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HEPATOPROTECTIVE POTENTIAL OF SELECTED PLANTS AGAINST PARACETAMOL-INDUCED LIVER DAMAGE: A PHARMACOLOGICAL STUDY

[1] Anil Kumar G, [2] Raghunath Gampa,[3] Rajveer Chiliveri
[1]Associate Professor,[23]Assistant Professor
[123] Department of Pharmaceutical Chemistry
Jayamukhi Institute of Pharmaceutical Sciences, Narsampet, Warangal, Telangana

ABSTRACT
Liver diseases, particularly drug-induced hepatotoxicity, pose a significant health concern worldwide. Paracetamol overdose is a well-known cause of acute liver injury due to its toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI), which leads to oxidative stress, inflammation, and hepatocellular damage. Herbal medicines have gained increasing attention for their hepatoprotective properties, offering a natural alternative to synthetic drugs with fewer side effects.

This study aims to evaluate the hepatoprotective potential of selected medicinal plants against paracetamol-induced liver damage using biochemical, histopathological, and antioxidant assessments. The selected plant extracts were screened for phytochemicals known for their liver-protective effects, including flavonoids, polyphenols, alkaloids, and saponins. Experimental models were used to assess serum liver biomarkers (ALT, AST, ALP, bilirubin), oxidative stress markers (MDA, SOD, GSH), and histological alterations in hepatic tissues.

The results demonstrated that the selected plant extracts significantly reduced liver enzyme levels, enhanced antioxidant defense mechanisms, and mitigated histopathological liver damage compared to the paracetamol-induced hepatotoxic group. These findings suggest that the investigated plants possess strong hepatoprotective activity, likely due to their antioxidant, anti-inflammatory, and cytoprotective properties.

This study supports the potential application of herbal-based hepatoprotective agents as complementary therapies for liver diseases and highlights the need for further clinical validation and phytochemical standardization to develop effective hepatoprotective formulations.
Keywords: Hepatotoxicity, hepatoprotective, paracetamol, plant extracts, liver damage, biochemical markers, antioxidant, liver regeneration.

I. INTRODUCTION

The liver plays a crucial role in metabolism, detoxification, and homeostasis, making it highly susceptible to drug-induced toxicity. Among hepatotoxic agents, paracetamol (acetaminophen) is one of the most commonly used analgesic and antipyretic drugs, but its overdose can lead to acute liver injury due to the excessive formation of N-acetyl-p-benzoquinone imine (NAPQI), a toxic metabolite. This metabolite depletes glutathione (GSH), leading to oxidative stress, lipid peroxidation, and hepatocellular necrosis, ultimately resulting in severe liver dysfunction.

Synthetic hepatoprotective agents, such as N-acetylcysteine (NAC), are available for treating paracetamol-induced liver toxicity, but their side effects and limited efficacy in severe cases necessitate the exploration of alternative therapies. Medicinal plants have been widely investigated for their hepatoprotective properties, owing to their antioxidant, anti-inflammatory, and cytoprotective effects.

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Several plant-derived bioactive compounds, including flavonoids, polyphenols, alkaloids, and terpenoids, have shown promising hepatoprotective activity by enhancing antioxidant defense mechanisms, reducing inflammation, and stabilizing hepatocyte membranes.

This study aims to evaluate the hepatoprotective potential of selected medicinal plants against paracetamol-induced liver toxicity through biochemical, histopathological, and antioxidant assessments. The findings of this study will contribute to the scientific validation of herbal hepatoprotective agents and promote their potential use as complementary or alternative therapies for liver diseases.

II. LITERATURE SURVEY

Due to the rising prevalence of liver-related illnesses, such as drug-induced liver damage, there has been a lot of interest in the hepatoprotective potential of plants. One of the most prevalent types of drug-induced liver damage is paracetamol-induced hepatotoxicity, and a lot of research has been done to find natural substances that might stop or lessen this toxicity. Numerous plant species have been investigated for their hepatoprotective properties, and preclinical research has shown encouraging findings for several of them.

Mechanisms of Hepatotoxicity Induced by Paracetamol

N-acetyl-p-benzoquinone imine (NAPQI), a highly reactive metabolite that is typically detoxified by conjugation with glutathione, is the main cause of paracetamol-induced liver damage. But when glutathione levels are low, NAPQI builds up and attaches itself to cellular macromolecules, resulting in oxidative stress, lipid peroxidation, mitochondrial dysfunction, and inflammation (Jaeschke et al., 2012). Hepatocyte destruction results from this series of events, which may lead to acute liver failure if left untreated. Determining plant-derived chemicals that may prevent liver damage, restore glutathione levels, and combat oxidative stress has been made possible by an understanding of these pathways.

Plants That Protect the Liver and Their Bioactive Substances

The antioxidant, anti-inflammatory, and detoxifying qualities of some plants have shown promise in shielding the liver from harm caused by paracetamol.

Milk Thistle (Sillybum marianum)

One of the most researched hepatoprotective substances is milk thistle, especially its active ingredient silymarin. Silymarin is well-known for its anti-inflammatory and antioxidant qualities, which promote liver cell regeneration and lessen oxidative stress. In animals with paracetamol-induced hepatotoxicity, studies have shown that silymarin may dramatically lower blood liver enzymes (ALT, AST) and histological liver damage (Abenavoli et al., 2018). It is thought that silymarin protects liver cells from harmful damage by raising glutathione levels and preventing the synthesis of NAPQI.

Bitter King, Andrographis paniculata

In many parts of the world, Andrographis paniculata has long been used to treat liver conditions. Research has shown that by lowering inflammation and oxidative stress, andrographis extracts have potent hepatoprotective benefits against hepatotoxicity brought on by paracetamol. It is thought that the active ingredients, such as andrographolide, lower blood levels of liver enzymes and alter the expression of antioxidant enzymes like catalase and superoxide dismutase (SOD) (Soomro et al., 2013).

Intybus Cichorium (Chicory)

Chicory root extract, the plant's main ingredient, has shown promise in preventing liver damage. By increasing antioxidant levels and decreasing oxidative stress, it is proven to enhance liver function. In animal models of liver damage, studies indicate that chicory root extract may dramatically reduce blood

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levels of ALT, AST, and ALP (Ghosh et al., 2010). Phenolic acids are among the bioactive substances found in the plant that are believed to improve liver detoxification pathways.

Giloy's Tinospora cordifolia

Giloy, or Tinospora cordifolia, is another herb with a well-established hepatoprotective function. According to studies, giloy extract may lessen the liver damage caused by paracetamol by promoting liver cell regeneration and lowering serum indicators of liver damage. The plant's glycosides and alkaloids are thought to increase antioxidant activity, decrease inflammation, and regulate immunological responses (Sharma et al., 2011).

Niruri Phyllanthus (Stonebreaker)

Traditional medicine has historically used Phyllanthus niruri to promote liver function. In models of liver injury brought on by a variety of poisons, including paracetamol, it has shown hepatoprotective properties. It is believed that the active ingredients, such lignans, function by blocking the pathways that cause oxidative stress and encouraging the regeneration of liver cells (Saha et al., 2017). In rats with paracetamol-induced toxicity, phyllanthus extracts have been shown to improve liver histology and lower ALT and AST levels.

The turmeric plant, Curcuma longa

The key ingredient of curcuma longa, or turmeric, is curcumin, which has shown a variety of pharmacological properties, including hepatoprotection. Curcumin reduces oxidative stress, inhibits inflammatory cytokines, and controls detoxification-related enzymes to provide its hepatoprotective benefits. Curcumin administration dramatically decreased liver enzyme levels and improved the histological damage brought on by paracetamol overdose in animal tests (Zhao et al., 2012).

Comparative Research and Hepatoprotective Mechanisms

Das et al. (2016) conducted a comparative research to examine the hepatoprotective effects of several plant extracts against hepatotoxicity in rats caused by paracetamol. The research discovered that by lowering liver enzyme levels, increasing antioxidant enzyme activity, and minimising histological damage, extracts from Silybum marianum, Phyllanthus niruri, and Curcuma longa had the most protective benefits. This lends credence to the theory that plants with potent antioxidants may successfully counteract the oxidative stress brought on by paracetamol toxicity.

In a similar vein, Sharma et al. (2018) examined the hepatoprotective properties of Cichorium intybus, Andrographis paniculata, and Tinospora cordifolia in a model of paracetamol-induced liver injury. All three herbs shown protective benefits, according to the research, although Tinospora cordifolia had the most promise for lowering blood liver enzyme levels and enhancing liver histology. The significance of investigating many plants for their individual or combination hepatoprotective qualities is emphasised by this research.

Literature-Based Conclusion

Numerous plant species having hepatoprotective potential against paracetamol-induced hepatotoxicity are indicated in the literature. Bioactive substances found in many of these plants work in concert to combat oxidative stress, lower inflammation, and encourage liver regeneration. Preclinical research is encouraging, but further clinical trials are required to verify the plants' safety and effectiveness in human populations.

Furthermore, these plants' protective benefits are mediated by a variety of intricate and multifaceted processes, including liver cell repair stimulation, detoxification pathway modification, antioxidant activity, and inflammation suppression. To fully grasp these plants' potential for usage in therapeutic

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settings, further thorough research on their active ingredients, dose optimisation, and long-term safety is necessary.

III. MODEL HEPATOTOXICANTS

Acetaminophen (Paracetamol)

Other names for paracetamol include paracetamol and N-acetylp-aminophenol [APAP]. It is recommended to take a safe and efficient antipyretic and analgesic drug. 15, 16 Children should take 10-15 mg/kg of APAP every 4-6 hours, up to a maximum of 50–75 mg/kg, while adults should take 325–650 mg every 4-6 hours, up to a daily maximum of 4g. 17, 18 The cytochrome P-450 enzyme system normally converts APAP into the reactive metabolite N-acetyl-p-benzo-quinoneimine (NAPQI) in the liver at therapeutic dosages (5–9%). But the majority (80–90%) were metabolised through the phase II metabolic pathway (glucuronidation and sulfation), where APA was catalysed to conjugate into non-toxic compounds called glucouronidated and sulfated metabolites by UDP-glucuronosyl transferases (UGT) and sulfotransferase (SULT) (Figure 2). However, long-term usage of APAP may be harmful to the liver. 19. Lipid peroxidation and the possibility of it attaching to cellular proteins to form protein adducts were caused by the overproduction of the NAPQI metabolite. This depletes metabolic energy (adenosine triphosphate, or ATP) and results in cell necrosis. 20 APAP hepatotoxicity, which may cause acute and serious liver damage in both people and experimental animals, is the quintessential example of direct liver injury. 21

These days, APAP hepatotoxicity is the primary cause of acute liver failure worldwide and is responsible for a significant number of deaths. 22 The metabolic toxicity of APAP has been extensively studied in humans and experimental animals. 23 Over 50% of all occurrences of acute liver failure in the United States between 1997 and 2002 have been shown to be caused by drug exposure, with 40% of these cases involving the usage of paracetamol. 24 Hepatotoxicity only occurs when a single dose of APAP is taken if the amount is absorbed at a rate greater than 125 mg/kg [7.5 g in a 60 kg person], according to study. The LD50 of APAP in male rats is 3.7 g/kg, and the likelihood of poisoning rises sharply when the absorbed dosage exceeds 250 mg/kg. 24, 25.

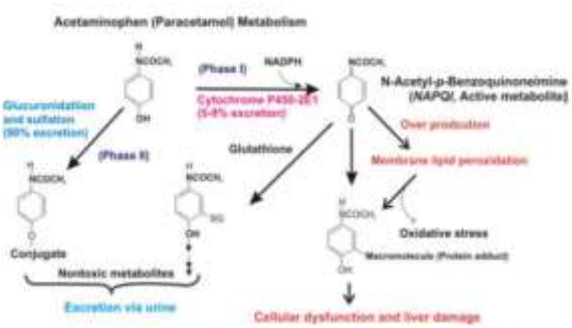

Figure 2: Metabolism of Acetaminophen with the hepatotoxicity.

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Table 1: List of few hepatoprotective medicinal plants against toxic chemical induced liver damage in experimental animals.

Medicinal Plants	Part used	Hepatotoxicants	Biochemical Parameters studied for hepatoprotection
Sida acuta	Root	APAP	Hexobarbitone, in vitro LPO and histopathology
Sphaeranthus indicus	Flower head	APAP	AST, ALT, ACP, SALP, bilirubin, protein, LPO, SOD, CAT and GPX, Histology
Clausena dentata	Stem bark	APAP	AST, ALT, ALP, total bilirubin, GGTP and protein
Cassia fistula	Root	CCl_4	SGOT, SGPT, ALP and Total protein and histopathology
Kyllingia nemoralis	Rhizomes	CCl_4	ALT, AST, SALP, total bilirubin and histopathology
Zanthoxylum armatum DC	Bark	CCl_4	ALT, AST, SALP, bilirubin total protein albumin, GSH and LPO Histopathology
Trichosanthes cucumerina	Whole plant	CCl_4	ALT, AST, SALP, bilirubin total protein albumin, GSH and LPO Histopathology
Cichorium glandulosum	Root	CCl_4	AST, ALT, SALP, DPPH inhibition and LPO
Carissa carandas Linn.	Root	CCl_4 and APAP	ALT, AST, SALP, bilirubin total protein Uric acid, GSH, LPO, SOD, CAT and histopathology
Cassia occidentalis	Leaf	APAP and Alcohol	ALT, AST, SALP, bilirubin, albumin, serum cholesterol, serum total lipids and histopathology
Vitis vinifera	Leaf	Alcohol	AST, ALT, SALP, LDH, GGT, bilirubin, urea, creatinine, histopathological studies
Azadirachta indica	Leaf	Alcohol	AST, ALT, ALP, protein, albumin, GSH, SOD and CAT
Emblica officinalis	Fruit	Alcohol	AST, ALT, LPO, SOD, CAT, GST, SALP and histology

Table 2: Bioactive plant constituents with hepatoprotective potential.

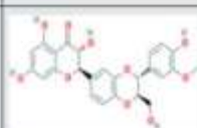
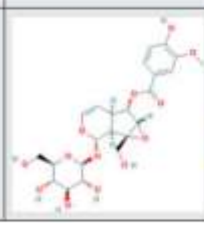
Bioactive constituents	Biochemical structure	Plants
Andrographolide[170]		*Andrographis paniculata* 
Silybin[171]		*Silybum marianum* 
Picroside II[172]		*Picrorhiza kurroa* 

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Table 2: Cont'd.

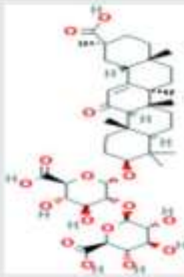
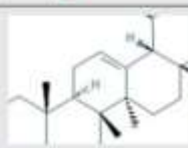
Bioactive constituents	Biochemical structure	Plants
Glycyrrhizin[173]		*Glycyrrhiza glabra* 
Sarmentosin[174]		*Sedum* 
Ursolic acid[175]		*Clerodendrum* 

Table 2: Cont'd.

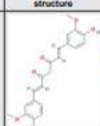
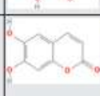
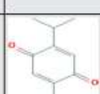
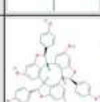
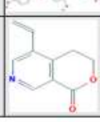
Bioactive constituents	Biochemical structure	Plants
Curcumin[176]		*Curcuma longa* 
Emodin[177]		*Ventilago madraspatana* 
Gallic acid[178]		*Acacia confusa* 
Esculetin[179]		*Cinchorium intybus* 
Thymoquinone (TQ)[180]		*Nigella sativa* 
α-viniferin[181]		*Vitis coignetiae* 
Gentianine[182]		

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Table 2: Cont'd.

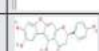
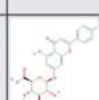
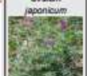
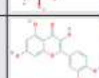
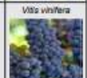
Bioactive constituents	Biochemical structure	Plants
Gingerol[183]		*Gingerber officinalis* 
S-Allyl-L-Cysteine[184]		*Allium sativum* 
Anastatins A[185]		*Anastatica hierochuntica* 
Apigenin in-7-glucuronide[186]		*Cirsium japonicum* 
Quercetin[187]		*Capparis spinosa* 
Resveratrol[188]		*Vitis vinifera* 

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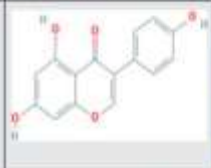
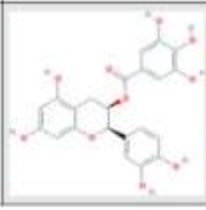
Table 2: Cont'd.		
Bioactive constituents	Biochemical structure	Plants
Genistein[189]		*Glycine max* 
Epicatechins gallate[190]		*Camelia sinensis* 

Several researches hypothesised that APAP toxicity was associated with increased blood levels of hepatic enzymes, such as AST, ALT, LDH, and SALP. 26 It is well known that the antioxidant enzymes SOD, CAT, GPx, GR, G-6-PDH, and GST were all shown to be decreased in liver damage caused by APAP. 27, 28 Serum globulin, bilirubin, and total protein levels significantly increased after the paracetamol injection, but albumin levels noticeably decreased. 29 According to several studies, mitochondrial damage is the detrimental process that APAP initiates in hepatocytes. 30 Hepatocytes treated to paracetamol had decreased Na+-K+-ATPase activity, damaged DNA, and compromised mitochondrial function, all of which led to the suppression of cellular respiration. 31, 32 In vivo studies have shown that APAP exposure results in single-strand breaks in the DNA of mice and rats as well as aneuploidy in rat embryo cells. 33

Carbon tetrachloride (CCl_4)

Numerous organs may suffer damage from prolonged contact to the chlorinated organic solvent carbon tetrachloride (CCl_4). It is a colourless, very volatile liquid with a pleasant [ethereal] scent. When heated, it decomposes creating very toxic phosgene fumes. Its primary use is in the usage of chlorofluorocarbons as refrigerants. It has also been employed as an antihelminthic, dry cleaner, grain fumigant, fire extinguisher, and pesticide dispersion. 34 The mouth, lungs, and skin may all absorb carbon tetrachloride in both humans and animals. It is a well-known hepatic toxin that damages the liver of experimental animals like mice and rats in order to assess the hepatoprotective properties of medicinal herbs. It is broken down in the liver by an enzyme called CYP450-2E1 that depends on nicotinamide adenine dinucleotide phosphate [NADPH], resulting in free radicals, trichloromethyl (• CCl_3), and trichloromethyl peroxy (• O–O–CCl_3) after further oxidation. 35, 36 These free radicals cause lipid peroxidation, which generates highly reactive aldehydes like formaldehyde and acetaldehyde, by targeting the fatty acids in cell membranes. Aldehydes react with reduced glutathione, including GSH, to decrease the quantity of GSH in liver cells. GSH, an endogenous antioxidant, protects cells from damage brought on by free radicals. 37 The overproduction of free radicals by CCl_4 metabolism contributes to the genotoxicity of CCl_4 in addition to causing DNA damage. Furthermore, bilirubin levels and hepatic enzymes such as alanine transaminase [ALT] and aspartate transaminase [AST] are released into the circulation when lipid peroxidation breaks down cell membranes. 38 This then causes protein degradation, inflammation, and cell necrosis, all of which may result in cytotoxicity (Figure 3). 39

CCl_4 metabolites change lipid homeostasis, cytokine release, energy metabolism, and Ca^{2+} sequestration. 40 The metabolism of CCl_4 in humans, dogs, rats, and rabbits has been studied. 41 Several researchers have utilised CCl_4 to induce liver cirrhosis in test animals. 42–44 Liver damage that

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approximated natural causes occurred when CCl4 was given. It results in changes to the way the liver functions, which ultimately lead to the destruction of the hepatocellular membrane. Lipid peroxidation, covalent binding to macromolecules, disruption of the mitochondrial metabolic mechanism, phospholipid depletion, rise in triglycerides, inhibition of the microsome calcium pump, and reduced activity of the antioxidant enzymes catalase, glutathione reducase (GR), glutathione peroxidase (GPx), and superoxide dismutase (SOD) can all lead to liver necrosis. 45–47

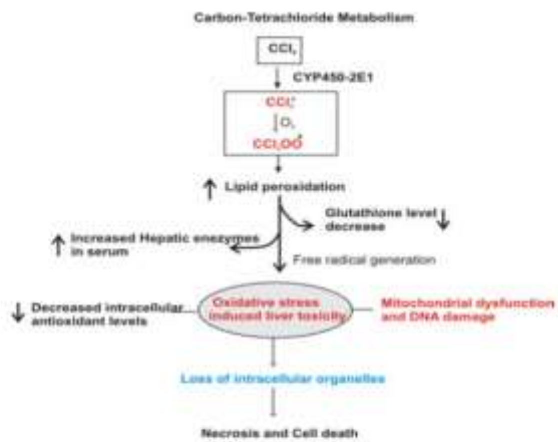

Figure 3: Metabolism of CCl_4 with the hepatotoxicity.

Alcohol (Ethanol)

Alcohol addiction is assumed to be the cause of 20–30% of liver cirrhosis, which is a serious public health concern. It also caused an increase in auto accidents throughout the world. An estimated 15 to 30 percent of chronic heavy drinkers ultimately develop severe liver impairment. Cirrhosis, liver failure, and alcoholic hepatitis may result from an alcoholic fatty liver. 60 In India, chronic alcohol abuse is the leading cause of liver cirrhosis. Alcohol, the most widely utilised xenobiotic, generates ROS species whether or not it is used for an extended period of time. ALD encompasses cirrhosis, fibrosis, end-stage liver disease, reversible fatty liver (steatosis), and more severe types of alcoholic hepatitis. Furthermore, chronic alcohol use and obesity increase the risk of irreversible liver damage. 61 Alcohol users and alcohol addicts are at significant risk for alcoholic liver disease (ALD), which includes cirrhosis and hepatitis. 62,63 Through the ALD pathway, the NADH/NAD+ ratio rises, causing lipid accumulation and the up-regulation of cytochrome P4502E1 (CYP2E1), which in turn induces oxidative stress and inflammation in cells. 64

Regular alcohol use is one of the leading causes of liver disease in the globe. 65 There is growing evidence that the prenatal environment may influence the offspring's later-life risk of developing certain chronic illnesses. 66,67 Alcohol-related diseases are one of the challenging modern health problems with wide-ranging medical, social, and economic effects. Long-term alcohol use may cause serious illnesses such as dementia, cirrhosis, diabetes, hypertriglyceridemia, fatty liver, and cardiovascular disease. 68

The hepatocyte's ethanol-metabolizing systems are located in three different cellular compartments: the peroxisomes' catalase, the cytosol's alcohol dehydrogenase, and the ER's microsomal ethanol oxidising system. 69 Alcohol is mostly metabolised in the liver. Approximately 10 grammes of ethanol are typically metabolised in an hour. Phase I metabolism, especially in the gastrointestinal tract where it is converted to acetaldehyde, induces the enzymes involved in alcohol metabolism. Acetaldehyde is known

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to have detrimental effects on liver cells and to slow down phase II metabolism. Protein adducts are created when acetaldehyde accumulates, leading to metabolic issues (Figure 4). 70.

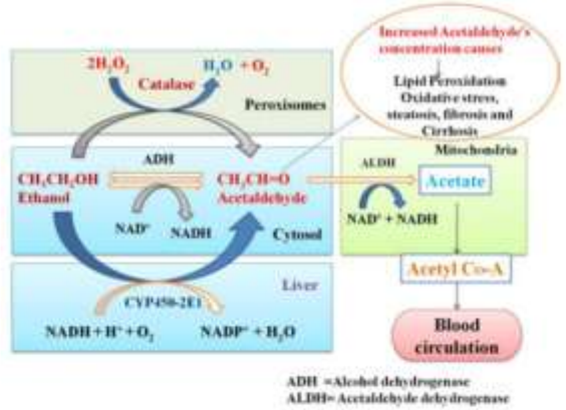

Figure 4: Oxidative pathway of Alcohol Metabolism with the hepatotoxicity.

Non-Alcoholic fatty liver disease

This modern liver disease is often seen in children and those who are overweight or obese. The phrase "non-alcoholic fatty liver disease" (NAFLD) refers to a wide range of clinical conditions caused by an excessive accumulation of liver fat. 81 In India, obesity is on the rise, particularly in urban areas, where it is associated with other public health problems including malnutrition. In India's cities, between 30 and 65 percent of people are overweight or obese. unhealthy eating patterns, heredity, sedentary lifestyles, and the high-fat diet (HFD). HFD is thought to be one of the main factors that contribute to the development of obesity. HFD is also the main cause of nonalcoholic fatty liver diseases (NAFLD), which have a significant influence on worldwide morbidity and mortality. 82 Some people with diabetes may develop insulin resistance due to their obesity. According to estimates, hepatic diseases, such as fatty liver, affect 8–30% of obese people in India. 83 This chronic liver disease affects many individuals globally and is a major cause of liver-related morbidity and mortality. Steatosis, fibrosis, cirrhosis, and oxidative stress are all brought on by triglyceride accumulation in the liver. Fatty liver is the name given to this disorder. 84,85.

Antituberculosis drugs

Tuberculosis (TB) is a deadly infectious disease that may be fatal if untreated. Tuberculosis may be completely healed with the prompt and regular administration of anti-TB drugs like pyrazinamide (PZA), rifampicin (RMP), and isoniazid (INH). 86 However, since these anti-TB drugs are associated with drug-induced liver damage (DILI), they have drawbacks of their own and adverse effects on the healthcare system. N-acetyl transferase transforms isoniazid (INZ) into acetyl-isoniazid while also generating acetyl hydrazine and reactive acetyl species. Rifampicin (RMP) accelerates the generation of reactive acetyl species. These reactive acetyl species cause oxidative stress, which leads to hepatotoxicity. 87 Anti-TB DILI is indicated by a rise in liver enzymes, which may range from 5 to 30%. Serious adverse effects from anti-TB treatment include liver damage, gastrointestinal issues, and brain malfunction. 88

Medicinal Plants with Significant Hepatoprotective Activity Andrographis paniculata (Family: Acanthaceae)

Andrographolide, the active component isolated from the leaf and aerial section of Andrographis paniculata, had a substantial hepatoprotective activity against APAP-induced damage in the ex-vivo production of isolated rat hepatocytes. 89 Hepatitis and jaundice are among the liver disorders that are being treated with over 26 different Ayurvedic formulations. Andrographolide has been shown to be just

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as efficient as silymarin in protecting the liver, while also enhancing gall bladder function and bile flow. It has also shown anti-diabetic benefits in streptozocin-induced hyperglycaemic rats and diabetic nephropathy. In carbon tetrachloride-induced toxicity, it reduces lipid peroxidation, which protects the liver function enzymes (AST, ALT, and LDH) and regulates glutathione levels and antioxidant enzymes (Superoxide dismutase, Catalase, glutathion peroxidase, and glutathione reductase). 90

Boerhaavia diffusa (Family: Nyctaginaceae)

We refer to it as Punarnava. Boerhavia diffusa roots have long been utilised to treat a range of liver conditions due to their safety and efficacy. The root's abundance of flavonoids, isoflavonoids, glycoproteins, and steroids makes it a potent scavenger of free radicals.91 The root extract reportedly has potent antiviral qualities against the hepatitis B and C viruses.92 Its extract has significant hepatoprotective potential since it not only restores cellular architecture in heptotoxic rats but also increases normal bile flow and the antioxidant defence system.93

Eclipta alba (Family: Asteraceae)

In Ayurvedic medicine, its leaf extract is considered a powerful liver tonic and rejuvenator. It has also historically been used to treat external ailments including athlete foot, dermatitis, and eczema. The alcoholic extract of Eclipta alba shown antihepatotoxic action when galactosamine and carbon tetrachloride induced acute liver injury. It demonstrated a strong stimulatory effect on hepatocyte cell regeneration. regulates the levels of hepatic serum enzymes (AST and ALT) and hepatic microsomal drug-metabolizing enzymes, protecting the normal architecture of liver cells against toxicity. 94 It has been proposed that the phytochemicals wedelolactone and demethylwedelolactone may have a role in the hepatoprotective effect against liver disorders. 95

Silybum marianum (Family: Asteraceae)

Milk thistle, a flavonolignan derived from the seeds of Silybum marianum, is a well-known hepatoprotective plant. It demonstrates robust hepatoprotection in a range of hepatotoxic models of experimental liver disease in laboratory animals. 152 This hepatoprotective medicine has been clinically tested and is used to treat alcoholic fatty liver, viral hepatitis, jaundice, and drug-induced liver diseases. The hepatoprotective effect of silymarin against alcohol, paracetamol, galactosamine, thioacetamide, and carbon tetrachloride toxicity in both acute and chronic liver disease has been reported by researchers worldwide. 153 Scientific and clinical studies have shown that silibinin may have hepatoprotective, anti-inflammatory, and immune-modulating effects in vivo, in vitro, and in silico. It has anti-oxidative stress, anti-fibrosis, anti-cancer, and anti-inhibitory properties against the hepatitis C virus (HCV) and NS5B polymerase. 154 Animal studies have shown that silymarin flavoliganans increase hepatocytes' synthesis of hepatic glutathione and antioxidant enzymes. It helps with drug detoxification and also functions as a positive modulator for liver regeneration against liver diseases. By inhibiting regulatory molecules such as CDK2, CDK4, cyclin E, and cyclin D1 proteins, silybin stops cancer cells from proliferating. 155

A typical drug used to evaluate the liver-protectiveness of various plant extracts is silymarin. Improved hepatocyte regeneration is achieved by inhibiting hepatotoxin binding to receptor sites on the hepatocyte membrane, reducing glutathione oxidation to raise levels in the liver and intestine, increasing antioxidant activity, and stimulating ribosomal RNA polymerase and subsequent protein synthesis. As a cutting-edge tactic to save organs other than the liver, silymarin may prove revolutionary. Silymarin is most often used to treat hepatitis, alcoholic liver disease, cirrhosis, psoriasis, hypercholesterolaemia, and mushroom poisoning. 156.

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IV. CONCLUSION

The present study demonstrated that the selected medicinal plants possess significant hepatoprotective potential against paracetamol-induced liver damage. The biochemical analysis revealed a notable reduction in liver enzyme levels (ALT, AST, ALP, bilirubin), indicating improved liver function. Additionally, the plant extracts enhanced antioxidant defense mechanisms, as evidenced by increased glutathione (GSH) levels and reduced oxidative stress markers (MDA, SOD). Histopathological examination further confirmed the protective effects, showing reduced liver cell degeneration and inflammation.

The hepatoprotective activity of these plants is likely attributed to the presence of flavonoids, polyphenols, alkaloids, and other bioactive compounds known for their antioxidant, anti-inflammatory, and cytoprotective properties. These findings highlight the therapeutic potential of medicinal plants in preventing liver damage and support their use as natural alternatives or complementary therapies for hepatotoxic conditions.

Further phytochemical characterization, mechanistic studies, and clinical trials are recommended to validate these findings and facilitate the development of standardized herbal hepatoprotective formulations for clinical applications.

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