

Role of herbal compounds to treat Drug-Induced Liver Injury (DILI)

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ABSTRACT

The liver produces hormones, plasma proteins, aids in detoxification, breaks down red blood cells, and regulates the body's glycogen storage. Liver diseases and its after effects causes illness and death. Drug-induced liver injury (DILI) is a major clinical problem, which leads to substantial morbidity and mortality. Although DILI is uncommon but it occurs in hospitalised individuals with undetected liver problems. Different drugs are used in drug-induced liver injury in Eastern and Western nations. In Western regions, antibiotics are used to treat DILI, but in East, traditional Chinese medicine are used. Due to the limited effectiveness of traditional pharmacotherapies for liver injury, research is being conducted into alternate treatment methods. Herbal medications are widely used and are popular. We identified many plant chemicals (silymarin, curcumin, andrographolide, hesperidin, naringin, glycyrrhetic acid, hawthorn extract, and epigallocatechin-3-gallate) with hepatoprotective properties. These substances have anti-inflammatory, anti-fibrotic and antioxidant properties. Additionally, herbal components alter drug metabolic pathways, to lessen the hepatotoxicity of pharmaceutical treatments. We address various drug-induced liver damage pathways and natural remedies for hepatotoxicity and also emphasized the significance of molecular mechanisms behind DILI and the reasons for choice of treatment drugs.

Key words: Antioxidant, DILI (Drug Induced Liver Injury), Epidemiology, Herbal Compounds, Pathophysiology, Pharmacotherapies.

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Graphical Abstract

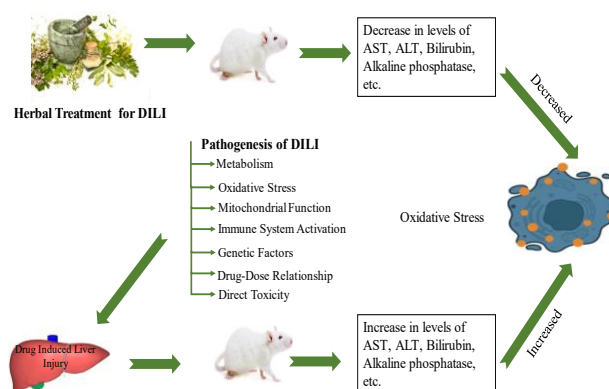


Figure 1. Graphical presentation of DILI and its herbal treatment

1. INTRODUCTION

Liver is one of the most vital organ, essential for the physiological functions of the body. It manages the body's storage of glycogen, breaking down red blood cells, producing hormones and plasma proteins and aiding in detoxification (23). Liver illnesses cause illness and death. Liver diseases include: cholestasis, fatty liver illnesses, DILI, liver fibrosis, and fatal end-stage hepatic disorders like cirrhosis, hepatocellular carcinoma and cholangiocarcinoma (44). An unpleasant reaction to medications or other xenobiotics is known as DILI, and it happens when a person is exposed to common drugs (7). This sets off a chain of cellular reactions (oxidative stress, cell death, immune system activation and an inability to adjust (15). DILI is the most prevalent reason for hepatic diseases nowadays. It is the leading cause of acute liver failure. DILI diagnosis is still difficult for doctors and research is underway. Every year, doctors, researchers and patients pay more attention to DILI because it is serious risk to patient health (11). Now new aspects of liver injury associated with chemotherapy have emerged, along with new medications such as sodium-glucose co-transporter-2 inhibitors that cause drug-induced liver injury (DILI). Several cases of previously reported hepatotoxins were confirmed by the DILIN approach (e.g., celecoxib) and/or the Roussel Uclaf Causality Assessment approach (RUCAM; e.g., norethisterone, methylprednisolone) (32).

Plant-based natural products are rich sources of ingredients for pharmaceutical development (2), hence, incorporating some therapeutic elements, is still a viable choice. These tactics not only address the illness but also have minimum negative effects. Most synthetic medications for liver illnesses are potent pro-oxidant scavengers, however their prolonged use results in inflammation (16). Numerous natural compounds (resveratrol, flavonoids, saponins, and β -carotene) present in food protects against DILI. This is

achieved by iron chelation, promoting apoptosis, antioxidative actions, reducing inflammation and inhibiting the proliferation of hepatic stellate cells and hepatocellular carcinoma cells (37). As per WHO, multifactorial disorders impacted over 600 million people in 2014 caused hepatic problems, which are expected to increase by 33% over the next 20 years (33). Natural products are promising sources to develop novel medications. This review addresses the hepatoprotective substances from plants. These protect the liver from drug- and alcohol-induced liver damage and viral hepatitis. This review shows most promising plant-derived hepatoprotective compounds and suggests further research to fully understand their potential health advantages (25).

2. HERBAL COMPOUNDS TO TREAT DILI

In recent years, exploring the capability and applications of botanical preparations to prevent drug-induced liver injury (DILI) is on the rise. The use of plant-based treatment from traditional medicines practices in India and China for liver ailments has attracted considerable attention. Bioactive medicinal compounds protect against hepatotoxicity (31). They have notable hepatoprotective advantages through inhibiting the mitochondrial dysfunction, inflammation, reducing oxidative/nitrative stress, and protecting macromolecular structures. Given their bioavailability and dietary origin, use of natural products alone medications holds promise (36).

2.1. Curcumin and Andrographolide

Curcumin is derived from plants of *Curcuma longa* L. species, while andrographolide is obtained from the stem and leaves of *Andrographis paniculata* (Burm.f.) Nees plant. Pipitone *et al.* (29) explored the various genes expression associated with development of oxidative stress and fatty liver. They studied the protective effects of curcumin, andrographolide, and their combination. Using microarray analysis, they assessed viability of cell, lipid and triglyceride levels, amount of Reactive Oxygen Species, and varying expression of genes. The findings indicated that curcumin, andrographolide and their combination reduces triglyceride levels and oxidative stress and also downregulates the genes involved in lipid collection (29).



Figure 2. Plant of *Curcuma longa* L.

2.2. Silymarin

Silymarin is a flavonoid extracted from *Silybum marianum* (L.) Gaertn. (milk thistle). Aktaş *et al.* (5) investigated the possible liver protective benefits of silymarin towards liver injury induced through valproic acid (VA) in rat liver using histological and biochemical parameters. Silymarin therapy significantly decreased serum alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase levels, while increased serum albumin levels ($p < 0.05$). It also markedly suppressed the elevated levels of MDA (malondialdehyde) and restored reduced levels of glutathione caused by VA in hepatic tissue ($p < 0.05$). The mixture of silymarin and valproic acid decreased the weight loss. Histologically, the valproic acid + silymarin group decreased liver damage than VA group ($p < 0.005$). Furthermore, when comparing the valproic acid group, the VA + silymarin group decreased oxidative stress, increased antioxidant activity and relieved histopathological changes (5).



Figure 3. Plant of *Silybum marianum* (L.) Gaertn.

2.3. Glycyrrhetic Acid

Glycyrrhetic acid is obtained from the *Glycyrrhiza glabra* L. Administering 18β -GA (glycyrrhetic acid) prior to cyclophosphamide treatment can decrease the hepatotoxicity, oxidative stress and liver damage (45). The activation of Nrf2 (nuclear respiratory factors 2) and PPAR γ (peroxisome proliferator-activated receptor gamma) pathways, which involve ERK (extracellular signal-regulated kinase) or Sirt1 (Sirtuin 1), is associated with these protective effects. The 18β -GA decreases inflammatory cell infiltration in paracetamol-induced hepatic inflammation, inhibits HMGB1-TLR4 (high mobility group box 1 protein-toll like receptor 4) signaling, attenuates CYP2E1 (catalase and cytochrome P4502E1) expression, and decreases Reactive Oxygen Species production. Additionally, 18β -GA pretreatment lowers hepatic ALT/SGPT (alanine transaminase/serum glutamate-pyruvate transaminase) and AST/SGOT (aspartate aminotransferase/Serum glutamic oxaloacetic transaminase) levels, carnitine levels, and serum fatty acid, improves acetaminophen-induced liver toxicity by reversing metabolism of fatty acid (45). Wang *et al.* (41) examined the defensive benefits of GA against cholestatic liver damage induced by lithocholic acid (LCA). Their research explored GA's dual mechanism of action, focusing on both inflammation and bile secretion processes. They assessed liver expression of PXR (pregnane X receptor) and FXR (farnesoid X

receptors), along with the genes these receptors regulate, which are involved in encoding metabolic enzymes and transporters. The expression of hepatic FXR and its target genes, BSEP (bile salt export pump), MRP3 (Multidrug-resistance protein 3), and MRP4 (Multidrug-resistance protein 4), was considerably elevated by GA. The GA increases hepatic FXR expression and inhibits the TLR2/NF- κ B (nuclear factor-kappaB) pathway to prevent cholestatic liver damage caused by LCA (lithocholic acid) (41).



Figure 4. Plant of *Glycyrrhiza glabra* L.

2.4. Plumbagin

Plumbagin (PB) is a naphthoquinone extracted from the roots of medicinal plant families: *Plumbaginaceae*, *Droseraceae*, *Ebenaceae*. Pan *et al.* (26) discovered that daily plumbagin injection protects the liver from damage caused by cholestasis. The liver protective effects of plumbagin were linked to the downregulation of several signaling pathways, including Transforming Growth Factor β 1 (TGF- β 1)/Smad, High Mobility Group Box-1 (HMGB1)/TLR4, Dynamin Related Protein-1, MDA, Interleukin-1 β (IL-1 β), p62/SQSTM1, and caspase 3. This plumbagin may be used to treat cholestatic hepatic damage. However, further research is necessary to confirm its effectiveness in clinical settings (26).

2.5. Epigallocatechin-3-gallate (EGCG)

Epigallocatechin gallate (EGCG), a polyphenol, is found in the tea plant (*Camellia sinensis* (L.) Kuntze) also referred to as epigallocatechin-3-gallate, is a catechin that forms as an ester of epigallocatechin and gallic acid. Almatroodi *et al.* (6) assessed the antioxidant capacity and protective function of EGCG against liver injury induced by DEN (diethyl nitrosamine). The effectiveness of EGCG in safeguarding the liver against DEN toxicity was examined by alterations in AST, ALT, and ALP (alkaline phosphatase) enzyme activities, pro-inflammatory marker and antioxidant enzyme serum levels, variations in histopathology, evaluation of cellular damage, and examination of cell cycle progression. Rats treated solely with DEN showed significantly higher amount of hepatic enzymes and pro-inflammatory cytokines, and reduced levels of antioxidant enzymes and histological irregularities. Additionally, there was increase in apoptotic nuclei (%) and a halt in cell cycle progression at the sub-G1 phase. EGCG protects against DEN-induced

liver injury by lowering serum liver enzyme levels, enhances overall antioxidant capacity, mitigates pathological alterations and apoptosis, and promotes cell cycle progression from the sub-G1 phase to S or G2/M phase. In summary, EGCG showed significant hepatoprotective effects by effectively attenuating DEN-induced liver toxicity and apoptosis (6).



Figure 5. Plant of *Camellia sinensis* (L.) Kuntze

2.6. N-trans-Caffeoyldopamine

N-Caffeoyldopamine is found in cocoa (*Theobroma cacao* L. Wu *et al.* (46) showed a considerable decline in serum levels of ALT and AST along with hepatic MDA content, accompanied by a notable recovery of hepatic superoxide dismutase activity and GSH (glutathione) content with N-trans-Caffeoyldopamine co-administration, compared to rats treated solely with INH-RFP (Isoniazid-Rifampicin) ($p < 0.01$). Moreover, treatment with N-trans-Caffeoyldopamine significantly improved histopathological liver damage and decreased the count of apoptotic hepatocytes. This N-trans-Caffeoyldopamine protects acute liver damage induced through INH and RFP in rats, primarily due to its antioxidative effects. It inhibits lipid peroxidation by downregulating cytochrome P450 2E1 (CYP2E1) (46).



Figure 6. Plant of *Theobroma cacao* L.

2.7. Resveratrol

Sources of resveratrol in food are: Grapes, blueberries, raspberries, mulberries and peanuts. De Moraes *et al.* (13) investigated liver damage induced by an acetaminophen overdose model (400 mg/kg/day for 15 days) in C56BL/6 mice. After 3 days of stopping acetaminophen administration, they analyzed histological, biochemical, and ultrastructural changes in mice's liver. Resveratrol (10 mg/kg/day) was given for 60 days, with blood and tissue evaluations conducted on 7th, 30th, and 60th day, was given after the treatment of mice with acetaminophen. The extended resveratrol therapy (60 days) mitigated acetaminophen-induced hepatic damage, restored histological features, ultrastructural integrity and serum biochemical parameters. Hepatocyte recovery markers, such as Ck18- and F4/80-positive cells, were normalized, and the α -SMA (alpha smooth muscle actin) positive cells returned to baseline after prolonged resveratrol therapy (13).

2.8. Ellagic Acid

Ellagic acid is found in pomegranates, strawberries, raspberries, blackberries, walnuts and pecans. Abdelkader *et al.* (1) investigated the protective effects of ellagic acid on hepatic damage caused through valproic acid in rats. The application of valproic acid caused a significant rise in serum enzyme activities such as ALT, ALP, AST, and GGT (gamma-glutamyl transferase). This also markedly increased levels of malondialdehyde and nitric oxide, while reducing the levels of GSH. Additionally, valproic acid also significantly elevated hydroxyproline content, TNF- α (tumor necrosis factor alpha) production, and NF-kB expression (1).

3. HERBAL PLANTS TO TREAT DILI

Hepatotoxicants pharmaceutical overdoses (acetaminophen, nimesulide, antitubercular drugs, isoniazid, rifampicin), industrial chemicals (alcohol, CCl₄, beta-galactosamine, thioacetamide), and other substances are exogenous agents that cause liver damage. Medicinal herbs contains a hepatoprotective drug (24). Plant-based therapies have been used for thousands of years to prevent and treat hepatic illnesses. Contemporary medicine is currently investigating the use of medicinal herbs to offer daily support for the liver. Hence, it becomes imperative to investigate herbal drugs that may be substitute to chemical counterparts (35). Moreover, pharmaceuticals, alcohol, and environmental pollutants induce oxidative stress leading to the regenerative capacity of liver and causing various diseases (12).

Table 1. List of medicinal plants used to prevent DILI

#	Botanical name	Active ingredients	M.O.A	Ref
1.	<i>Annona squamosa</i> L. (Annonaceae)	anthocyanidins, flavones, flavonols, and alkaloids.	A notable reduction in total bilirubin, and a substantial decrease in the levels of AST, ALT, and ALP.	4
2.	<i>Azadirachta indica</i> A. Juss. (Meliaceae)	Nimbolide, azadirachtin, and gedunin	TB↓, ALP↓, ALT, TP↑, AST	19,39
3.	<i>Bombax ceiba</i> L. (Malvaceae)	4,5,7- trihydroxy-flavone-3-O-β-Dglucopyranosyl (1-4)-α-Lrhamnopyranoside, lupeol	Reduces the level of Lactate Dehydrogenase, Glutathione-S-transferase, Glutathione Reductase and increases the Catalase level.	20,43
4.	<i>Cissampelos pareira</i> L. (Menispermaceae)	Quercetin, β-sitosterol, cissampeline, berberine	Reduce the levels of serum biochemical parameters, including SGOT, SGPT, ALP, and bilirubin.	8
5.	<i>Citrus reticulata</i> Blanco. (Rutaceae)	Naringin, hesperidin, nobiletin, tangeretin	Reduction in AST, ALT and bilirubin levels, rise in TP (total protein) content.	9
6.	<i>Cleome viscosa</i> L. (Capparaceae)	coumarinolignoids (cleomiscosins A, B, and C), lupeol	Decrease cholesterol levels and stimulate the immune system	14,28
7.	<i>Crocus sativus</i> L. (Iridaceae)	quercetin, crocetin, rutin, fisetin, safranal, crocin, Flavonol, morin.	ALP↓, ALT, TNF-α, COX-2↓, AST, TP, MDA, SOD↑	10,40
8.	<i>Embelia tsjeriamcottam</i> Burm.f. (Primulaceae)	Gallic acid, hyperin, quercetin, rutin.	Decrease the MDA level.	34
9.	<i>Flacourtia indica</i> (Burm.f.) Merr. (Salicaceae)	β-sitosterol, β-D glucopyranoside, ramontoside, butyrolactone Scoparone,	Diminish the levels of serum of aspartate transaminase, serum alanine transaminase, and serum alkaline phosphatase.	21,27
10.	<i>Phyllanthus debilis</i> J.G. Klein ex Willd. (Phyllanthaceae)	Phytosterols, lignans, polyphenols.	AST, ALT, ALP↓, MDA↓, Thiols↑	22
11.	<i>Silybum marianum</i> (L.) Gaertn. (Asteraceae)	Silymarin	Marked reduction in the levels of aminotransferases, alkaline phosphatase, and bilirubin.	17,42
12.	<i>Solanum xanthocarpum</i> L. (Solanaceae)	Solanacarpine, solanacarpidine, carpesterol, solamargine, steroids, aesculin, diosgenin.	AST, ALP, MDA↓, albumin↑, TP, LDH (lactate dehydrogenase), total bilirubin, cholesterol, GSH, SOD (superoxide dismutase), ALT	18,38
13.	<i>Wedelia calendulacea</i> L. Pruski (Asteraceae)	Methanolic extract	Gradual dose-dependent decline in elevated serum enzyme activities, simultaneous rise in total proteins and bilirubin.	3,30

4. CONCLUSIONS

Persistent liver ailments with liver cirrhosis and DILI are major causes of mortality. While the characteristics and dosage of a medication are pivotal factors in cellular injury, additional considerations such as a person's gene expression profile, anti-oxidant status, and regenerative ability also hold significance. Liver cell damage stems from various mechanisms that exacerbate ongoing injury processes. Herbal compounds (curcumin, andrographolide, silymarin, glycyrrhetic acid etc.) have shown promising potential in the treatment of drug-induced liver injury (DILI). Such key phytochemicals demonstrate hepatoprotective effects through various mechanisms (anti-inflammatory, antioxidant, and antifibrotic properties). These natural compounds offer a complementary approach to conventional treatments, underscoring the importance of exploring herbal remedies for liver health. It's expected that these natural products will not only mitigate the threat of DILI and also provide alternative approaches for addressing hepatotoxicity caused by medications. Natural remedies serve as a promising avenue for exploration and exploitation in the development of novel pharmaceuticals. This review establishes a scientific basis for comprehending the mechanisms of action of herbal compounds utilized in treating DILI. Further clinical studies and research are needed to fully understand their therapeutic efficacy and safety for DILI management.

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AUTHOR'S CONTRIBUTION

In this current review, A. delved into the pathophysiology of hepatotoxicity and explored herbal compounds utilized in treating liver impairment. The significant contribution to crafting the manuscript was made by BP, DP, AM, RM, and DS, who conducted the systematic evaluation and provided detailed conclusions. The final article has been carefully examined and approved by all authors.

CONFLICT OF INTEREST

It is declared by the authors that they have no competing interests.

DECLARATION

We declare that all authors of this Ms. have made substantial contributions. We did not exclude any author who substantially contributed to this Ms. We have followed our ethical norms established by our respective institutions.

ETHICAL STATEMENT

This is to inform you that in this study, we have not been involved in any animal and human studies.

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