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A REVIEW OF POTENTIAL HEPATOPROTECTIVE COMPOUNDS FROM MEDICINAL PLANTS

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ABSTRACT

Diseases of the liver are among the leading causes of death in humans around the world. A variety of factors, including alcoholism, hepatitis B and C, cirrhosis, and cancer, can contribute to the development of liver disease. Some liver diseases are treatable with medication, but others require surgery or a liver transplant. Hepatoprotective agents are substances that protect the liver from damage. It is the hope of the many researchers who are currently working on the development of new types of hepatoprotective agents that they will eventually be able to provide an adequate level of protection for individuals who are at an increased risk of developing liver disease. It is without a doubt that natural products can be valuable sources of drug leads. In the pharmaceutical industry, natural products have long been recognized as potential leads for the development of new medicines. The potential benefits of phytochemicals and their hepatoprotective mechanism understanding is a scientific challenging, but their importance has been largely unrecognized. This review discusses a wide range of hepatoprotective compounds derived from different plant sources. The study includes both extracts of medicinal plants and isolated compounds. It appears that these agents may be effective in protecting the liver against various insults, including viral hepatitis, alcohol-induced and drug-induced liver damage. Overall, this review provides an overview of some of the most promising hepatoprotective compounds from plant sources and suggests that further research is necessary to fully understand their potential health benefits.

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Introduction

The extraction of pharmaceuticals from their natural sources has been an essential component of the drug discovery process. In general, "drugs" derived from natural sources are believed to be less toxic than those produced from synthetic substances [1]. To promote and treat health issues, Ayurveda, Siddha, and other traditional systems of medicine, as well as nutritional supplements containing phytochemicals derived from plants, are used. Phytochemicals derived from plants can prevent and treat a variety of chronic disorders, including obesity and cancer. The human body liver is vital organ and more than 75% of the hepatic parenchyma composes the hepatocytes responsible for liver function and the need to support the body's physiological processes. The liver is also responsible for removing toxins from the body, breaking down food for absorption, storing nutrients, and producing bile. The liver has many functions, which can lead to serious health complications if damaged. The liver breaks down fat and converts glucose into glycogen.

Furthermore, it produces bile, which aids digestion and the absorption of fats, vitamins, minerals, and other nutrients. Prothrombin, fibrinogen, and heparin, among other blood clotting factors, are synthesized in the liver in order to prevent blood clots within the circulatory system. Lipids, proteins, and carbohydrates are all metabolized by the liver. The liver also assists in detoxifying the body by converting toxic substances into less harmful ones. It can aid in maintaining blood sugar levels, lowering blood pressure, and diminishing cholesterol levels. In a basic way, liver diseases can be divided into two categories: acute and chronic. An acute liver illness is characterised by a quick onset and short duration of symptoms. In general, chronic liver illnesses are long-lasting, lasting longer than six months, and are characterised by recurrent liver damage and regeneration [2]. In recent decades, there has been an increase in the global burden of liver disease, which has had a significant impact on the population of the entire world. The liver is responsible for protecting the body from hazardous external substances by bio-transforming medicines and chemicals. Hazardous substances and their metabolites are exposed to the liver in high

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concentrations during this process, resulting in the possibility of liver damage [3]. Liver diseases are caused by various factors, including microorganisms, metabolic disorders, xenobiotics, and autoimmune diseases. In different ways, each of these factors can influence the formation of liver disease. It is common knowledge that each of these factors contributes in some way to the overall incidence of liver disease around the world. The three most common causes of liver disease are cirrhosis, hepatitis, and obesity in the liver. The burden of hepatic disease on a global scale is significant. In countries with a high standard of living, the most common causes of death from hepatic disorders are alcoholic liver disease and viral hepatitis. Melanoma of the liver is the primary reason for death due to hepatic disorders in countries that are still developing. A liver ailment diminishes the quality of life and shortens the lifespan. This is as well as an economic burden on the individual and society as a whole.

It has been demonstrated that liver-protective substances derived from natural sources exhibit biological features such as antioxidants and hepatoprotection. Some of the most common liver protective agents include flavonoids, carotenoids, and terpenes. Higher plants contain a wide variety of naturally occurring hepatoprotective agents, which are capable of shielding the liver from a wide range of threats, including viral infections, environmental pollutants, and persistent inflammation. The World Health Organization has reported few effective treatments are available for liver diseases, primarily as a result of the lack of liver protective agents in modern medicines [4]. As a result, many patients with widespread liver disease do not respond well to standard treatments, leading to death. The efficacy of medications like corticosteroids and interferon varies significantly [5]. They pose a considerable risk of ill effects and are often prohibitively expensive. Better therapies at an affordable cost are urgently needed to prevent or cure these diseases. A phytoconstituent is a plant chemical derived from the secondary metabolism of medicinal plants. Medicinal plants produce phytoconstituents to protect them against pests, pathogens, and predators. Chemically defined phytochemicals with hepatoprotective properties have been reviewed. It has been reported that several phytoconstituents possess hepatoprotective properties and have been classified as alkaloids, polyphenolic compounds, terpenoids, flavonoids, steroids, essential oils, and many others [6]. Chemicals of herbal origin that were purified or partially purified have been found to possess marked hepatoprotective properties. In this review article, we focused on several plant-active constituents considered to be most promising for treating liver disease. It is also acknowledged that experimental pharmacological studies are being conducted on medicinal plant constituents. However, the completion of clinical trials is far behind schedule and must be expedited. Hence, this review deals with phytocomponents being tested experimentally with or without clinical studies. There has been a severe underestimation of the significance of those phytochemicals in discovering hepatoprotective drugs. This review paper aims to examine the different phytochemicals that have been shown to protect the liver over the past 30 years.

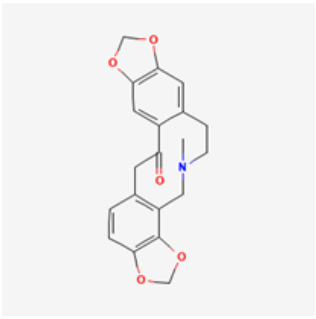
Materials and Methods

A literature search was conducted (from January 1991 to December 2021) using Google Scholar, ScienceDirect, SpringerLink, Pubmed, and Google Scholar. This search included the following keywords: "liver protective plants", "hepatoprotective plants", "phytoconsituents against liver disease", "phytocompounds against liver disease", cross-referenced with "liver diseases", "hepatoprotective activity". The relevant terms “hepatoprotective”, OR "liverprotective" were paired with phytochemicals namely- “alkaloids”, “terpenoids”, “glycosides”, “flavonoids”, “lignans”, and “polyphenolic compounds”. Afterwards, references found in the search were consulted for more information regarding the *in vivo* models or *in vitro* assays used to test the plant extracts or phytoconstituents against liver disease, and only English-language publications were included. The search turned up 182 results. The list was then reduced to 154 references, and each one was further examined by reading its abstract; based on the quality of the data 55 rejecting, 99 articles were considered.

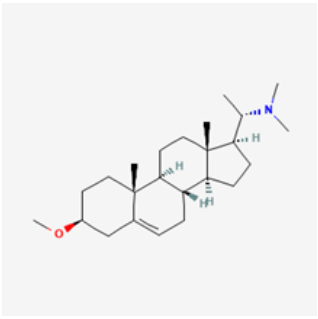
Alkaloids

An alkaloid is a nitrogenous compound that can be found in a wide variety of natural sources, including plants, animals, and microorganisms, but most commonly in plants. Approximately 12,000 different alkaloids have been identified. Alkaloids are a type of secondary metabolite that makes up one of the largest classes of phytochemicals. Fumaria indica Pugsley (Papavaraceae), also called in Sanskrit as "Fumitory" and "Parpat" in Hindi, has been prescribed as a hepatoprotective as part of the Indian traditional medical system. Fumaria indica's butanol fraction offers higher liver defence against d-galactosamine-activated hepatotoxicity in rats. In chromatography (HPTLC) analysis, it was determined that the butanol fraction of *Fumaria indica* contains the isoquinoline alkaloid protopine (PRO) (10–20 mg p.o.) and is responsible for its hepatoprotective properties [7]. The pretreatment of rats with PRO (11 mg/kg) also significantly decreased AST and ALT levels in hepatic damage induced by paracetamol and carbon tetrachloride [8]. The Buxaceae family includes the steroidal alkaloids sarcovagine-D, alkaloid-C, and holaphylline, which were isolated from the entire plant of *Sarcococca saligna*. In male albino rats, CCl_4-induced toxicity is better combated by alkaloid-C and holaphylline. Steroid alkaloids reduced liver inflammation in the vicinity of the wounded central vein by decreasing both the quantity and the activation of hepatic macrophages caused by CCl_4. Holaphylline was the least toxic and safest compound among the isolated compounds [9]. A steroidal alkaloid terminlaline isolated from the *Sarcococca saligna* was a substantial decrease in liver inflammation was observed because of terminaline, as well as a reduction in serum enzyme levels elevated by CCl_4 [10]. Numerous medicinal plants contain the isoquinoline alkaloid berberine (BBR), which is extensively distributed. According to reports, BBR has a wide range of pharmacological actions. Several beneficial pharmacological applications are shown berberine, including vasodilation, antihypertension, immunoregulation, erectile dysfunction, anti-inflammatory, and cancer treatment [11]. Rats given BBR demonstrated dose-

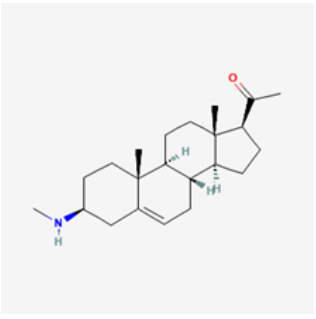
dependent substantial reductions in blood ALT and AST activity during CCl_4-induced hepatotoxicity in both the pre-treatment and post-treatment groups. In response to berberine treatment, in the liver increased SOD activity, and histopathological examination results confirm its hepatoprotective properties. BBR is hepatoprotective against CCl_4-induced hepatotoxicity and is curative and preventive [12]. BBR hepatoprotective effects may be attributed to AMPK, Nox4, and Akt activation [13]. Berberine exhibits hepatoprotective properties by eliminating free radicals, reducing oxidative/nitrosative stress, and suppressing liver inflammation [14]. Increasing antioxidants and reducing lipid peroxidation and hepatic stellate cell proliferation, BBR may be able to protect experimental liver fibrosis in animal models [15]. Acetaminophen has long been recognized for its antipyretic and analgesic properties. A higher dose and continuous intake of a drug that results in liver damage. BBR significantly reduced acetaminophen's hepatotoxicity in the experimental study. The antioxidant properties of BBR may explain the protective effect. The BBR treatment reduced inflammation, oxidative stress, and necrosis in the hepatotoxin-treated group [16]. Methotrexate is well-known drug for its anticancer and immune-suppressing properties, and liver damage is one of its more dangerous side effects. Pretreatment of methotrexate-treated rats with BBR dramatically elevates serum levels of ALT and AST. In addition to enhancing GSH and GPx activity in liver tissue, it also reduces MDA levels. BBR therapy is beneficial in reducing the hepatic damage caused by methotrexate as a result of its high antioxidant activity and anti-inflammatory properties [17]. By regulating SIRT1 in hepatic cell line L02, BBR inhibits H_2O_2-induced apoptosis, indicating that its antioxidant abilities may be attributable to this process. Pro-inflammatory molecules, including IL-1 and TNF- α, were generated by acetaldehyde, a metabolic byproduct of ethanol, and hindered the growth of HepG2 cells, likely through the NF-B pathway [18].



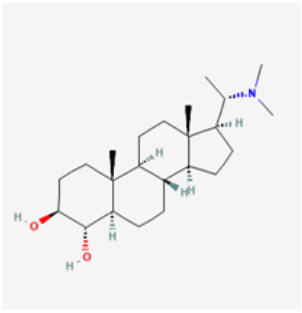
1. Protopine



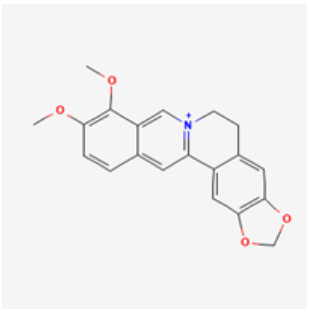
2. Alkaloid-C



3. Holaphylline



4. Terminaline

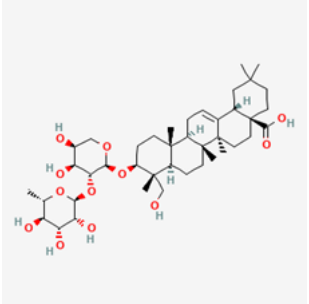


5. Berberine

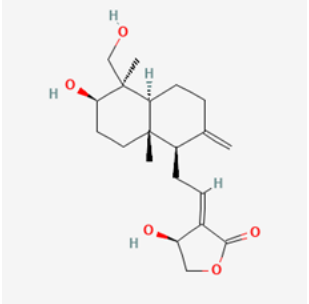
Terpenoids

Terpenoids are natural products found in all types of living organisms. There are a wide variety of terpenoid bioactive molecules present in plants, animals, and microorganisms. Terpenoids are one of the major classes of plant phytoconstituents. Terpenoids are major phytoconstituents are responsible for many plants' aroma and flavor. A wide range of infectious diseases and cancers have been treated with terpenoids due to their biological activity. There have been a number of terpene-based pharmaceuticals developed; taxol is one of them, used to treat a variety of cancers. There were nearly $12 billion in sales of terpene-containing medications in 2002. Agents that protect the liver come from terpenoids, which are one of the most important types of natural compounds. Several medicinal plants contain α-hederin (α-HN), a monodesmosidic triterpenoid saponin with significant biological activity. A hepatoprotective effect of α-HN and sapindoside B (20 mg/kg/s.c/3 days) on mice is attributed to its suppression of liver cytochrome P-450 [19]. According to another study, α-HN protected mice treated with CCl_4. Pretreatment with α-HN prior to CCl_4 injection reduced the dose-dependent increase in ALT and LDH activity as well as lipid peroxidation. The administration of α-HN to mice inhibits the expression and activity of the P450 2E1 enzyme, decreases the biotransformation of CCl_4, and mitigates carbon tetrachloride-induced liver damage [20]. Andrographolide (AP), a diterpene lactone found in the leaf of *Andrographis paniculata*, is quickly absorbed after oral administration to rats and humans. Several pharmacological properties are associated with these phytoconstituents. For example, it has been shown to be effective at treating diseases like liver protection, anti-cancer properties, and inflammation. AP has been found to protect the liver from damage caused by carbon tetrachloride. Treatment with CCl_4 caused hepatic damage, which was demonstrated by a notable increase in ALT, AST, and MDA. The hepatocyte necrosis was confirmed by histopathological examination.

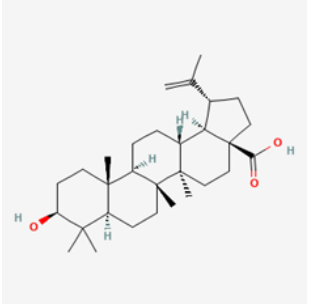
Pretreatment with AP results in a considerable decrease in ALT, AST, and hepatic MDA activity as well as a large increase in GSH levels. AP reduced the CCl_4-induced major increase in tumour necrosis factor-a (TNF-a), and it accelerated the CCl_4-induced dramatic increase in heme oxygenase-1 (HO-1) at both the transcriptional and protein levels. The hepatoprotective treatment of AP may involve reducing oxidative stress and inflammatory responses [21]. Although acetaminophen is a common pain reliever used to treat people with chronic pain, prolonged use causes liver fibrosis. Long-term use of analgesics causes liver fibrosis, which is prevented by Nrf2, and AP lessens this effect by lowering oxidative stress injury [22]. In mice, the AP offers superior defence against acute liver damage brought on by LPS and D-GalN. The injection of AP improved liver histology and reduced ALT, AST, MPO, IL-1, TNF-, MDA, and ROS levels in hepatic tissues in a dose-dependent manner. AP also reduced NF-B activation produced by LPS/D-GalN and elevated the expression of Nrf2 and HO-1. NF-kB inhibition and Nrf2 signalling pathway activation provided protection from LPS/D-GalN-induced liver damage via AP [23]. AP and arabinogalactan were isolated from *Andrographis paniculata* Nees. Pretreatment of mice with AP (500 mg/kg/BW) and arabinogalactan (125 mg/kg/BW) reduced toxicity in comparison to mice treated with ethanol, according to numerous enzymatic assays carried out in liver and kidney tissues. The combined effects of both medications may be what prevents animals from developing ethanol-induced poisoning [24]. Multiple biological functions are carried out by the pentacyclic lupane-type triterpene betulinic acid (BA). BA protects mice's livers from alcohol-induced damage. BA may protect the liver by improving the tissue redox system, keeping the antioxidant system in good shape, and lowering the amount of lipid peroxidation in the liver [25]. Mercury is well-known to be a particularly harmful environmental toxin that can harm a wide range of bodily functions, including the liver, through oxidative stress. In adult albino male rats, BA and rotundic acid both provide superior protection against the hepatotoxicity brought on by Mercuric chloride. In toxicated rats, BA and rotundic acid treatments greatly improved the defence mechanism by raising SOD, CAT, and GPx enzymes, raising GSH levels, and lowering increased LPO levels. Rotundic acid and BA counteract hepatotoxicity caused by $HgCl_2$ by reversing oxidative stress and liver damage [26]. The compounds BA and ricinine are isolated from the seeds of *Tetracarpidium conophorum*. BA and ricinine displayed binding energies of -11.2 kcal/mol and -5.4 kcal/mol, respectively, in molecular docking tests, indicating robust interactions with Hepatitis B virus DNA polymerase. Both compounds exhibited hepatoprotective activity against liver damage induced by CCl_4 [27]. BA's poor bioavailability and limited solubility are two of its main drawbacks. Nanoemulsions containing BA are able to overcome this problem by improving solubility, increasing bioavailability, and promoting hepatoprotective effects [28]. From *Kleinhovia hospita*, a brand-new class of cycloartane triterpenoids has been discovered. Cycloartan-1,24-diene-3,23-dione is one of these substances, and it shown positive hepatoprotective properties against nitrofurantoin-induced cytotoxicity in human liver-derived Hep G2 cells (EC_{50} = 66.4±7.1 µM) [29]. Paeoniflorin (PF), a water-soluble monoterpene glycoside isolated from *Paeonia suffruticosa* Andr., *Paeonia lactiflora* Pall., or *Paeonia veitchii* Lynch, has a number of medicinal benefits [30]. A build-up of bile acids in the liver results in cholestasis, which in turn causes fibrosis and liver failure. Alpha-naphthylisothiocyanate (ANIT), which is used to cause hepatotoxicity in animal models, is a substance that imitates the drug-induced cholestatic liver damage that occurs in people. ANIT-induced cholestasis can be prevented in rats by PF, which stimulates Nrf2 through the PI3K/Akt pathway [31]. During the course of a number of investigations, PF was isolated from the roots of *Paeonia lactiflora*. LPS treatment increases serum biomarkers and decreases antioxidant levels. PF enhances antioxidant levels in addition to lowering the high levels of glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, lactate dehydrogenase, and malondialdehyde. PF can counteract oxidative damage brought on by lipopolysaccharide [32]. Pentanorcucurbitacin B and 25,26,27-trinorcucurbit-5-ene-3,7,23-trione, two norcucurbitane-type triterpenoids, were discovered in methyl alcohol extract of *Momordica charantia* stems. With a cell survival rate of 55.2%, pentanorcucurbitacin B (5mM) displayed cytoprotective effects against t-BHP-induced toxicity in $HepG_2$ cells. The positive control silybin has a similar effect [33]. In male BALB/c mice, both oleanolic and ursolic acids (UA) exhibit hepatoprotective effects against the effects of antitubercular drug therapy [34]. Chemically induced liver injury in mice can be reduced more effectively by UA than by OA [35]. UA was administered to the rats in three different doses (10, 20 and 40 mg/kg body weight). The 20 mg/kg dose had the most significant liver-protecting effects, which were similar to those of silymarin, a well-known liver-protector [36]. UA consumption reduced the long-term liver damage caused by alcohol. ALD may be caused through CYP450- and glutathione-dependent antioxidation, lipid transport enhancement, and ethanol metabolism restoration [37].



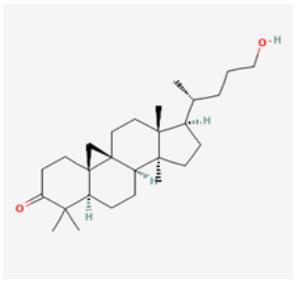
6. Alpha-hederin



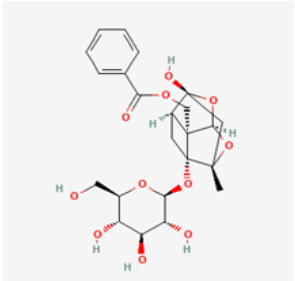
7. Andrographolide



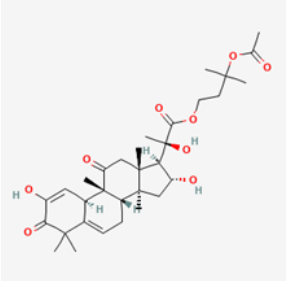
8. Betulinic acid



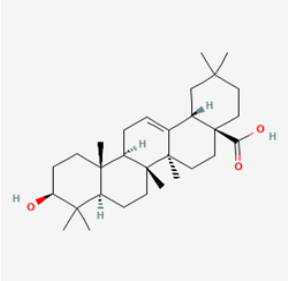
9. Cycloartan-1,24-diene-3,23-dione



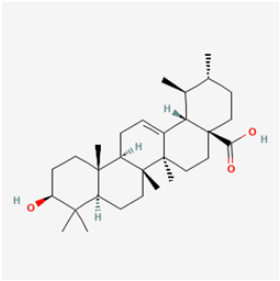
10. Paeoniflorin



11. Pentanorcucurbitacin B



12. Olenolic acid



13. Ursolic acid

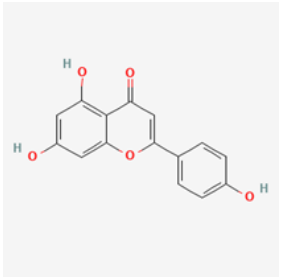
Flavonoids and Phenolic Compounds

Scientists are increasingly aware of flavonoids and polyphenolic compounds, a type of secondary metabolite in plants [38]. These metabolites have been shown to have antioxidant, hepatoprotective, and other biological properties. Many phytoconstituents like phenols, and flavonoids present in therapeutic plants provide better hepatoprotection against hepatotoxic substances. Flavonoids are natural products; they are most usually found in medicinal plants, green leaves, and fruits. Flavonoids belong mostly to the secondary metabolites that plants create through a phenolic molecule. Phytochemicals, also known as flavonoids, are responsible for a vast variety of products that are beneficial to one's health and serve as a multifaceted ingredient in a wide variety of nutraceuticals, medicines, therapeutic effects, and cosmetic applications [39]. Their ability to scavenge free radicals, fight microbes, prevent cancer, and reduce inflammation, as well as their anticarcinogenic properties, can modify primary enzyme functioning within the cells. Flavonoid chemicals are also responsible for blocking a large number of biological enzymes, including phosphoinositide 3-kinase, xanthine oxidase, cyclooxygenase, and lipoxygenase. Flavonoid phytoconstituents are naturally occurring phenolic compounds with a low molecular weight that can be found in a variety of plants used for therapeutic purposes. Over 9,000 different compounds are included in the category of flavonoids, which is one of the most influential categories of natural products. The name "flavonoid" is applied to compounds that are structurally propylbenzene derivatives and have a C15, C16 skeleton. Apigenin, wogonin, luteolin, diosmin, and baicalein are all components of this subgroup. Isoflavones can be found in very high quantities in legumes and in goods made from soy. They are molecules that act in a manner similar to that of biological estrogens, which implies that they are substance regulate estrogens. Researchers believe that managing the faults of hormonal malignancies such as prostate, breast, and endometrial could be advantageous, despite the fact that the study findings are currently mixed. Examples of these cancers are breast cancer, prostate cancer, and endometrial cancer. Isoflavones have good activity for scavenging free radicals, but it is unknown what effect they have on cancerous growths. Isoflavones were also investigated as a potential method to alleviate the symptoms of menopause. The flavonoid apigenin, present in a various medicinal plants like grapefruit, blueberries, and blackcurrants, has a variety of pharmacological characteristics. Apigenin has hepatoprotective properties against N-nitrosodiethylamine-induced hepatotoxicity. The treatment with apigenin considerably decreased blood and liver enzyme levels, suggesting that it may possess liver-protective properties. Rats given N-nitrosodiethylamine and apigenin had significantly decrease the protein carbonyl and lipid peroxidation. A comet assay in rat hepatocytes provided evidence in favor of these findings [40]. Apigenin (APG), a potent antioxidant, may reduce liver damage by reducing inflammation by inhibiting the noncanonical NF-B pathway [41]. APG, isolated from *Ixeris chinesis* (Thunb.) Ankai, protects the liver from CCl_4 toxicity. Studies on apigenin *in vivo* and *in vitro* studies indicate that it has liver-protective abilities. It might have a protective effect because of its strong antioxidant properties, which help get rid of reactive oxygen species [42]. Together, apigenin and paracetamol reduced ALT and ALP activity as well as other hepatotoxic markers. Significant histopathological changes that weren't present in the group receiving paracetamol alone were seen in the group receiving paracetamol with APG. MDA level rises brought on by paracetamol were reversed by APG. In rats challenged to paracetamol-induced hepatotoxicity, APG dramatically inhibited lipid peroxidation [43]. *Curcuma longa's* primary chemical constituent is the polyphenol curcumin (CUR) (Turmeric rhizome). Because it is an antioxidant, decreases inflammation, and has antimicrobial properties, turmeric used Asian nations. One of the negative consequences of cisplatin is hepatotoxicity. Cisplatin caused an increase in MDA while a decrease in SOD and catalase. Hepatic enzyme concentrations like ALT and AST rose as a result. The NADPH oxidase gene's expression was also increased by cisplatin. Hepatic enzymes, lipid peroxidation biomarkers, liver histology, and NADPH oxidase gene expression were all enhanced by CUR at a dose of 200 mg/kg [44]. Scavenging ROS, raising GSH levels, and other antioxidant enzyme-related

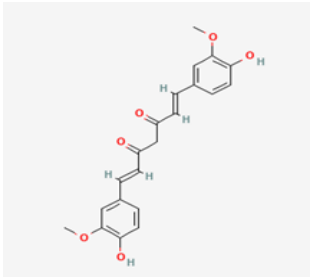
mechanisms significantly reduced cadmium-induced hepatotoxicity in conjunction with CUR and vitamin C [45]. Mycotoxin The fungus *Aspergillus flavus* and *Aspergillus parasiticus* produce aflotoxin B1 and It causes hepatocellular carcinoma in both humans and animals and is mutagenic, genotoxic, immunosuppressive, and linked with the disease. Reactive oxygen species are created when cytochrome P450 bioactivates AFB1 and produces AFB1-exo-8, 9-epoxide. In a another experiment, administration of CUR-12 mol/kg/b.w/i.p. rats decreased the toxicity brought on by a first dose of mercuric chloride [46]. The CUR treatment protects the liver, kidney, and brain from various metallic oxidative stress enzymes. The antioxidant properties of CUR guard against oxidative damage brought on by mercury [47]. Humans and animals can acquire arsenic through the environment or through drugs. Because of arsenic's toxicity, people can develop liver conditions such cirrhosis, hepatoportal sclerosis, ascites, and hepatomegaly. By lowering lipid peroxidation, raising GSH levels, elevating the antioxidant enzymes like GST, SOD, and CAT, and lowering thiol depletion, arsenic-induced liver damage was lessened. CUR can eliminate free radicals and bind to arsenical chemicals, protecting the liver from arsenic damage [48]. In rats, the combination of CUR and potassium dichromate decreased the toxicity of chromium. CUR's protective impact is mostly attributable to its capacity to enhance antioxidant enzymes, including SOD, CAT, GPx, GR, and GST. Further proof of its protective properties was provided by histopathological examination, which showed a reduction in hepatocyte damage. Chromium toxicity is a common problem that can lead to hepatotoxicity. In rats, the combination and potassium dichromate decreased the toxicity of chromium. Examination of cellular observation demonstrated a decrease in hepatocyte injury, providing further evidence of its protective effects [49]. Daidzein (DAI, 7,4′ -dihydroxy isoflavone) is an isoflavone phytoestrogen found mostly in leguminous plants [50]. Multiple oxidate stress reduced enzymes were downregulated in mice treated with DMBA. DAI's antioxidant activity protects the livers of mice from 7,12-dimethylbenz [a] anthracene-induced oxidative damage [51]. DAI, the principal isoflavone isolated from *Puerariae Radix*. The DAI administration reduces apoptosis, enhances antioxidant enzyme activity in the liver, and decreases caspase-3 expression [52]. The ethanol extract from the roots of *Maackia amurensis* Ruper et Maxim, which can restore the liver damage produced on by CCl_4, contains a combination of isoflavonoids, including DAI. Treatment with root extract enhances erythrocyte tolerance to hemolytic agents, lowers glutathione levels, normalizes the pattern of phospholipids in the liver, and promotes antioxidant protection enzyme activity [53]. The herb *Emblica officinalis* Gaertn or *Phyllanthus emblica* Linn is one of the most widely used medicinal and food herbs on the Indian subcontinent. In traditional and folk medical systems, the fruits are used both as food and for therapeutic purposes. The fruits contain polyphenolic compounds such as emblicanin A and B [54]. There is a strong correlation between the antioxidant properties of the fruit and the presence of tannoid compounds known as emblicanin A and B. In rats, administration of both emblicanin A (37%) and B (33%) enriched fractions of fruit juice of *Emblica officinalis* Gaertn increases the hepatoprotective efficacy against iron-induced hepatotoxicity. After a pretreatment period of ten days, the levels of serum biomarkers reverted to normal, and the levels of lipid peroxidation were significantly decreased. The results were detected in a comparable manner in the group that had been treated with silymarin. Emblicanin A and B make important contributions to the function of protection as a result of the potent antioxidant characteristics they possess [55]. The polyphenolic compound honokiol (HK), obtained from the *Magnolia* genus, exerts hepatoprotective properties through a variety of mechanisms. HK and magnolol protect rat hepatocytes from tBH- and D-GalN-caused damage. In rat primary hepatocytes, HK and magnolol protected against tBH-induced cellular leakage of LDH and AST, cell death, LPO, ROS formation, and intracellular glutathione depletion. As a result of their strong antioxidant properties, they provide protection. Additionally, D-GaIN-induced hepatotoxicity, a second model of oxidative stress, was prevented. As an antioxidant, they prevented glutathione depletion within cells [56]. Rats given HK in a related experiment demonstrated hepatoprotective qualities against CCl_4-induced liver injury. When rats exposed to CCl_4 received HK at a dose of 0.1 mg/kg, this lessened morphological damage and impaired billirubin levels while also reducing some of the loss of sinusoidal area [57]. HK demonstrates liver protective properties in male Balb/c mice against acetaminophen-induced liver injury. The ability of HK to lessen the development of APAP-protein adducts, which may be mediated by reducing the activity of CYP2E1 and CYP2A1, as well as to increase the production of GSH via the route of NRF2, may be responsible for its effects on acetaminophen-induced liver injury [58]. The C-glycosyl flavone isoorientin (ISO), which is made up of 3′, 4′, 5,7-tetrahydroxy-6-C-glucopyranosyl flavones. The medicinal plant species *Phyllostachys pubescens*, *Patrinia* spp., buckwheat, and corn silks all contain ISO. ISO is extracted from the *Gentiana olivieri* Griseb ethyl acetate fraction. It has hepatoprotective properties against the toxicity mediated by CCl_4 in rats. Five days of treatment with ISO (15 mg/kg/b.w) [44]. The hepatoprotective properties of ISO were examined in C57BL/6J mice and HepG2 cells. ISO (50 mg) significantly reduced acetaminophen-induced hepatotoxicity. In addition, levels of myeloperoxidase (MPO), glutathione (GSH), and superoxide dismutase (SOD), as well as the production of malondialdehyde (MDA), were all reduced [59]. From unripe soybean leaves, kaempferol galactopyronoside was extracted (*Glycine max. L.* Merr.). A pretreatment with isolated compound showed a normalization of liver enzyme levels in mice that were challenged with CCl_4 [60]. In the leaves of a plant native to Vietnam named Phyllanthus acidus (L.) Skeels, a novel derivative of kaempferol glycoside known as kaempferol-3-O-(2—L-rhamnopyranosyl)—D-glucuronopyranosyl methyl ester was identified. This compound is a kaempferol works through the STAT3 signalling pathway, the methyl ester of kaempferol-3-O-(2-L-rhamnopyranosyl)-D-glucuronopyranosyl suppresses TNF-alpha while simultaneously activating IL-10. It also controls the production of IL-6 cytokines at different times. The liver-protective activity of *Phyllanthus acidus* may be due to kaempferol glycosides [45]. Kaempferol has hepatoprotective benefits against drug-induced liver injury. Regarding kaempferol's impact on alcoholic liver disease, there is no information available. By lowering the activity and expression of CYP2E1 and boosting the antioxidative defence system, kaempferol guards against alcohol-induced liver damage [46]. In a similar fashion, it has been proved that kaempferol can

raise levels of HO-1 and NQO1 protein expression while simultaneously lowering levels of CYP2E1 expression. This, in turn, can restore antioxidant indices and alleviate the pathological damage associated with acetaminophen-induced liver damage [47]. In Huh-7 and SK-Hep-1 human hepatocellular carcinoma cell lines, kaempferol caused Matrix Metalloproteinase-9 and Akt signaling pathways to slow down. This made the cells less likely to spread and invade [61]. In rats with acute alcoholic liver injury, kaempferol administration decreased plasma ALT and AST levels and suppressed ethanol-induced pathomorphological abnormalities in the liver and intestine. In addition, expression of the tight junction protein was restored in the ileum mucosa and the proximal colon [62]. *Cedrela odorata* L. leaf kaempferol glycosides reduce paracetamol toxicity. The glycosides of kaempferol control paracetamol-induced oxidative stress by raising GSH levels, decreasing MDA levels, and decreasing nitrotyrosine levels. In comparison to the normal hepatoprotective agent silymarin, the effects of kaempferol glycosides on nitrotyrosine, Raf-1 kinase, c-JNK, and GSH were significantly stronger [63]. In another study, kaempferol 3-O-rutinoside and kaempferol 3-O-glucoside were isolated from *Carthamus tinctorius* L flowers. Treatment with kaempferol glycosides improved total protein and diminished AST, ALP, and MDA in CCl_4-treated mice. Compared to toxin-treated animals, Kaempferol glycosides effectively restored GSH levels and CAT and SOD activity [64]. Naringenin (NAR) is a natural flavonoid aglycone that is derived from naringin. Its chemical structure is that of a 4', 5,7-trihydroxyflavanone. Because of its powerful antioxidant capabilities, it is utilized in the treatment of a wide variety of diseases. Because NAR has a lot of hydroxyl substitutions, it can donate hydrogen to reactive oxygen species. This makes its structure stable and allows it to get rid of free radicals [65]. A disadvantage of NAR is its limited bioavailability. In mice, nanoparticles loaded with naringenin (NARN) are better able to protect the liver against the toxic effects of CCl_4. *In vivo*, NARN increased NAR's bioavailability and was followed by better hepatoprotective effects. In comparison with NAR, NARN is more soluble and releases more quickly. As compared to NAR, NARN demonstrated greater liver protective effects. In addition to reducing liver function index and lipid peroxidation, NARN also increased levels of antioxidant enzymes. NARN blocks caspase-3, -8, and -9 signaling, although NAR just blocks caspase-3 and -9 [66]. In male Swiss mice, NAR protects the kidney from CCl_4-induced renal toxicity. The hepatoprotective effect of NAR is attributed to its ability to neutralize ROS by enhancing the expression and activation of antioxidant enzymes [67]. In a similar fashion, Naringenin and Naringenin /b-cyclodextrin complexes reduced CCl_4-induced damage. As a result of the pretreatment phase, naringenin and Naringenin and Naringenin /b-cyclodextrin complexes reduced levels of AST and ALT while increasing antioxidant parameters such as GPx, SOD, CAT, and GSH [68]. Likewise, NAR protects rats from arsenic toxicity. NAR dose-dependently restored blood biomarkers and antioxidant enzymes in tissues. Histopathological investigations demonstrate NAR co-treatment reduces arsenic-caused liver and kidney alterations [69]. Four flavonoids and two phenolic compounds were found in methanol extracts of *Equisetum arvense* L. aerial parts. In human liver-derived HepG2 cells, the phenolic compound ornitin and the flavonoid luteolin had hepatoprotective effects against tacrine-induced cytotoxicity, demonstrating EC_{50} values of 85.8±9.3 µM and 20.2±1.4 µM, respectively. The EC_{50} value was 69.0±3.3 µM in the presence of silybin, which served as a positive control. Additionally, it was discovered that both compounds had stronger scavenging abilities against superoxide radicals and DPPH free radicals (IC_{50} values of 35.8±0.4 µM and 22.7±2.8 µM, respectively) [57]. Quercetin (QUE) (5,7,3',4',5'-Penta hydroxy flavanone) is a flavonoid that is found in fruits and vegetables and has a number of pharmacological properties. Among its many pharmacological benefits, QUE is an antioxidant that helps protect the body from free radical damage. CCl_4 is a hepatotoxin that induces liver damage in experimental animals. In mice, QUE therapy restored CCl_4-induced liver dysfunction and histological alterations. QUE prevents oxidative stress and inflammation in CCl_4-treated mice. QUE diminished TLR2/4 expression levels in the liver of mice treated with CCl_4 and prevented both MAPK and NF-kB activation [58]. In rats, CCl_4 causes fibrosis. A 16-week administration of CCl_4 (150 µmol/kg body weight/day) caused cell necrosis, fibrosis, and inflammatory infiltration. Through treatment with QUE for three weeks, liver damage is prevented, and excessive nitric oxide synthase (iNOS), which is induced by a variety of inflammatory stimuli, is suppressed [70]. Isolated QUE fractions from the ethanolic extract of leaves of *Psidium guajava* exhibit cytoprotective effects *in vitro* against CCl_4 toxicity in HepG2 cells [59]. Recent research has showed that quercetin has a greater impact on hepatic fibrosis than other antioxidants. QUE diminished bile duct ligation and CCl_4-induced liver fibrosis. This hepatoprotective effect is attributable to QUE's ability to suppress HSC activation and diminish autophagy through modulating cross-talk between the TGF-β1/Smad and PI3K/Akt pathways [60]. Cadmium chloride is one of the most prevalent environmentally hazardous heavy metals, causing oxidative stress and histological abnormalities in the liver and kidneys. By increasing metallothionein concentrations, quercetin protects the liver and kidneys from the toxicity caused by Cadmium. As an antioxidant and heavy metal scavenger, metalothionein (MT) is an effective scavenger of hydroxyl radicals and can serve as a substitute for SOD in instances of oxidative stress. The combination of cadmium and QUE greatly decreased oxidative stress and enhanced MT and endothelial nitric oxide synthase expression (eNOS) [71]. The fruits of methanolic extracts of *Physalis peruviana* L. have been shown to protect against hepatorenal toxicity caused by $CdCl_2$. QUE is abundant in methanolic extracts of *Physalis peruviana* fruits (93.7 mg of quercetin equivalent per gram extract). The methanolic extract of *Physalis peruviana* fruits protects against cadmium-induced testicular oxidative stress and apoptosis and appears to mitigate cadmium-induced rat liver toxicity [72]. Rutin and QUE reduce ethanol-induced hepatotoxicity in HepG2 cells by lowering hepatic aminotransferase activity and inflammatory responses through the Nrf2/ARE antioxidant pathway [73]. Moreover, it has been revealed that QUE inhibits ethanol-induced cell death in HepG2 cells through activating the Nrf2/ARE antioxidant pathway [74]. Treatment with thioacetamide (TAA, 350 mg/kg with an interval of 8 hours) induced hepatic necrosis, substantial increases in serum transaminase activity, and significant increases in hepatic lipoperoxidation in rats. Following the injection of thioacetamide, the flavonoid QUE (50 mg/kg/i.p.) was

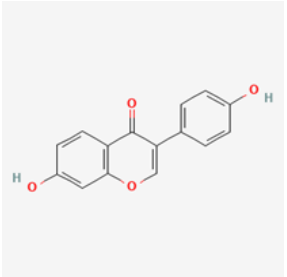
administered for four consecutive days. QUE treatment improves serum biomarkers, hepatic architecture, lipid peroxide levels, and the antioxidant enzymes SOD, CAT, and GPx. Under oxidative stress, QUE lowers the pro-apoptotic Bax gene and raises the anti-apoptotic Bcl-2 gene in normal cells [75]. Furthermore, QUE and ellagic acid have been shown to reduce hepatotoxicity caused by thioacetamide in mature male rats by acting as antioxidants, metal chelators, and anti-inflammatory agents [76]. The leaves of *Premna intergrifolia* L. ethanol extract have been shown to exhibit protective effects against aflatoxin B1-induced toxicity in mice by inhibiting apoptosis and oxidative stress. Flavonoids, including QUE, may contribute to the protective properties of extracts [77]. Another study indicated that the presence of QUE nanoparticles led to a reduction in the amount of ROS that was produced. This assisted in reversing the effects that AFB1 had on the viability of hepatocytes, as well as lipid peroxidation and functioning of the mitochondria [78]. Resveratrol (RES), is a polyphenolic chemical that can be found throughout nature, although grapes contain an especially high concentration of it. RES has been linked to a variety of different biological processes, some of which include the treatment of cancer, oxidative stress, and the slowing of the ageing process. RES is an antioxidant that has been proven to be useful in treating a range of liver disorders, including as fatty hepatitis, liver steatosis, liver cancer, and liver fibrosis. This is due to the fact that resveratrol prevents the formation of free radicals in the liver. This is due to the fact that resveratrol prevents the formation of free radicals in the liver. Poor dissolution and adsorption are among the main disadvantages of RES in clinical use. When compared to free RES, novel resveratrol nanoparticle exhibits superior therapeutic efficacy against CCl_4-induced toxicity in rats. Compared to free RES, resveratrol nanoparticle exhibits twice the anti-inflammatory activity, reduces oxidative stress, and inhibits the production of inflammatory cytokines [79]. The effects of RES on liver cells have been demonstrated in several *in vitro* and animal studies. In order to achieve these effects, SIRT1 and AMPK signaling pathways seem to be activated, and the NF-kB pathway appears to be inhibited [80]. RES regulate the inflammatory mediated pathways and also control liver fibrosis [81]. A number of scientific studies have demonstrated that polyphenols are powerful antioxidants. Taurisolo® is a novel nutraceutical formulation containing grape pomace and enriched with RES and polyphenols. It has been demonstrated that Taurisolo® has beneficial benefits both *in vitro*, using HuH-7 cells at 400 and 800 mg/L, and *in vivo*, using wild-type male and female C57BL/6 mice given an HFD at 123 mg/kg/diet. Both of these studies were conducted on mice. In both non-alcoholic fatty liver disease and cardiovascular disease, the polyphenolic SIRT1 activator resveratrol improves mitochondrial dysfunction and antioxidant capability [82]. RES offered hepatoprotection against ethanol-induced oxidative stress in HepG2 cells and C57BL/6J mice by reducing ROS generation and enhancing the expression and activity of SOD1 [83]. Rosmarinic acid (RA) is a polyphenolic phytoconstituents observed various medicinal herbs that has health-promoting benefits. RA is a polyphenolic compound that has been identified in diverse medicinal plants to have health-promoting benefits. RA has been shown to have antiviral, anticancer, antibacterial, antimutagenic, and antioxidant properties. RA isolated from *Perilla frutescens* protects D-GalN-sensitized mice from LPS-induced liver damage. Superoxide or peroxynitrite scavenging may be responsible for the liver's protective effect of RA rather than the suppression of TNF-α production [84]. RA protects adult male albino rats from CCl_4-induced liver damage (3ml/kg twice weekly for 4 weeks i.p.). The four-week treatment with toxin and RA (50 mg/kg/day/p.o.) decreased blood inflammatory enzyme levels and increased MDA levels and proapoptotic protein expression. CCl_4-induced histological and ultrastructural alterations are improved [85]. In another study, mice intoxicated with CCl_4 developed hepatic necrosis and had an increase in serum marker enzyme levels. In addition to improving histological and serum markers of liver damage, the expression of TGF-β1 and CTGF was inhibited. As a result of treatment with RA (50 mg/kg), oxidative/nitrosative stress and inflammation were reduced and expressions of Nrf2 and heme oxygenase-1 were increased [86]. A flavone glycoside, scutellarin (SCU) exhibits many pharmacological properties, including anticancer properties [87]. SCU is abundant in *Erigeron breviscapus* (Vant.) Hand. -Mazz. and has a protective effect against CCl_4 induced liver damage. In mice treated with CCl_4, SCU showed potent hepatoprotective effects by improving CYP2E1 and IκBα/NF-κB signaling pathways [87]. In China, *Dioscorea bulbifera* is used in the treatment of thyroid conditions and cancer. The active component of this plant is Diosbulbin B, a diterpene lactone. Diosbulbin B causes severe liver damage, as shown by both animal experiments and clinical practise. SCU protects male ICR mice from diosbulbin B-induced liver damage by blocking NF-kB-mediated hepatic inflammation and reducing liver oxidative stress [88]. Baicalein, Baicalin, and Wogonin have been isolated from the entire plant of *Scutellaria rivularis* Benth. Rats were treated with the hepatotoxin CCl_4 and D-GalN, with Wogonin (5 mg/kg i.p.) demonstrating the most promising protective effect. Baicalein and Baicalin provide the significant effect at 20 mg/kg i.p. in rats treated with D-GalN and APAP; at 10 mg/kg i.p. in rats injected with CCl_4. An investigation of SGOT, SGPT, and histopathology also revealed protective effects [89].



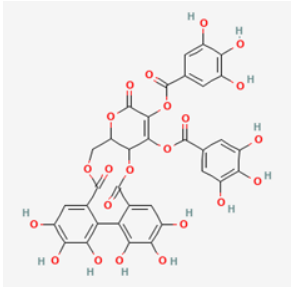
14. Apigenin



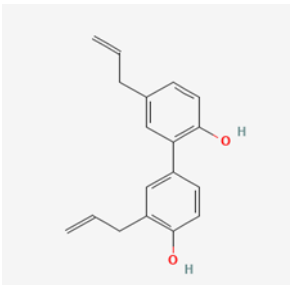
15. Curcumin



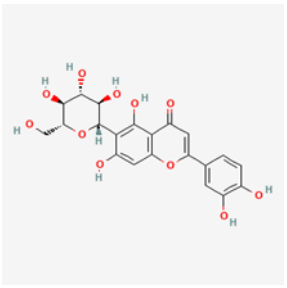
16. Daidzein



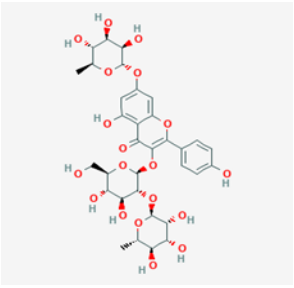
17. Emblicanin A



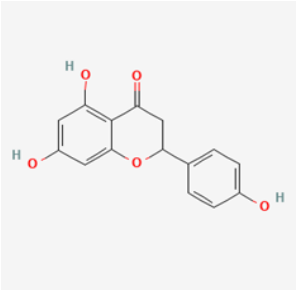
18. Honokiol



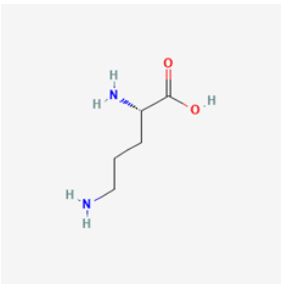
19. Isoorientin



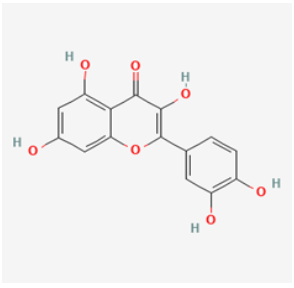
20. Kaempferol 3-O-β-D- (2,6-di-O-α-L rhamnopyranosyl) galactopyronoside



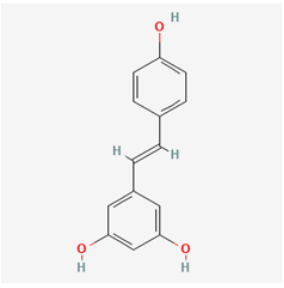
21. Naringenin



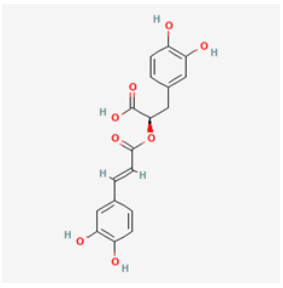
22. Ornitin



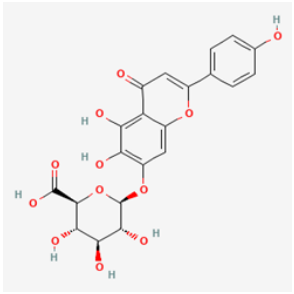
23. Quercetin



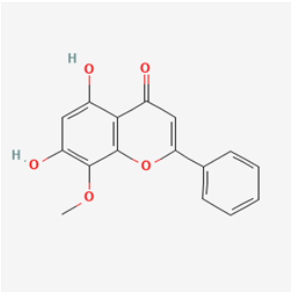
24. Resveratrol



25. Rosmarinic acid



26. Scutellarin

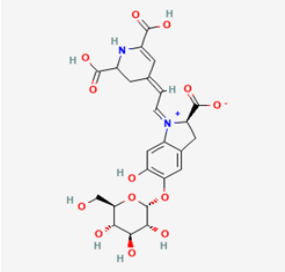


27. Wogonin

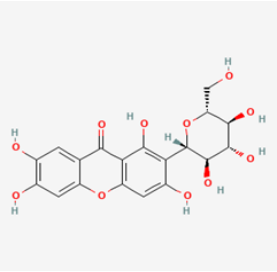
Miscellaneous

Plants include the water-soluble plant pigments known as betalains. It has been isolated from various sources, including red beetroot, which is a rich source of betalains. There are a number of health benefits associated with betalain, which is a promising nutraceutical. The antioxidant, anti-inflammatory, diabetic, anti-lipidemic, antibacterial, and hepatoprotective properties of betalains have been described. It was demonstrated that giving red beetroot methanolic extract to rats prevented the hepatotoxicity brought on by CCl_4 and returned the liver's enzyme activities of ALT and AST, as well as bilirubin, WBC, RBC, polycythemia vera (PCV), and hepatic lobule architecture, to levels that were close to normal [90]. In rats, beetroot juice prevents liver damage and inflammation markers initiated by the hepatotoxin N-nitrosodiethylamine. A variety of inflammatory indicators (LDH, AST, GGT, and ALT) caused by N-nitrosodiethylamine treatment were significantly reduced by beetroot juice [91]. Mangiferin (MG), a C-glucosyl xanthone that is existing in most parts of mango (*Mangifera indica*). It has been extensively studied, including its antibacterial, antioxidant, antiviral, and hepatoprotective effects *in vivo* and *in vitro* [92]. MG (400 mg/kg/b.w) exhibits hepatoprotective properties against Galactosamine-induced toxicity. The potential of MG to promote antioxidant defence by blocking the Nrf2 pathway and to reduce inflammation by inhibiting NF-kB has been assigned as the mechanism of its hepatoprotective benefits [93]. MG 50 mg/kg used to prevent liver damage induced by alcohol. MG having the limited solubility and poor intestinal absorption are the major drawbacks. Herbosome formulation of MG meaningfully reduced hepatic damage markers and enhanced liver antioxidant defences. MG herbosomes were found to have a hepatoprotective effect comparable to silymarin [94]. Similarly, MG prevents liver damage caused by acetaminophen.

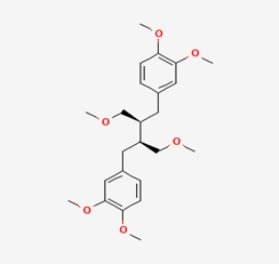
MG 25 mg/kg reduced the formation of acetaminophen-cysteine adducts, enhanced the levels of GSH and SOD. Moreover, MG inhibited JNK pathway, reducing acetaminophen-induced inflammation [95]. A hepatoprotective lignin produced from the plant *Phyllanthus amarus* Schum. et Thonn is called phyllanthin (PLN). Mixed micellar lipid formulations comprising PLN and piperine provide improved protection against CCl_4 induced liver injury in rats. A formulation of complex phosphatidylcholine with PLN and piperine (30 mg/kg/p.o.) significantly decreased blood biomarker enzymes and enhanced antioxidant activity. A micellar lipid formulation containing PLN and piperine increased PLN levels in serum for a longer period of time. PLN- and piperine-containing micellar lipid formulations have increased bioavailability and hepatoprotective effects [78]. Rat liver cells are protected from ethanol-induced damage by PLN, a major component of *Phyllanthus amarus*. Primary cultures of rat hepatocytes (24 hours culturing) were pre-treated with PLN (1, 2, 3, and 4 µg/mL) for 24 h. After the primary treatment, the cells were subjected to a treatment with ethanol at a concentration of 80 µL/mL for a period of two hours. Ethanol lowered MTT and elevated ALT, AST, and intracellular reactive oxygen species production. It has been proven that PLN contributes to protection by counteracting the effects of ethanol. PLN also restored antioxidant capacity in rat hepatocytes, including glutathione levels and activities of super oxide dismutase and glutathione reductase, which had been reduced by ethanol [96]. A stilbenoid glucoside, polydatin (POD) is a major resveratrol derivative found in grape juices. It is well known that POD possesses a wide range of medical benefits. The administration of streptozotocin to mice on a high-energy diet for four weeks results in the induction of a diabetic state as well as hepatopathy in the mice. Compared to mice that had not been treated with POD, mice that were supplemented with POD (50 or 100 mg/kg/day, for example) for an additional four weeks showed reduced signs of liver damage. In diabetic mice, POD may reduce hepatic injury by promoting the activation of the peroxisome proliferator-activated receptor alpha/beta signalling pathway [97]. POD or POD-loaded chitosan nanoparticles have been shown to prevent diabetes-related liver damage caused by nicotinamide and streptozotocin. Diabetes-related liver damage can be alleviated by POD or POD-loaded chitosan nanoparticles by modulating glucose transporter 2 expression, altering carbohydrate metabolism enzyme activity, and suppressing oxidative stress and inflammation. The higher bioavailability and prolonged release of POD-loaded chitosan nanoparticles make them more effective than POD, most likely due to their higher bioavailability [98]. In another study, POD was isolated from roots and rhizomes of *Polygonum cuspidatum* and exhibit its ability to protect ICR mice against CCl_4 (50 µl/kg)/i.p.) -induced toxicity. Treatment with the toxin results in an increase in the levels of AST, ALT and hepatic MDA, as well as a significant increase in the levels of hepatic TNF-α, IL-1β, COX-2, iNOS and NF-κB. The POD pre-treatment (5 days) reverses all of these levels to their normal levels. In addition, POD pre-treatment increases levels of GSH, GST, SOD, CAT, and GPx. POD pre-treatment also alters the mRNA and protein expression levels of hepatic transforming growth factor-β1[98]. POD has demonstrated hepatoprotective properties against acute alcohol-related liver damage in C57BL/6 mice. In mice, liver damage was caused by five doses of 50% ethyl alcohol (10 ml/kg body weight). By reducing ALT and AST levels in the serum, POD pre-treatment (50 or 100 mg/kg, orally, for 8 days) significantly alleviated alcohol-induced liver injury, attenuated oxidative stress and restored antioxidant balance in hepatic tissues. As well as preventing alcohol-induced mitochondrial damage, POD pre-treatment also restored the levels of matrix metalloproteinases within hepatocytes [99].



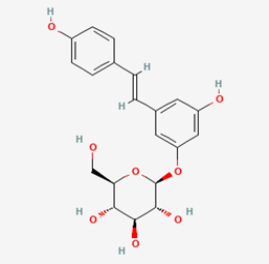
28. Betalains



29. Mangiferin



30. Phyllanthin



31. Polydatin

Conclusion

In the past few decades, extensive research has explored the use of phytochemicals produced from medicinal plants as hepatoprotective agents against a range of hepatotoxin. In accordance with the evidence, the liver is protected by

phytochemicals against poisons, like alcohol, carbon tetrachloride, and polycyclic aromatic hydrocarbons. Several medicinal plants and their phytochemicals have shown efficacy in the treatment of chronic liver illness by scavenging free radicals, acting as anti-oxidants and anti-inflammatory agents, reducing fibrogenesis, eradicating viral infections, and preventing or inhibiting tumors development. The utilization of phytochemicals produced from medicinal plants, which are easily available, inexpensive, and safe to consume, is one of the key benefits of this approach. This review will provide us with a unique outlook from which to explore the therapeutic potential of bioactive compounds as hepatoprotective agents. According to our literature review, Berberine, Betalain, Curcumin, Honokiol, Kaempferol, Mangiferin, Naringenin, Paeoniflorin, Phyllanthin, Polydatin, Quercetin, and Scutellarin have strong hepatoprotective properties with different mechanisms against diverse hepatotoxins. In order to prove its efficacy in treating chronic liver disease, A randomized, placebo-controlled clinical trial must be conducted to evaluate phytochemical treatment. Phytochemicals and medicinal plants need safety studies just as much as efficacy studies. It is necessary to investigate the potential toxicity and adverse effects of medicinal plants and their phytochemicals in future research. In the future, more safe and effective therapeutic medicinal plants and phytochemicals will be identified for chronic liver disease.

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