver diseases are still a big health problem and cause a lot of sickness and death. Oxidative stress plays a central role in the pathogenesis of various hepatic disorders, including drug-induced liver injury, non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, viral hepatitis, and cirrhosis. Excessive generation of ROS (Reactive oxygen species) results in cellular redox dyshomeostasis followed by lipid peroxidation, protein oxidation, DNA damage, mitochondrial dysfunction, inflammation, and hepatocellular apoptosis. In recent years, plant-

derived antioxidants have gained significant attention as potential therapeutic agents for the prevention and control of oxidative stress–mediated liver injury. Finally, the review also identifies the molecular pathways underlying antioxidant hepatoprotection including modulation of the Nrf2/Keap1/ARE signaling pathway, inhibition of NF-κB–mediated inflammatory cascades, regulation of apoptotic markers (Bax/Bcl-2, caspases) and attenuation of pro-fibrotic mediators. Special emphasis is placed on bioactive phytoconstituents such as flavonoids, phenolic acids, alkaloids, terpenoids and saponins that possess potent free radical scavenging and cytoprotective properties. Experimental in vitro and in vivo models commonly used for hepatoprotective activity evaluation are also discussed. In this regard, new evidence to back the therapeutics potential of little explored medicinal plants such as Corchorus trilocularis is critically analysed with reference to their phytochemical and antioxidant potential. However, bioavailability, standardization, dose optimization, and clinical translation challenges represent significant barriers despite promising preclinical evidences. Antioxidants from plants, in general, offer an integrative and mechanistic validated remedy of oxidative stress–induced hepatic injury. Future researches focusing on molecular targeting, advanced drug delivery systems, and well-designed clinical trials are essential to translate these phytopharmacological interventions into effective hepatoprotective therapies.

Keywords: Oxidative stress; Hepatoprotection; Plant-derived antioxidants; Nrf2 pathway; Reactive oxygen species; *Corchorus trilocularis*; Phytopharmacology.

INTRODUCTION :

1. Introduction to Liver Disorders and Global Burden

The liver is a vital organ with a wide range of functions, including metabolism, detoxification, protein synthesis, and immunological roles (1). Liver disorders include viral hepatitis, alcoholic liver disease (ALD), metabolic dysfunction-associated steatotic liver disease (MASLD, previously known as non-alcoholic fatty liver disease [NAFLD], cirrhosis, acute liver failure, and hepatocellular carcinoma (HCC)(2). These disorders account for significant morbidity and mortality worldwide, making them a significant public health burden globally(1,3).

Chronic liver disease (CLD) and its complications cause many deaths worldwide. Liver diseases are responsible for about 2 million deaths per year, accounting for around 4 percent of all deaths worldwide, according to global figures (1). These liver diseases are either complications of cirrhosis and liver cancer or cause them, making liver disease one of the causes of death worldwide. Despite the decrease in cirrhosis from viral hepatitis in many regions, liver cirrhosis alone continues to experience incidence and prevalence with metabolic and lifestyle-linked etiologies predominant, including MASLD and alcohol use (4).

MASLD has emerged as the widest chronic liver disease worldwide, with estimated global prevalence exceeding 30% of the adult population. MASLD has emerged as the most popular form of chronic liver disease worldwide, with the estimated global prevalence standing at over 30% of an adult population, with obesity, type 2 diabetes mellitus and metabolic syndrome being responsible for this dramatic increase. MASLD may progress to non-alcoholic steatohepatitis (NASH), hepatic fibrosis, cirrhosis, and HCC, thus increasing morbidity and mortality significantly. Viral hepatitis remains another major global contributor to liver disease burden – chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections combined cause over 1.1 million deaths per annum, a mortality rate comparable to tuberculosis and one that exceeds those of HIV or malaria.

Alcohol-related liver disease (ALD) is another significant liver disease globally relevant with its prevalence largely depending on the prevailing regional alcoholism patterns. Liver cirrhosis and CLD, on the other hand, contribute a significant proportion of DALYs, especially in LICs and MICs, the surviving years, and otherwise.

The economic impact of liver diseases is profound owing to health care costs, loss of productivity, and long-term management requirements. Also, liver cancer – mainly HCC is still among the highest leading cancer deaths globally. This makes it important to advance prevention, early diagnosis, and therapeutic interventions aimed at the key etiologies of liver disease (5).

2. Role of Oxidative Stress in Hepatic Injury

Oxidative stress is the major factor in the initiation and progression of acute and chronic liver diseases. This happens when the generation of reactive oxygen species (ROS) surpasses the detoxification capacity of endogenous antioxidant mechanisms, thus causing a disruption in the cellular redox homeostasis. Overproduction of ROS prompts lipid peroxidation, protein oxidation, mitochondrial dysfunction, inflammatory signaling, and apoptosis of hepatocytes that worsen liver injury (6)(7).

- **Sources of Reactive Oxygen Species in the Liver**

The liver is very vulnerable to oxidative stress

because it is highly metabolic and possesses a lot of mitochondria. The main intracellular sources of ROS are the electron transport chain in mitochondria, cytochrome P450 enzymes (CYP2E1), NADPH oxidases (NOX), and peroxisomal β-oxidation. In alcohol-related liver disease, induction of CYP2E1 results in enhanced ROS formation and culminates in oxidative damage and mitochondrial impairment (8). Similarly, in metabolic dysfunction-associated steatotic liver disease (MASLD), this enhances mitochondrial ROS generation and promotes the progression from simple steatosis to steatohepatitis (9). In viral hepatitis, oxidative stress results from viral protein-mediated mitochondrial damage along with a chronic inflammatory immune response, worsening the hepatocellular damage and fibrogenesis.

- **Mechanisms of Oxidative Cellular Damage**

Reactive oxygen species such as superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH) initiate lipid peroxidation of the polyunsaturated fatty acids of the hepatocytes membrane. These toxic aldehydes include malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) and amplify cellular injury (10). Lipid peroxidation of polyunsaturated fatty acids in hepatocyte membranes caused by reactive oxygen species:
superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH) results in the production of toxic aldehydes malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), which enhance cellular injury (10). Mitochondrial dysfunction is one of the key outcomes of prolonged oxidative stress. Mitochondrial membrane damage leads to cytochrome c release and induction of caspase-dependent apoptotic cascades (10). Necrosis is also a possible sequela of severe oxidative injury, precipitating further inflammatory reactions and fibrosis progression.

- **Inflammatory Signalling and Fibrosis**

Oxidative stress activates redox-sensitive transcription factors such as nuclear factor-κB (NF-κB), upregulating pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) (11). This inflammatory cascade further worsens the condition by exerting stress on the hepatocytes hence, contributing to disease progression. In addition, ROS induce the stimulation of hepatic stellate cells (HSCs), which are essential for liver fibrogenesis. Activated HSCs produce excessive extracellular matrix proteins, leading to fibrosis and eventually cirrhosis (12). Hence, persistent oxidative stress provides the molecular links between inflammation, fibrosis, and hepatocellular carcinoma.

- **Endogenous Antioxidant Defence Mechanisms**

Antioxidant systems that are inherent in the liver include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and the reduced glutathione (GSH) (13)(14).
Nuclear factor erythroid 2-related factor 2 (Nrf2) pathway governs the transcription of antioxidant response element (ARE)-dependent genes involved in detoxification and cytoprotection (15). However, the protective mechanisms may get overwhelmed by the oxidative stress resulting in progressive hepatic injury.

3. Molecular Mechanisms (ROS, Nrf2, NF-κB, Apoptosis pathways)

The oxidative stress mechanisms that affect hepatocyte harm are complex and involve a range of signalling pathways involving ROS, redox-sensitive transcription factors, inflammatory mediators and programmed cell death pathways. The most important mechanisms that are all known to have an important role in liver pathophysiology are the cascade of events that lead to the generation of ROS, the antioxidant pathway based on the Nrf2/Keap1 system, the signalling pathway of inflammation (NF-κB pathway) and the pathway of apoptosis mediated by mitochondria (16)(7)
• ROS and Redox Signalling ROS are also both signalling molecules and mediators of cellular injury. ROS have an important role to play in regulating many cellular functions associated with cellular proliferation and differentiation as long as their level is tightly regulated within the body during normal physiology. An excess of ROS causes the oxidative damage of cellular lipids, proteins and nucleic acids (16). Mitochondrial dysfunction is one of the main sources of ROS production in the hepatocyte. An overflow of electrons from Complexes I and III in the electron transport chain produces superoxide radicals, which can turn into H2O2 and then OH (17)(18). Additionally, ROS are also produced as a result of the activation of NADPH oxidases (NOX1, NOX2, NOX4, etc. (19), which play a significant role in the development of oxidative stress in chronic liver disease. An accumulation of ROS can result in the activation of downstream signalling pathways which, in the long run, can lead to inflammation, fibrosis and liver cancer.

- **Nrf2/Keap1/ARE Antioxidant Signaling Pathway**

The main way we protect ourselves from oxidative injury within each cell is by using the protein Nrf2. Normally Nrf2 is attached to the cytoplasmic protein Keap1 which leads to its destruction by a cellular process called proteasomal degradation.

However, when we experience any outside influence such as free radicals / oxidative stress that modify Keap1 cysteine amino acids; this results in Nrf2 entering into the nucleus where it then binds to an area on the DNA called an antioxidant response element (ARE). This binding allows transcription of genes that help to protect the cell (20)(15).

Some of the genes that are regulated by Nrf2 include heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase-1 (NQO1), glutamate-cysteine ligase (GCL), superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). There has been evidence showing that activation of Nrf2 leads to the attenuation of drug-induced liver disease (such as liver injury, fatty liver, and liver fibrosis) through restoration of the redox balance and inhibition of inflammatory response (21)(22).

On the other hand, when Nrf2 signaling is impaired; oxidative stress leads to increased oxidative injury and accelerated progression of chronic liver diseases (23). Thus, pharmacologically activating the Nrf2 pathway may provide a viable therapeutic option for protecting the liver.

- **NF-κB–Mediated Inflammatory Signaling**

NF-κB (nuclear factor κB) is an important redox-sensitive transcription factor that contributes to inflammation in the liver (also known as hepatic inflammation)(24)(25). In cases where there is oxidative stress, the ROS (reactive oxygen species) activate the iκB kinase (IKK) its degradation causes iκB to be released from NF-κB so that NF-κB can translocate to the nucleus. Once NF-κB is activated, it induces the transcription of proinflammatory cytokines such as TNFα, IL1β, and IL6, and chemokines that recruit inflammatory cells to the liver. Chronic activation of NF-κB can create a sustained inflammatory state, damage to hepatocytes, and increase the risk for fibrogenesis. The cross talk between NF-κB and Nrf2 signaling pathways creates a balance between antioxidant defense mechanisms and inflammatory damage. NF-κB signaling has been demonstrated to downregulated the development of steatohepatitis and liver fibrosis (24).

- **Mitochondrial Apoptosis Pathways**

Oxidative stress induces hepatocyte apoptosis via the intrinsic (mitochondrial) pathway of apoptosis. In this case, excess ROS are produced which leads to disruption of the mitchondrial membrane potential ($\Delta\psi$) which then causes the opening of the mitochondrial permeability transition pore (mPTP) resulting in the release of cytochrome c into the cytosol. Thus, the initiation of the intrinsic apoptotic pathway is upon the activation of caspase-9 which then activates caspase-3 leading to hepatocyte apoptosis (26)(27).

The mitochondrial apoptosis networks are regulated by members of the Bcl-2 protein family, with the pro-apoptotic (Bax/Bak) promoting the permeabilization of mitochondria, while the anti-apoptotic (Bcl-2/Bcl-xL) prevent cytochrome c release. The activation of oxidative stress will shift the Bax/Bcl-2 ratio towards an apoptotic response, therefore enhancing cell damage in the liver (28).

Alongside apoptosis, severe oxidative stress may also activate necroptosis and ferroptosis pathways furthering the progression of liver disease (29).

- **Integration of Signaling Pathways in Liver Disease Progression**

The pathways of ROS generation, impaired activation of Nrf2, chronic activation of NF-kB, and apoptosis form an orchestra of molecular players perpetuating injury to the liver (24). In the early stages of liver injury from toxins, adaptive activation of Nrf2 can help to balance oxidative stress, however chronic exposure to a toxic insult will overwhelm the liver's ability to produce antioxidant defence mechanisms leading to the development of inflammation, fibrosis, and cancer. Targeting these molecular pathways with validated mechanisms of action through the use of antioxidant rich phytoconstituents is a promising strategy for providing hepatoprotection (30).

- **Plant-Derived Antioxidants and Their Mechanisms in Hepatoprotection**

Medicinal plants are rich in biologically active phytochemicals that have antioxidant activity. Antioxidants of plant origin have received increased interest as a new type of therapeutic agent used to prevent and prevent oxidative stress-induced liver damage (31). Furthermore, these natural substances have hepatoprotective properties by acting as free-radical scavengers, modulating redox-sensitive signalling pathways, inhibiting the production of inflammatory mediators and regulating the activity of apoptotic cascades (32).

Phytochemical Classes with Hepatoprotective Potential (33)(34).

- **Flavonoids**

Flavonoids are some of the most widely studied polyphenols found in plants and flavonoid compounds exhibit antioxidant activity and anti-inflammatory properties. For example, flavonoid compounds such as quercetin, kaempferol, luteolin and catechins have a high capacity for scavenging free radicals because they contain many hydroxyl groups (35). Flavonoid compounds are also able to activate the nrf2/are pathway leading to increased expression of endogenous antioxidant enzymes such as sod, cat, and ho-1 and inhibiting NF-KB-mediated inflammatory signalling (36). Quercetin, For Example, Has Been Shown to Protect Against Drug-Induced Liver Injury by Reducing Lipid Peroxidation and Returning Glutathione Levels

Back to Normal (37)

- **Phenolic Acids**

Phenolic acids, such as gallic acid, caffeic acid, ferulic acid and chlorogenic acid, have hepatoprotective effects through hydrogen donating antioxidant mechanisms (38) and modulation of the intracellular redox balance.
These compounds have a protective effect and have antioxidant activity because they inhibit the production of cytokines by suppressing oxidative stress-induced apoptosis via inhibition of the activation of the nf-κb signalling pathway (39)

- **Terpenoids and Triterpenes**

Ursolic acid, oleanolic acid, and glycyrrhizin are examples of terpenoids which have a strong hepatoprotective effect through stabilization of the mitochondrial membrane and reduction in production of reactive oxygen species (40). Further, these compounds inhibit fibrotic signalling pathways such as transforming growth factor-β (TGF-β) and thus prevent the advancing to cirrhosis (41).

- **Alkaloids and Saponins**

Alkaloids and saponins from plants show antioxidant potential through enhancement of endogenously produced enzymatic defence mechanisms as well as inhibiting inflammatory mediators. Silymarin is a composite of flavonolignans that is derived from the Silybum marianum and has a well-documented hepatoprotective role through stabilisation of membranes, scavenging of free-radicals and activation of Nrf2 (42)(31).

4.1. Molecular Mechanisms of Plant-Derived Antioxidants

- **Activation of Nrf2 Pathway**

The activation of many phytoconstituents occurs through their interaction with Keap1 in order to modify cysteine residues. This leads to increased nuclear translocation of Nrf2 and synthesis of genes that encode for antioxidant proteins such as HO-1, NQO1, and GCL; and increases the ability of cells to withstand oxidative stress (43)(44).

- **Inhibition of NF-κB–Mediated Inflammation**

Plant antioxidants inactivate IKK and limit the ability of NF-κB to translocate to the nucleus and subsequently decrease the release of pro-inflammatory cytokines (i.e., TNF-α, IL-1β, IL-6) (44). Thus, the combination of both antioxidant and anti-inflammatory effects will contribute in the prevention of progression from steatosis to steatohepatitis (42)(45).

- **Regulation of Apoptosis and Mitochondrial Protection**

Phytochemicals reinstate mitochondrial membrane potential, control Bax/Bcl-2, and inhibit caspase activity, so that oxidative stress-induced apoptosis is prevented (46). There are also other compounds that regulate autophagy pathways and leads to cellular homeostasis (47)(48).

- **Anti-Fibrotic Effects**

Plant antioxidants inhibit ROS-mediated hepatic stellate cell activation to decrease extracellular matrix deposition and inhibit fibrogenesis induced by TGF (49)(50).

4.2. Emerging Evidence from Experimental Models

Hepatoprotective properties of plant extracts have been shown in vivo and in vitro in carbon tetrachloride (CCl4) and paracetamol, alcohol, and high-fat diet induced liver damage (51). Their therapeutic potential is also supported by the restoration of such biochemical markers as ALT, AST, ALP, bilirubin, and antioxidant enzymes. Other antioxidant phytoconstituents, such as flavonoids, phenolics, and other antioxidant phytoconstituents, include the genus Corchorus, which are lesser-explored medicinal plants and which may lead to hepatoprotection. Nonetheless, mechanistic studies and clinical validation are still not very detailed, which also means that there is a major gap in research (52).

5. Experimental Models for Hepatoprotection

The assessment of hepatoprotective effect is based on the well-established in vitro and in vivo experimental models which simulate liver injury caused by oxidative stress. These models are critical in the study of pathophysiological mechanisms and in the screening of the possible therapeutic agents, especially antioxidants that are found in plants (53)(54).

5.1 In Vivo Experimental Models

1. **Carbon Tetrachloride (CCl_4)-Induced Hepatotoxicity Model**

CCl4 model is one of the most common experimental systems that are used in the evaluation of hepatoprotective agents. CCl 4 is broken down by hepatic cytochrome P450 enzymes (especially CYP2E1) into trichloromethyl radicals (•CCl_3), which trigger lipid peroxidation and oxidative stress-induced hepatocellular injury. This model is very similar to oxidative damage, inflammation, and fibrosis present with chronic liver disease. The common assessment of biochemical parameters includes ALT, AST, ALP,

total bilirubin, and antioxidant enzymes (SOD, CAT, GSH) (55)(56).

2. Paracetamol (Acetaminophen)-Induced Hepatotoxicity

Paracetamol overdose leads to formation of the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI), which depletes glutathione and causes mitochondrial oxidative stress and necrosis (57). This model is particularly useful for evaluating antioxidant-mediated hepatoprotective effects. Histopathological changes include centrilobular necrosis and inflammatory infiltration (58).

3. Alcohol-Induced Liver Injury Model

Chronic administration of ethanol leads to the expression of CYP2E1 and the increase of ROS production, which causes steatosis, inflammation, and oxidative damage (59). This model is a commonly used model to study antioxidant and anti-inflammatory plant extracts in alcohol related liver disease (8).

4. High-Fat Diet (HFD)–Induced NAFLD Model

The steatotic liver disease model that is associated with metabolic dysfunction is replicated in the high-fat diet model. Overload of lipid enhances the generation of mitochondrial ROS and inflammatory signaling (60)(61). The model can be useful in assessing phytoconstituents that can regulate lipid metabolism, oxidative stress, and fibrosis.

5. Thioacetamide (TAA) and D-Galactosamine Models

Thioacetamide causes hepatic fibrosis and cirrhosis by means of oxidative stress and chronic inflammation. D-galactosamine is an acute liver toxicant, which interferes with the RNA and protein synthesis, resulting in apoptosis and necrosis of hepatocytes (62)(63). These models are popular in the research of antifibrotic and antioxidant treatments (64)(65).

5.1 In Vitro Experimental Models

1. Hepatocyte Cell Lines

Mechanistic studies are commonly done on human hepatoma cell lines like HepG2 and Huh7. Hydrogen peroxide (H_2O_2), tert-butyl hydroperoxide (t-BHP) or CCl_4 metabolites are used to induce oxidative stress to determine cytoprotective effects of test compounds (66)(67)(7).

2. Primary Hepatocyte Cultures

Primary rat or human hepatocytes can give more physiologically relevant data than immortalized cell lines. These models permit the evaluation of the functioning of mitochondria, the production of the ROS, indicators of apoptosis, and the activity of antioxidant enzymes (68)(69)

3. Mechanistic Assays

Common biochemical and molecular endpoints include:

- Lipid peroxidation (MDA levels)
- Reduced glutathione (GSH) content
- Antioxidant enzymes (SOD, CAT, GPx)
- Pro-inflammatory cytokines (TNF-α, IL-6)
- Western blot or RT-PCR analysis of Nrf2, NF-κB, Bax, Bcl-2, caspase-3 expression
- Histopathological examination of liver tissue (70)(42)(7)(64)

- **Translational and Emerging Models**

Recent advances include:

- 3D liver organoids
- Microfluidic "liver-on-a-chip" systems
- Genetically modified mouse models targeting Nrf2 or NF-κB pathways (71)(72)

These advanced systems enhance translational relevance and reduce limitations associated with conventional animal models.

Experimental hepatotoxicity models provide critical platforms for evaluating antioxidant-mediated hepatoprotective effects of medicinal plants. Among them, CCl_4 and paracetamol models remain gold standards for oxidative stress–based studies, while high-fat diet and alcohol models are more relevant for metabolic and chronic liver diseases. Integration of molecular endpoints (Nrf2, NF-κB, apoptosis markers) strengthens mechanistic validation of hepatoprotective agents (42)(7)(9).

6. Corchorus trilocularis (Phytochemistry & Pharmacology)

6.1 Botanical Overview and Ethnomedicinal Importance

Corchorus trilocularis L. Family Malvaceae (formerly Tiliaceae) is an annual herb that is widely disseminated in the tropical and subtropical areas, such as India, Africa, and Southeast Asia. Historically, several species of Corchorus have found applications in folk medicine as remedies to fever, inflammation, gastrointestinal diseases, liver diseases and skin diseases (73). Even though there is more research on Corchorus olitorius, C. trilocularis has also been mentioned in ethnomedicinal literature due to its possible therapeutic use, such as hepatoprotective and antioxidant (74)(75)

6.2 Phytochemical Constituents

Phytochemical investigations of Corchorus trilocularis have revealed the presence of diverse bioactive compounds, including:
Flavonoids (quercetin, kaempferol derivatives)

- Phenolic compounds
- Alkaloids
- Saponins
- Tannins
- Glycosides
- Steroids and triterpenoids

of interest are flavonoids and phenolic constituents, which exhibit a high free radical-scavenging capacity and metal-chelating capacity. These are substances that make the plant add to the antioxidant activity (76)(74). The ethanolic extracts have also shown significant antioxidant activity based on total phenolic content and flavonoid content which is comparable to the common antioxidants like ascorbic acid (74)(77). The availability of polyphenolic compounds implies that hepatoprotection is based on a mechanistic foundation of regulating oxidative stress processes, specifically activation of the Nrf2 pathway and inhibition of NF-KB-mediated inflammation (42)(7).

6.3 Antioxidant Activity

Several in vitro studies have evaluated the antioxidant activity of C. trilocularis extracts using DPPH, ABTS, hydrogen peroxide scavenging, and reducing power assays (78)(74). Ethanolic extracts have shown dose-dependent free radical scavenging effects, indicating strong hydrogen-donating ability.
The antioxidant activity is attributed to:

- Direct scavenging of ROS
- Inhibition of lipid peroxidation
- Enhancement of endogenous antioxidant enzymes
- Prevention of oxidative DNA damage

These findings provide a scientific rationale for exploring its hepatoprotective potential (7)(79).

6.4 Hepatoprotective Activity

In preclinical studies of the hepatoprotective effect of Corchorus species in CCl4 and paracetamol-induced hepatotoxicity models, the species have shown a significant decrease in serum biomarkers (ALT, AST, ALP, and total bilirubin) (76)(80). Histopathology showed the restoration of normal architecture of hepatics, and decreased necrosis. The hepatoprotective processes are hypothesized to include: Decrease in lipid peroxidation (- MDA levels) Restoration of glutathione (GSH) levels Increase in antioxidant enzymes (SOD, CAT, GPx) Inhibition of inflammatory mediators. Apoptotic marker (Bax/Bcl-2 ratio) modulation. These processes are consistent with the well-known antioxidant-mediated pathways of hepatoprotection (79)(7).

6.5 Anti-Inflammatory and Other Pharmacological Activities

Besides antioxidant and hepatoprotective activities, Corchorus trilocularis has also been reported to have:
Anti-inflammatory activity, antimicrobial properties, Antidiabetic effects, Analgesic activity. The anti-inflammatory properties can be attributed to the inhibition of the production of prostaglandins and the inhibition of pro-inflammatory cytokines through the regulation of the NF- 0B pathway (81)(82).

6.6 Research Gaps and Future Perspectives

In spite of encouraging early results, a number of gaps still persist:
Poor mechanistic investigations assessing Nrf2/NF-kB pathway regulation. Absence of molecular apoptosis studies. Lack of standardization of extract composition. Lack of clinical research. Limited toxicological profiling More studies on the isolation of bioactive compounds, molecular docking, validation of pathways, and designed in vivo models should be done. Considering its phytochemical endowment, C. trilocularis is a prospective source of antioxidant-based hepatoprotection therapy (83)(84).

7. Future Perspectives and Research Gaps

Although there is significant progress in clarifying the role of oxidative stress in causing hepatic injury and the therapeutic value of plant-based antioxidants, there are a number of gaps in translation and mechanism. It is necessary to bridge these gaps to take phytopharmacological agents through experimental validation to clinical use (7)(83)(85).

7.1 Need for Mechanistic and Molecular Validation

Even though most medicinal plants exhibit hepatoprotective effects in experimental models, a number of studies are mostly descriptive and have not been validated in detail in terms of the pathways. Future studies need to look at distinct molecular targets such as Nrf2/Keap1/ARE signaling, NF- 0B regulation, mitochondrial dysfunction, apoptosis regulators (Bax /Bcl-2, caspases), ferroptosis regulators, and autophagy pathways. The use of recent omics methods like transcriptomics, proteomics, and metabolomics will enable complete mapping of pathways and the discovery of new molecular targets in hepatoprotection (7)(79)(86).

7.2 Standardization and Phytochemical Characterization

Geographical variability in phytochemical composition because of geographical origin, harvesting factors, and extraction technique is a significant constraint in the researches of herbs. To provide reproducibility and quality control,

standardization with validated methods of analysis, including HPLC, LC-MS/MS, and NMR profiling, is essential. In the case of Corchorus trilocularis, active flavonoids and phenolics have not been fully studied using detailed phytochemical fingerprinting and quantification. Isolation and structural elucidation of bioactive constituents is needed so that structure-activity relationships and therapeutic consistency can be established (84)(87)(88).

7.3 Bioavailability and Pharmacokinetics

One of the major drawbacks of most plant polyphenols is low oral bioavailability related to low absorption and rapid metabolism. Bioavailability-improving strategies, including nanoformulations, lipid-based carriers, phytosomes, and polymeric nanoparticles, can be used to improve hepatic targeting and therapeutic efficacy. Nanotechnology-phytoconstituents integration is one of the potential solutions to address the pharmacokinetics barriers and maximize the antioxidant-based hepatoprotective treatment (89)(90).

7.4 Translational and Clinical Studies

Although there is emerging positive preclinical data, there are still few well-designed randomized clinical trials that assess plant-derived hepatoprotective agents. Clinical verification should be done rigorously to ascertain safety, dosing schedules and long-term therapeutic outcomes. In addition, to achieve regulatory approval and clinical acceptance, detailed toxicological evaluations, such as acute, sub-chronic, chronic toxicity investigations, and herb-drug interaction investigations, are necessary (91)(92).

7.5 Emerging Molecular Targets

Recent data shows a role of ferroptosis, inflammasome activation (NLRP3) and gut-liver axis dysbiosis in the progression of liver disease. Future studies ought to examine whether Corchorus trilocularis regulates these new pathways. The multi-target pharmacological and systems biology approaches can be more helpful in explaining the pleiotropic effects of plant-derived antioxidants in hepatic disorders (93).

7.6 Conclusion

Oxidative stress remains a central mediator of hepatic injury in both acute and chronic liver diseases. Plant-derived antioxidants exert multi-target hepatoprotective effects by:

- **Activating Nrf2 signaling**
- **Suppressing NF-κB–mediated inflammation**
- **Regulating apoptosis pathways**
- **Attenuating fibrogenesis**

However, translation into evidence-based clinical therapy requires molecular validation, extract standardization, improved delivery strategies, comprehensive toxicological profiling, and robust clinical trials.

Corchorus trilocularis represents a promising but underexplored phytotherapeutic candidate, warranting interdisciplinary research integrating phytochemistry, molecular pharmacology, and advanced drug delivery technologies.

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Abbreviations

- **ABTS** – 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) assay
- **ALD** – Alcohol-related liver disease
- **ALP** – Alkaline phosphatase
- **ALT** – Alanine aminotransferase
- **ARE** – Antioxidant response element
- **AST** – Aspartate aminotransferase
- **Bcl-2/Bcl-xL** – Anti-apoptotic proteins of the Bcl-2 family
- **Bax/Bak** – Pro-apoptotic proteins of the Bcl-2 family
- **CAT** – Catalase
- **CCl_4** – Carbon tetrachloride
- **CLD** – Chronic liver disease
- **DALYs** – Disability-adjusted life years
- **D-Gal** – D-galactosamine
- **DPPH** – 2,2-diphenyl-1-picrylhydrazyl assay
- **ETC** – Electron transport chain
- **GPx** – Glutathione peroxidase
- **GSH** – Reduced glutathione
- **HBV** – Hepatitis B virus
- **HCC** – Hepatocellular carcinoma
- **HCV** – Hepatitis C virus
- **HFD** – High-fat diet
- **HO-1** – Heme oxygenase-1
- **HSCs** – Hepatic stellate cells
- **IL-1β** – Interleukin-1 beta
- **IL-6** – Interleukin-6

- **IKK** – IκB kinase
- **Keap1** – Kelch-like ECH-associated protein 1
- **LICs/MICs** – Low-income countries / Middle-income countries
- **MDA** – Malondialdehyde
- **MASLD** – Metabolic dysfunction-associated steatotic liver disease
- **mPTP** – Mitochondrial permeability transition pore
- **NAPQI** – N-acetyl-p-benzoquinone imine
- **NF-κB** – Nuclear factor kappa-light-chain-enhancer of activated B cells
- **NOX** – NADPH oxidases
- **NQO1** – NAD(P)H quinone oxidoreductase-1
- **Nrf2** – Nuclear factor erythroid 2-related factor 2
- **ROS** – Reactive oxygen species
- **SOD** – Superoxide dismutase
- **TAA** – Thioacetamide
- **TGF-β** – Transforming growth factor-beta
- **TNF-α**

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