Review Article

Hepatoprotective Herbal Plants- A Review

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Abstract

A major new issue in global health is the emergence of liver diseases. Multiple hazardous substances, including chemotherapeutic medications, thioacetamide, carbon tetrachloride, certain antibiotics, excessive alcohol use, and pathogenic microbes, can induce these disorders. Consequently, keeping the liver healthy is crucial to overall wellness. Despite advances in pharmacology, the risks of synthetic drugs have outweighed their advantages. Undeveloped nations cannot afford the modern medical treatments for liver illness since they are ineffective, associated with serious side effects, and extremely expensive. Illnesses may have alternative treatments, and there appears to have been a worldwide boom in interest in studying medicinal plants. It is not necessary to employ labor-intensive pharmaceutical manufacturing procedures to obtain these plants, and they are also cheap. Traditional herbs that work well with little side effects and cost effectively have been the main emphasis so far. A literature search utilizing numerous databases, such as Google Scholar, ISI Web of Knowledge, and PubMed, was conducted and the results are presented in this research. We combed through every piece of literature on medicinal plants from around the world that may offer liver protection. We also highlighted forthcoming studies in the field and discussed phytochemical compounds with hepatoprotective characteristics.

Keywords: Bioactive compounds, hepatotoxicity, liver diseases, medicinal plant, pharmacology

Introduction

The liver is the most crucial organ because of all the work it does for the body. Not only does it aid in the excretion of waste metabolites, but it is also involved in the metabolism of carbohydrates, proteins, and lipids. Because it receives toxins from the intestines first, the liver plays a role in their breakdown and elimination from the body. Toxins might include drugs and other foreign chemical compounds. The specific functions of the liver in the human body are listed below.

Glycogen, minerals, vitamins, and iron are just a few of the many compounds that could be stored in it. When the body's energy demands exceed its blood sugar levels, the liver releases glucose from glycogen stores. This process eliminates a wide variety of substances from the bloodstream, including pathogenic

organisms, alcohol, chemicals, heavy metals, drugs, and toxic by-products. The liver filters the blood of many waste products and contaminants, including chemicals, drugs, viruses, bacteria, parasites, fungi, herbicides and pesticides, lipids, food additives, alcohol, and dead cells. Additionally, because it accomplishes all of its functions via a variety of organs, such as the skin, the lungs, and the mouth, the liver is occasionally called the biochemical unit of the body. In the bloodstream, it breaks down substances before distributing them to other parts of the body. The liver produces bile as part of its digestive function [4]. Bile is necessary for digesting and emulsifying lipids, oils, and other chemicals, including vitamins A, D, E, and K. Some of the proteins it could make include hormones, clotting factors, immunological factors, and blood proteins. Finally, when blood sugar levels are low, the liver may produce cholesterol, a lipid transporter necessary for the creation of adenosine triphosphate, an energy source for the body.

Hepatotoxicity and Liver Diseases

One of the most critical global health issues is the prevalence of liver diseases in poor countries. Hepatosis without inflammation, hepatitis with inflammation (acute or chronic), and cirrhosis or fibrosis caused by degeneration are all forms of liver disease. Heavy metals, toxins, hunger, and the unapproved use of over-the-counter medications are common culprits in their onset and progression. The aforementioned causes destroy and damage hepatocytes, leading to alcoholic liver disease, hepatitis, jaundice, and fibrosis of the liver. Elevated cholesterol levels in the blood are a symptom of liver disease or injury. A higher risk of cardiovascular disease is associated with elevated levels of triacylglycerols and low-density lipoprotein cholesterol (LDL-C).[5]

Hepatic cell overconsumption, toxic substances like thioacetamide (TAA), drug abuse (e.g., paracetamol), chemotherapeutic agents (e.g., carbon tetrachloride, CC14), aflatoxin, microbes, and viral infections (e.g., hepatitis A, B, C, and D) are additional factors that have been demonstrated to cause damage to hepatic cells in previous research.When the endoplasmic reticulum and mitochondrial cytochrome P-450 metabolize CC14 between 6 and 8, a chain reaction happens that could start lipid peroxidation, resulting in the production of reactive oxygen species (ROS, $CCl3O^{-}$).

Analgesic and antipyretic properties of PCM make it a common medicine for treating pain and fever. Damage to the liver cells, and thus disease or injury to the liver, occurs when this medicine is overdosed.[9] The majority of liver cells die (necrosis), which is characterized by nuclear pyknosis and eosinophilic cytoplasm, and when PCM is injected in excess, it can cause severe excessive hepatic damage. While the liver processes PCM, an oxidative byproduct called N-acetyl-P-benzoquinoneimine is created. Cytochrome P-450 enzymes are among the proteins that this chemical binds to covalently via their sulfhydryl groups. Peroxidative degradation of glutathione (GSH) lipids is the end cause of this process, and it leads to hepatocyte necrosis.

In addition to other chemicals, trimethylammonium (TAA) damages membranes by preventing RNA from freely passing between the nucleus and cytoplasm. Because of the TAA metabolite, this liver damage occurs.[9] It is possible that TAA reduces the quantity of hepatocytes and also decreases the frequency of oxygen consumption. Also, the concentration of bile salts and deoxycholic acid, as well as the quantity of bile, are reduced. Abnormal bile excretion, brought on by hepatotoxin-

associated liver injury, manifests as an increase in blood toxin levels.[10] This liver must always be able to function regularly for human health to be maintained.From 11–13, the liver is continually exposed to dangerous environmental pollutants including xenobiotics and chemotherapeutic medications, which can hinder its natural defense systems and lead to liver malfunction and damage, despite its incredible regenerative potential.[14]

On the flip side, hepatotoxic chemicals disrupt kidney function by damaging hepatocytes, typically through oxidative mechanisms such lipid peroxidation. When the liver is damaged, the antioxidant mechanisms in the body are unable to do their job. Radiation from X-rays, pollutants, ultraviolet light, or metabolic processes within mitochondria are among the external sources that can generate radon oscillations (ROS).The intracellular concentration of reactive oxygen species (ROS) is solely dictated by the rate of ROS formation and clearance by different endogenous antioxidants, which can be achieved by both enzymatic and nonenzymatic methods.[15]

Research shows that oxidative stress, brought on by free radicals, leads to hepatocyte degeneration, swelling, necrosis, and apoptosis. Free radicals typically injure or harm the liver by lipid peroxidation and covalent binding, which then leads to tissue degeneration. Atherosclerosis, diabetes, kidney and lung damage, liver disorders, cancer, inflammatory diseases, and cardiovascular diseases are all linked to reactive oxygen species (ROS), which destroy the lipids, proteins, and nucleic acid in cell membranes.Lipid peroxidation weakens the structural and functional integrity of cell membranes (pages 16 and 17). The cell's capacity to maintain constant ion gradients and transport is subsequently diminished.On the flip side, the liver can be damaged by chemical exposure and heavy drug use.[14] Table 1 and Figure 1 demonstrate the reported effects of numerous medications on the liver.

Free Radicals and Lipid Peroxidation

To prevent free radical-induced lipid peroxidation, the free radical scavenging process is crucial.The metabolic pathway that begins with ethanol exposure enhances lipid peroxidation, which in turn causes hepatitis and, ultimately, cirrhosis [19].

In recent decades, hepatoprotective medicines derived from less toxic plant compounds have been used. Therefore, there has been significant study in this sector focused on continuously exploring plant diversities for new hepatoprotective potential.In [20], It is important to maintain a balance between reactive oxygen species (ROS) and antioxidant enzymes like glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), and catalase (CAT) in order to prevent damage caused by oxidative stress, as earlier research has shown that an excess of ROS intensifies oxidative stress, leading to health problems like diabetes, kidney and liver injury, cancer, and heart disease.Natural lipid peroxidation defenders, the enzymatic antioxidant defence systems [22] include Cu-Zn, Mn-SOD, CAT, and GSH reductase; they work by directly or sequentially removing ROS, therefore halting or decreasing this process.[23] Glutathione (GSH) is a crucial cytosolic antioxidant that plays a role in the detoxification and excretion of xenobiotics; keeping its level high is vital for avoiding lipid peroxidation.CCl4 is one of the xenobiotics that may cause acute damage to liver cells by generating free radicals, namely trichloromethyl radicals [24].[25] The Typically, the liver has an increasingly protective mechanism for compounds that enhance the activity of glutathione S-transferase, an enzyme that may transform harmful molecules into innocuous ones.

Because they have less of an impact on the body's processes, natural goods, such as medicinal plants and their constituents, have the potential to cure and prevent a wide range of disorders.references 26 and 27 Research has shown that some herbal extracts may have a protective effect on an overloaded liver.8,13, and 28

Table 1: Example of some drugs with hepatotoxicity effects

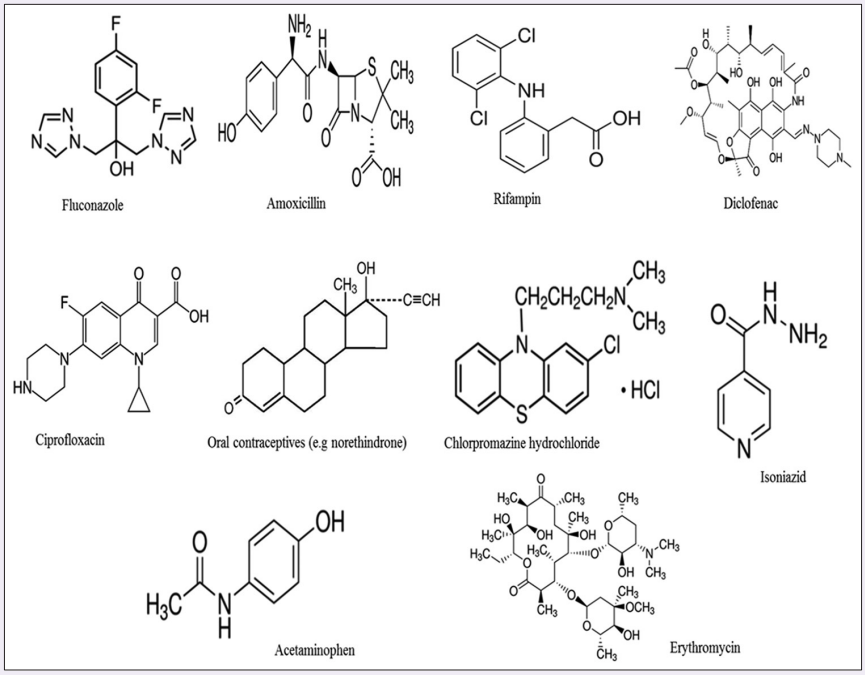
Drugs	Implication
Fluconazole	It leads to hepatitis; it increases the transaminase level, fulminant hepatic failure, and cholestasis
Amoxicillin	It moderates or brings about an increase in SGPT and SGOT levels, hepatic failure such as jaundice, acute cytolytic hepatitis, and hepatic cholestasis
Diclofenac	It elevates AST and ALT levels, jaundice, fulminant hepatitis, and liver necrosis
Rifampin	It leads to hepatitis, hyperbilirubinemia, and cholestasis Ciprofloxacin Elevation of SGOT alkaline phosphatase and SGPT levels occurs from cholestatic jaundice
Oral	Benign neoplasm, hepatic vein occlusion, and jaundice, contraceptives but rarely neoplasm of the liver
Chlorpromazine	It leads to infectious hepatitis with obstructive jaundice as a biomarker
Isoniazid	It elevates the serum transaminase level, severe and

SGOT=Serum glutamic oxaloacetic transaminase, ALT=Serum alanine aminotransferase, AST=Aspartate aminotransferase, SGPT=Serum glutamic pyruvic transaminase, NAPQI=N-acetyl-P-benzoquinoneimine

Diseases of the Liver and Alcohol

In today's world, a major contributor to liver issues is drinking too much alcohol.[14] The liver is involved in alcohol metabolism, which impacts lipoprotein and lipid metabolism, which in turn links ethanol use to alcoholic liver disease. Additionally, cytochrome P4502E1 is activated during the alcohol dehydrogenase-to-acetate conversion of ethanol to ROS.The numbers [29,30] The liver goes through a series of events that culminate in oxidative stress [Figure 2], which in turn causes damage to the liver and alters the structural stiffness of the cell membrane, allowing cytosolic enzymes to seep into the circulation. As a result, elevated levels of cytosolic enzymes in the blood are the most prevalent biochemical indicator of liver injury.[31] in Both the cytoplasm and mitochondrial concentrations of aspartate transaminase (AST) and alanine transaminase (ALT) rise in injured liver cells. A change in the structure of the liver cell membrane,

brought about by membrane leakage, leads to an elevation in serum hepatospecific enzymes. Furthermore, elevated blood bilirubin levels indicate a quickening of the erythrocyte degradation rate. Therefore, maintaining a healthy liver is critical to human wellbeing.[32] The process of alcohol-induced liver damage is shown in Figure 2.



Medicinal Plants as an Alternative Treatment

Metabolic diseases, including liver impairment, account for the vast majority of deaths and illnesses worldwide. The harmful effects of numerous allopathic medications on the liver have recently brought liver injury therapies into the spotlight on a worldwide scale. Therefore, researchers have paid a lot of attention to folkloric herbs that have hepatoprotective properties for treating liver damage or illness. This is mostly because these herbs are therapeutic and have minimal toxicity. Animal studies have recently looked at the hepatoprotective effects of many traditional medicines. The positive effects of herbal medicine on human health have long been recognised and used in traditional medicine. Scientists have isolated several molecule types and investigated their pharmacological and physicochemical characteristics. It is important to synthesise compounds and extracts correctly so that they may achieve their physiological aim and exert their pharmacological effects. The absorption and delivery of bioactive compounds may be impacted by factors including poor solubility and permeability.[32] However, to ensure their stability during the duration of usage, it is important to assess the shelf life of herbal medications. Environmental factors such as heat, moisture, acidity, oxygen, and light speed up the degradation process. Herbal remedies include a wide variety of chemical components, including primary and secondary

metabolites, carbohydrates, proteins, and lipids.[33]

Numerous efforts have been undertaken to discover new sources of hepatoprotective agents due to the adverse effects associated with synthetic medicines.on page 34 These days, the majority of hepatoprotective medications used to treat various liver illnesses are derived from plants, either in the form of individual plants or complex mixes of herbs. Rural residents, particularly in underdeveloped nations without appropriate modern healthcare facilities, rely heavily on folkloric herbs to enhance their quality of life.[1] The medicinal value of plants exceeds 70,000 species. While plants have gained popularity as natural treatment options, the science behind their preparation and dosage is often unclear. Despite their effectiveness and cost-effectiveness, it is imperative to prioritise plants with low toxicity. There are many herbal drugs on the market, but only a few bioactive ingredients have been proven to have antiviral, antioxidant, anticarcinogenic, antifibrotic, and anti-inflammatory effects.35 and 36

In Vitro and In Vivo Hepatotoxicity Assays

The choice of appropriate treatment for the liver disease relies solely on the suitability of the model the system preferred for hepatic damage. Although a number of prototypes exist to assess the hepatoprotective prospect of any chemical or plant extract, most of these models have limitations. Hence, it will be appropriate to combine these models for better results.[37] In a study carried out by Cerný et al.[38] In vitro assays such as hepatocyte cultures, perfused hepatocytes study with pathophysiological damage caused by various chemical substance (e.g., hypoxia hepatotoxins, or anoxia assays in perfused immobilized hepatocytes were documented. Some of the reported in vivo models are presented in Table 2. The majority of these studies on the hepatoprotective role of some medicinal plants are still based on the laboratory experiments.

Most organisms have their own antioxidant-based defense mechanisms which combat the activity of free radical species. The protective role of the endogenous antioxidant system in humans is not always adequate when the free radical species are much greater than the available antioxidant, and hence, additional antioxidants from different sources become important. Various antioxidant agents of plant origin appear to be effective in scavenging free radicals that lead to liver injuries.[39] Phytochemicals such as phenolics, thiols, and caretonoids present in herbal plants protect the human body against oxidative damage by ROS.[17] Therefore, attention is being diverted to promising medicinal plants that have the hepatoprotective potential to treat different kinds of liver disease. The folkloric herbs for treating all kinds of diseases have been in existence since ancient times due to their therapeutic efficacy and safety, and several herbs have been investigated for their hepatoprotective potential for the treatment of different types of liver disorders.[14] Numerous herbal formulations have proved to be effective therapeutic agents against various kinds of liver disorders [Table 2], and this review mainly focused on available literature on those that have been confirmed around the globe to have hepatoprotective properties.

Some Medicinal Plants with Hepatoprotective Activity

Dodonaea viscosa (Sapindaceae)

The flowering plant Dodonaea viscosa is a member of the soapberry family. Sapindaceae may be found all throughout the Southern Hemisphere, from the subtropics to the warm and tropical temperate zones of Africa, the Americas, and Australia.[47] Traditional healers in this area have used this plant, which they name "Sanatha," for decades to control

their patients' diabetes.[132] The antihyperlipidemic and hepatoprotective effects of an aqueous: methanolic (70:30) D. viscosa leaf extract were recorded in a study by Ahmed et al., [47]. The rabbits were induced with diabetes by alloxan. The results showed that as compared to the control group, the experimental group had lower blood levels of TAG, total cholesterol, LDL-C, HDL-CHL, ALT, and AST. In addition, levels of HDL-CHL, AST, and ALT were significantly raised by the extract. These results demonstrate that D. viscosa leaf extract has hepatoprotective properties.

Phyllanthus muellarianus (Euphorbiaceae)

The straggling, monoecious, glabrous, climbing shrub or small tree known as Phyllanthus muellarianus is widely distributed in many African countries, including Senegal, Uganda, Mali, Congo, Togo, South Africa, and Ivory Coast.[40] A wide range of medical conditions, including paralysis, fever, and bacterial infections, have been treated using extracts from this plant.On pages 133 and 134, A phytochemical analysis of an extract from P. muellarianus leaf showed the presence of phytochemical components that may be responsible for the therapeutic action, including furosin, isoquercetin, phaselic acid, corilagin, nitidine, geraniin, and gallic acid.13, 35, 136 The hepatoprotective ability of an aqueous extract of P. muellarianus leaf was studied in 2017 by Ajiboye et al. in relation to hepatocellular indices, proinflammatory factors, oxidative stress, and lipid peroxidation in Swiss albino mice that had been injured in the liver by b-acetaminophen.[40] The results demonstrated that the acetaminophen-induced changes in the ALT, ALP, AST, ALB, and TB were significantly reduced by the aqueous leaf extract ($P < 0.05$), according to this research. The potential antioxidant properties of the water-based leaf extract may be due to its capacity to counteract the increase in these liver enzymes caused by acetaminophen, suggesting a protective benefit against acetaminophen-induced liver damage. It has been shown that gallic acid, a phytochemical component of this plant extract and a well-known antioxidant, may reverse AST, ALT, and ALP, as well as acetaminophen-induced liver damage.[137]

Similarly, the rat liver showed a substantial reduction in the activities of SOD, GSH, CAT, G6PH, and GSH-Px when acetaminophen was used. Aqueous leaf extract from the plant under study considerably reduced the increase in levels of several compounds, including malondialdehyde, lipid hydroperoxides, fragmented DNA, protein carbonyl, and tumour necrosis factor-alpha. Because of its preventative properties, the plant was also determined to have promising future use as a dietary supplement.[40]

Aquilaria agallocha (Thymelaeaceae)

This massive tree may reach heights of 60–80 feet and has a trunk that is three to four feet in diameter. Its original habitat is in South-east Asia. Similar to Betula's usage of tree bark for writing, the bark is papery thin and was sometimes used for that purpose. The thin, leathery leaves may grow to be three inches in length. White blossoms accompany smooth, slender fruit that is one to two inches in length. Aquilaria agallocha is a plant with a wide range of pharmacological effects, including but not limited to: protecting against cancer, inflammation, diabetes, anxiety, ulcers, and seizures; alleviating pain; reducing fever; and antidiabetic, antihistaminic, antipyretic, laxative, antidiarrheal, antidiabetic, antihistaminic, sedative, antibacterial, and antimicrobial properties.[138] A study conducted by Alam et al. [72] shown that a 400 mg/ml ethanolic extract of A. agallocha (AAE) leaves protected the livers of Sprague-Dawley (SD) rats against PCM-induced hepatotoxicity. The findings demonstrated that AAE leaves

have a hepatoprotective effect, as they prevented PCM-induced histopathological changes in the liver, increased ALB and total protein concentration, and significantly reduced AST, ALP, ALT, LDH, CHL, and TB in SD rats.[72]

Bioactive Molecules with Hepatoprotective Potentials

Past research has led to the isolation of several plant biomolecules with intriguing hepatoprotective properties. Humans have not yet been the subjects of comprehensive clinical studies with these pure substances. The presence of biomolecules such as resveratrol, curcumin, silymarin, glycyrrhizin, and quercetin gives some of the bioactive compounds their various biological properties, which include antiviral, antioxidant, anticancer, antiaging, antifibrotic, antidiabetic, and anti-inflammatory potentials (Table 3).

Table 3: Examples of reported phytochemical compounds with hepatoprotective potential

Phytochemical compounds	Plants
Glycyrrhizin	Glycyrrhiza glabra
Resveratrol	Hygrophila auriculata
Curcumin	Curcuma spp.
Colchicine	Colchicum autumnale
Silymarin (silybin)	Silybum marianum
Quercetin	Hibiscus vitifolius
Fumaric acid	Sida cordifolia
Coumarins	Artemisia abrotanum
Schizantherin A	Schisandra chinensis
Kutkoside	Picrorhiza kurroa
Catechin	Anacardium occidentalis
Papyriogenin	Tetrapanax papyrifer
Cronin	Gardenia jasminoides
Syringopicroside	Syringa oblata
Piceid	Polygonum cuspidatum
Gomishins	Schisandra chinensis
Saikosaponin	Bupleurum falcatum
Cosmosiin	Cupressus sempervirens L.
Patuletin	Ficus ingens

Conclusions and Future Prospects

In spite of the fact that everyone is worried about being sick, health issues have grown into a big problem in our culture. Despite the liver's critical function, liver diseases and injuries rank high among the most common medical issues globally. The most common causes of liver damage are unhealthy eating habits, drinking too much alcohol, using herbal supplements, having a microbial infection, an autoimmune disease, cancer, metabolic disorder, or being addicted to drugs. Preventing harm to the liver from the aforementioned sources is, then, of paramount importance.

Current treatments for liver diseases are either ineffective or associated with harmful consequences on renal function; thus, there is an immediate need to find novel treatments that can cure liver damage. Therefore, it is

critical to find new hepatoprotective medications that can be made from plants. The majority of herbal remedies for liver problems are based on their hepatoprotective effects and antioxidant properties. These are the cornerstone scientific ideas that will allow for the development of novel hepatitis treatments with few side effects on the kidneys. Therefore, additional studies are needed to determine the likelihood of creating more effective hepatoprotective drugs using new phytochemical candidates.

These medicines have gained global fame since half of the population in impoverished nations uses herbal remedies to treat liver disorders. The majority of herbal extracts that are sold in stores have demonstrated promising effects in reducing the symptoms of liver disease or injury. There is still a lack of evidence about the scientific validity of herbal extracts; so, additional research is needed, especially in this area, to establish protocols for the safe and effective production and administration of herbal extracts. It is of the utmost importance to do preclinical testing on these herbal treatments prior to conducting clinical trials. Next, we may evaluate how well these herbal remedies work as a treatment, and we can use the dosage schedule that was created in the clinical trials to guide the creation and distribution of future medications. To top it all off, the tried-and-true medical approach to drug discovery and design has the potential to bring numerous life-saving drugs to market.

Identifying active principles and developing them into medicines requires significant investment of time and resources. The treatment of liver disorders, especially those that seek to restore the structural integrity of the hepatic cell membrane, should prioritize the availability of drugs generated from plant extracts, whether those extracts be individual or blended. The vast majority of liver diseases cannot be remedied by a single plant extract. This means that to maximize the efficacy of the treatment, it may be necessary to formulate a herbal combination utilizing components from multiple plants. To ensure the plant combination is safe for use, additional research is needed, including toxicity tests. The rationale for this is that there is a high likelihood that one of the plant extracts is toxic, rendering the blend ineffective. Because most people in impoverished rural areas employ plant extracts, traditional healers in underdeveloped countries also need training on how to properly prepare plants for use. When making herbal extracts, it is important to avoid or remove any possibility of contamination.

Ultimately, for the purpose of creating more effective plant-based hepatoprotective medications, additional investigation into the structural modifications of the active principles derived from herbal extracts by computational chemistry approaches is necessary.

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