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Review Article

Natural Treatments for Liver Conditions: A Review on Phytochemicals and Hepatoprotective Plants

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ABSTRACT

One of the most important organs in the body is the liver. The liver being a very important organ of the body depends on the food we take, which is agreeable to an extent. The functions performed by the liver include regulating numerous processes such as the metabolism, secretion, storage, and detoxification of chemicals whether internal or external. Liver diseases remain among the major threats to public health and continue being a problem worldwide. Despite the significant advances made in medicine, there are no drugs that can offer full protection for the liver, improve its functioning or contribute to the formation of new liver cells. Therefore, it is necessary to look for other drugs that could be used to effectively treat liver diseases. Plants have played a crucial role in human healthcare. Scientific investigations have proven that the beneficial effects of the plants are provided by phytochemicals contained in them. The main objective of the present study was to summarize data obtained from scientific research regarding the use of several plants that are often consumed by humans, including spirulina, chamomile, silymarin, and cactus pear (nopal) as well as its fruits demonstrating hepatoprotective properties, and the investigation of a resin (propolis) as well as several phytochemicals isolated from plants, yeasts, and algae examined in hepatotoxicity models.

INTRODUCTION

1.1. The significance of the liver

The regulation of several physiological functions is dependent on the functioning of the liver, which in turn is associated with several vital functions like metabolism, secretion, and storage[1,2]. There have been many studies conducted since the 1970s regarding the capacity of the liver to produce helpful substances as well as detoxify other substances of organisms.

1.2 The Liver's Primary Functions

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The metabolic processes of growth, nutrition, energy, and reproduction are also carried out by the liver. It also helps with bile secretion, vitamin storage, and the metabolism of fats and carbs.

1.3 Public Health Issues and Liver Diseases

Hepatic disorders remain among the major risks to public health owing to all of the aforementioned functions, and they are a worldwide phenomenon. Damage to the liver cells, tissues, structure, or its functions is termed "hepatic disease" and can be caused by biological organisms such as bacteria, viruses, and parasites, along with autoimmune disorders like primary biliary cirrhosis and immune hepatitis, as well as the effect of various agents, including drugs (paracetamol (PCM) and antitubercular drugs in large amounts), toxins (carbon tetrachloride (CCl4), thioacetamide, dimethylnitrosamine (DMN), D-galactosamine/lipopolysaccharide (GalN/LPS)), and certainly excessive consumption of alcohol[3-5].Despite significant advancements in contemporary medicine, there are currently no medications that fully preserve the liver, promote hepatic cell regeneration, or increase hepatic activity[6-10]. Furthermore, certain medications have negative side effects. In order to treat hepatic illnesses, it is therefore vital to find alternative medications that are less harmful and more effective.

1.4. Fruits and Plants' Potential for Medicine

Human health care has been greatly influenced by the use of some plants. The traditional medicine, which is predominantly composed of plant materials, has been practiced as a form of medical treatment for more than 80% of the world population. Phytochemicals can be defined as biologically active substances or chemical compounds that do not form an essential part of nutrition for survival. Several studies conducted on medicinal plants and consumption of fruits have proved that these properties might be accountable for their beneficial role. There have been several scientific studies conducted on certain phytochemicals on the effect they have on health. Some of the most frequently discussed examples include: (1) anthocyanins (cranberries), (2) betalain pigments (betanin and indica xanthine), (3) vinca alkaloids (vincristine, vinblastine and vindesine), and (4) resveratrol, all these have generally been studied in relation to their chemoprotective characteristics against cancer.

All therapeutic plants and the consumption of particular fruits have had various effects on biological systems. Most studies have concentrated on studying their sedative, analgesic, antipyretic, cardioprotective, antibacterial, antiviral, antiprotozoal, and anticarcinogenic properties despite other studies conducted on their hepatoprotective nature.

1.5. Hepatoprotective herbs

The traditional medicine, which is predominantly composed of plant materials, has been practiced as a form of medical treatment for more than 80% of the world population[11-15]. Phytochemicals can be defined as biologically active substances or chemical compounds that do not form an essential part of nutrition for survival. Several studies conducted on medicinal plants and consumption of fruits have proved that these properties might be accountable for their beneficial role[16-19]. There have been several scientific studies conducted on certain phytochemicals on the effect they have on health. Some of the most frequently discussed examples include: (1) anthocyanins (cranberries), (2) betalain pigments (betanin and indica xanthine), (3) vinca alkaloids (vincristine, vinblastine and vindesine), and (4) resveratrol, all these have generally been studied in relation to

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All therapeutic plants and the consumption of particular fruits have had various effects on biological systems. Most studies have concentrated on studying their sedative, analgesic, antipyretic, cardioprotective, antibacterial, antiviral, antiprotozoal, and anticarcinogenic properties despite other studies conducted on their hepatoprotective nature[22].

1.5.1. Annona squamosal

Histological examination showed that the hepatotoxic group possessed portal triaditis associated with hepatocyte necrosis and inflammation in the centrilobular region. In the therapy group, lobular pattern was normal and they exhibited mild portal triaditis and low inflammation[23-26]. Another study evaluated the protection against hepatotoxicity induced by diethyl nitrosamine. From this study, it was clear that extracts from Annona squamosa have hepatoprotective effects and may serve as a potential therapy for liver injury due to chemicals[27-30].

1.5.2. Silybum marianum

The protection provided by the polyphenolic extracts of Silybum marianum and Cichorium intybus against the toxicity of the liver induced was evaluated by thioacetamide[31-33]. Both plants were injected into rats at a dosage of 25 mg kg-1 of body weight, while the thioacetamide dosage was 50 mg kg body weight. Rats administered both extracts and thioacetamide displayed a marked decrease in bilirubin, alkaline phosphatase, and aminotransferase activity as compared to the rats administered thioacetamide only. No major changes were observed in terms of the amount of Na+, K+ or the liver weight in the different groups. In view of the flavonoid content of the extracts and their antioxidant properties, the experiments indicated that Silybum marianum and Cichorium intybus had a hepatoprotective effect[34-37].

1.5.3. Chamomile capitula

To evaluate the potential mechanism of hepato-protection, the influence of an ethanolic extract of Chamomile recutita capitula (400 mg kg-1, P.O.) on glutathione levels, Na+ K+-ATPase enzyme activity, serum marker enzymes, serum bilirubin levels, glycogen levels, and thiobarbutiric acid reactive substances against the effect of paracetamol induced hepatotoxicity in rats. It is observed that the extract of Chamomile recutita showed reverse effects on all these parameters against paracetamol-induced hepatotoxicity[38-40].

1.5.4. Coccinia grandis

Hepatotoxic rats exposed to CCl4 were administered an alcoholic extract of fruits from Coccinia grandis Linn (Curcubitaceae), and the concentrations of AST, ALT, ALP, total proteins, and total and direct bilirubin were evaluated. The alcoholic extract was found to have a hepatoprotective activity at the dose of 250 mg/kg through a marked ($p<0.05$) decrease in blood enzyme activities (AST, ALT, and ALP) and bilirubin, similar to that of silymarin[41-44].

1.5.5. Wedelia calendulacea

The ethanolic extract of Wedelia calendulacea L. (Asteraceae family) was examined for its hepatoprotective action on acute toxicity induced by CCl_4 in rats.

The results showed that Wedelia calendulacea ethanolic extract exhibited dose-dependent reduction in serum enzymes activity induced by CCl_4 along with elevation of total protein and bilirubin content, which indicated the capability of

the extract to enhance the normal functional status of the liver as well as rats. The weight of the organs including liver, heart, lung, spleen, and kidney increased significantly with administration of ethanolic extract of Wedelia calendulacea in mice having impaired liver function due to CCl_4[45-48].

1.5.6. Prostechea michuacana

Prostechea michuacana (PM) extracts in methanol, hexane, and chloroform were studied for their anti-liver damage activity in CCl4-induced liver damage in albino rats. Pretreatment of methanolic extract reduced the biochemical parameters of liver damage activity and demonstrated dose-dependent inhibition of in vivo peroxidation caused by CCl4. In addition, pretreatment of PM extracts against paracetamol-induced hepatotoxicity and its possible mechanism of action were evaluated in rats after administering PM extracts at doses of 200, 400, and 600 mg/kg[49-53]. The blood biochemical analysis was carried out to evaluate the degree of protection offered. It was found that methanolic extract of orchid had a pronounced hepatoprotective activity, indicated by decreased enzyme and bilirubin activities in the serum. Thus, these results suggested that the methanolic extract of Prostechea michuacana could prevent paracetamol-induced lipid peroxidation, thereby eliminating the harmful effects of toxic metabolites of paracetamol.

1.5.7. Aegle marmelos

In the Indian medical system, leaves of Aegle marmelos (Bael), which belong to the Rutaceae family, were used as herbal drugs.

The essential marker biochemical parameters were used for evaluation of the hepatoprotective potential of Aegle marmelos on liver injury induced by ethanol in rats. The results revealed that Bael leaves are highly hepatoprotective. Similar results were also obtained by other investigators[54-58].

1.5.8. Cassia roxburghii

Seeds from Cassia roxburghii DC have been utilized in the treatment of various diseases affecting the liver as a result of the hepatoprotective properties of the seeds. In rats, the toxicity induced by ethanol-CCl4 mixture was effectively reversed in a dose-dependent manner by methanolic extract of Cassia roxburghii.

This extract produces actions that are comparable to Liv-52® which is one of the most known hepatoprotective drugs from plants[59-63].

1.5.9. Orthosiphon stamineus

The hepatoprotective activity of O. stamineus methanol extract against paracetamol induced hepatic damage in rats has been assessed. The biochemical parameters such as AST, ALT, ALP, and lipid peroxidation have been determined for the animals treated with paracetamol as well as for the untreated group. From the results obtained it appears that the treatment with 200 mg/kg body weight of O. stamineus leaf methanolic extract accelerates the recovery of altered biochemical parameters towards normal in a dose-dependent manner[64-68].

1.5.10. Ficus carica

The methanolic extract of the leaves of Ficus carica Linn. (Moraceae) was evaluated for its possible hepatoprotective effect using rats with CCl4-induced liver damage. Significant reductions were noted in serum AST, ALT, total serum bilirubin, and malondialdehyde equivalents (a measure of lipid peroxidation of liver cells) following oral administration of the extract at 500 mg/kg[69-73].

1.5.11. Lepidium sativum

The protective effect of the methanol extract of Lepidium sativum at doses of 200 and 400 mg/kg against the harmful effects of carbon tetrachloride-induced hepatic injury in rats was evaluated[74-79]. Groups that received treatment with Lepidium sativum demonstrated significant reduction in all biochemical indices. In the groups that received Lepidium sativum, the extreme fatty changes observed in the livers of rats due to CCl4 were insignificant.

1.5.12. Sargassum polycystum

Rats suffering from D-galactosamine induced hepatitis were employed for assessing the preventative efficacy of Sargassum polycystum ethanol extract. D-Galactosamine induced increases in the concentrations of diagnostic markers (AST, ALT and ALP) in the plasma of rats were markedly ($P<0.05$) reduced following the administration of S. polycystum extract orally [125 mg/kg body weight/day for 15 days]. By inhibiting the activation of lipid peroxidation and preserving the hepatic antioxidant defense system near normal level, it is also demonstrated antioxidant activity against D galactosamine induced hepatitis. Sargassum polycystum has potent anti-hepatotoxic activity due to its antioxidant and membrane stabilizing effects[80-84.]

1.5.13. Solanum nigrum

The effects of *Solanum nigrum* extract (SNE) on hepatic fibrosis in mice caused by thioacetamide (TAA) were investigated. Throughout the course of the trial, mice in the three TAA groups received daily gastrogavage treatments of distilled water and SNE (0.2 or 1.0 g/kg). In TAA-treated animals, SNE decreased the levels of α-smooth muscle actin protein and hepatic hydroxyproline. Growth factor-β1 TGF-β1 RNA levels in the liver were transformed by SNE's inhibition of TAA-induced collage α1) (I).Additionally, histological analysis verified that SNE lessened the amount of fibrosis brought on by TAA therapy. Oral SNE administration dramatically lessens TAA-induced hepatic fibrosis in rats, most likely via lowering TGF-β1 seretio[85-87].

In another investigation, rats with chronic hepatotoxicity caused by CCl4 were used to test the preventive effects of aqueous extract of SN (ASNE) against liver damage. The findings demonstrated that ASNE treatment considerably reduced the CCl4-induced blood levels of hydroxyl radicals, superoxide, and hepatic enzyme indicators. According to liver histology, ASNE decreased the frequency of liver diseases in rats, such as hazy swelling of the liver cells, lymphocyte infiltration, hepatic necrosis, and fibrous connective tissue growth brought on by CCl4. Thus, the study's findings imply that ASNE may shield rats' livers from oxidative damage caused by CCl4. This hepatoprotective effect may be attributed to ASNE's modulation of detoxification enzymes as well as its antioxidant and free radical scavenging properties[88-90]. DNA is protected from oxidative damage to its deoxyribose sugar moiety by the addition of plant extracts of Solanum nigrum and Cichorium intybus in the processing mixture including calf thymus DNA and a free radical producing apparatus. The concentration of plant extracts had an impact. On the other hand, Cichorium intybus had a far stronger effect than Solanum nigrum. According to these investigations, the ability of these crude plant extracts to inhibit the oxidative destruction of DNA in the tissue debris may be the cause of the observed hepatoprotective effect[91-94]. Given that these herbs are widely recognized as hepatoprotective agents and have demonstrated their effectiveness in preventing CCl4-induced liver injury[95-97], it is possible that their

effectiveness can be linked to their capacity to scavenge free radicals.

Table 1: Mechanism of herbal sources exhibiting hepatoprotective action

Sr. No.	Plant/Herbal Source	Experimental Model	Dose/Extract Used	Key Findings	Proposed Mechanism
1	Annona squamosa	Diethyl nitrosamine-induced hepatotoxicity	Plant extract	Reduced hepatocytic necrosis, portal triaditis, and centrilobular inflammation; restored normal lobular architecture	Antioxidant and hepatoprotective activity against chemical-induced liver injury
2	Silybum marianum	Thioacetamide-induced hepatotoxicity in rats	Polyphenolic extract, 25 mg/kg	Significant reduction in bilirubin, ALP, and aminotransferase levels	Flavonoid-mediated antioxidant and membrane stabilizing effect
3	Chamomile recutita	Paracetamol-induced hepatotoxicity	Ethanolic extract of capitula, 400 mg/kg (P.O.)	Restored glutathione, Na+/K+-ATPase activity, glycogen, bilirubin, and serum marker enzymes	Hepatostimulant action with antioxidant potential
4	Coccinia grandis	CCl4-induced hepatotoxicity	Alcoholic fruit extract, 250 mg/kg	Reduced AST, ALT, ALP, and bilirubin levels comparable to silymarin	Hepatocellular membrane protection and antioxidant effect
5	Wedelia calendulacea	Acute CCl4-induced hepatotoxicity	Ethanolic extract	Dose-dependent normalization of serum enzymes and bilirubin; improved organ weight changes	Restoration of normal liver function and antioxidant activity
6	Prostechea michuacana	CCl4 and paracetamol-induced hepatotoxicity	Methanol extract, 200–600 mg/kg	Reduced serum enzymes, bilirubin, and lipid peroxidation	Prevention of toxic metabolite-induced oxidative stress
7	Aegle marmelos	Alcohol-induced liver damage	Leaf extract	Significant hepatoprotective activity with restoration of biochemical markers	Antioxidant and liver regenerative properties
8	Cassia roxburghii	Ethanol-CCl4-induced hepatotoxicity	Methanolic seed extract, 250 and 500 mg/kg	Dose-dependent reversal of hepatotoxicity similar to Liv-52®	Hepatotoxin modulation and antioxidant activity
9	Orthosiphon stamineus	Paracetamol-induced hepatotoxicity	Methanol leaf extract, 200 mg/kg	Restored AST, ALT, ALP, and lipid peroxide levels near normal	Antioxidant-mediated recovery of hepatic tissue

10	Ficus carica	CCl4-induced hepatotoxicity	Methanolic leaf extract, 500 mg/kg	Significant reduction in AST, ALT, bilirubin, and lipid peroxidation	Free radical scavenging and hepatocellular protection
11	Lepidium sativum	CCl4-induced hepatotoxicity	Methanolic extract, 200 and 400 mg/kg	Decreased biochemical markers and reduced fatty liver changes	Antioxidant and anti-steatotic effects
12	Sargassum polycystum	D-galactosamine-induced hepatitis	Ethanol extract, 125 mg/kg/day for 15 days	Reduced AST, ALT, ALP and lipid peroxidation; maintained antioxidant defense system	Membrane stabilization and antioxidant action
13	Solanum nigrum	TAA and CCl4-induced hepatotoxicity/fibrosis	Aqueous extract and SNE (0.2–1.0 g/kg)	Reduced fibrosis, TGF-β1 expression, hydroxyproline, oxidative stress, and hepatic necrosis	Antifibrotic, antioxidant, free radical scavenging, and detoxification enzyme modulation
14	Cichorium intybus	Oxidative DNA damage and hepatotoxicity models	Plant extract	Strong inhibition of oxidative DNA damage and hepatoprotection	Potent antioxidant and DNA protective activity

Table 2: Summary of Hepatoprotective Plants and Their Major Pharmacological Actions

Pharmacological Action	Plants Showing Activity
Antioxidant activity	Silybum marianum, Solanum nigrum, Sargassum polycystum, Aegle marmelos
Reduction of serum liver enzymes (AST, ALT, ALP)	Coccinia grandis, Orthosiphon stamineus, Ficus carica
Anti-inflammatory activity	Annona squamosa, Solanum nigrum
Antifibrotic activity	Solanum nigrum
Prevention of lipid peroxidation	Prostechea michuacana, Ficus carica, Sargassum polycystum
Membrane stabilizing effect	Silybum marianum, Sargassum polycystum
Restoration of normal liver histology	Lepidium sativum, Annona squamosa
DNA protective/free radical scavenging effect	Solanum nigrum, Cichorium intybus

Table 3: Comparative Overview of Experimental Hepatotoxicity Models

Hepatotoxic Agent	Mechanism of Toxicity	Plants Evaluated
CCl4	Lipid peroxidation and oxidative stress	Coccinia grandis, Wedelia calendulacea, Lepidium sativum, Ficus carica, Solanum nigrum
Paracetamol	Toxic metabolite (NAPQI)-induced oxidative damage	Chamomile recutita, Orthosiphon stamineus, Prostechea michuacana
Thioacetamide (TAA)	Hepatic necrosis and fibrosis	Silybum marianum, Solanum nigrum
D-galactosamine	Hepatic inflammation and oxidative stress	Sargassum polycystum
Diethyl nitrosamine	Chemical-induced hepatocellular injury	Annona squamosa
Ethanol + CCl4	Combined oxidative and inflammatory liver damage	Cassia roxburghii
Alcohol	Chronic oxidative liver injury	Aegle marmelos

DISSCUSSION

At least 25% of patients with liver problems use ethnobotanicals, and the use of herbal medicines is growing worldwide. In order to solve the mysteries surrounding the plants, more work needs to be done on methodological scientific evaluation for their safety and efficacy through rigorous preclinical investigations and clinical trials. By standardizing the dosing regimen based on evidence-based findings, this strategy will assist explore the true therapeutic efficacy of these natural pharmacotherapeutic substances and go beyond a passing fad[98]. There are numerous herbal remedies available to promote health, reduce symptoms, and treat illnesses. Nevertheless, scientific pharmacological confirmation is lacking for the majority of these products. Several herbal remedies showed hepatoprotective and curative properties in laboratory or higher animals' experimental hepatotoxicity models, which calls for their clinical study. The majority of herbal formulations cannot be recommended for the treatment of liver problems due to a lack of scientifically supported pharmacological data[99-100].

Only four terrestrial plants have been scientifically explained while adhering to internationally recognized scientific protocols, despite the fact that Indian systems of medicine have more than 300 preparations (using more than 87 Indian medicinal plants) for the treatment of jaundice and chronic liver diseases. Extensive research has demonstrated Sylibum marianum's anti-oxidative, anti-lipid peroxidative, antifibrotic, anti-inflammatory, immunomodulating, and liver-regenerative properties. It has been demonstrated that Glycyrrhiza glabra is both endogenous interferon-producing and hepatoprotective.

CONCLUSION

Liver cirrhosis and drug-induced liver injury rank as the ninth most common cause of mortality in both western and developing nations, making chronic hepatic illnesses one of the biggest health issues in the world. Western medicine-based therapies are frequently ineffective, have the potential to have negative side effects, and are excessively expensive, particularly for developing nations. Therefore, it seems quite appealing to treat liver illnesses with readily available plant-derived chemicals that don't require time-consuming pharmaceutical production. The reported hepatoprotective plants from India and other countries have been compiled in this review article, which may be helpful to medical professionals, scientists, and academics working in the fields of pharmacology and therapeutics to develop evidence-based alternative medicine to treat various liver diseases in humans and animals.

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