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Current Prospects of Medicinal Plants and Their Constituents for Treatment of Liver Diseases

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Abstract: Nature has always been a remarkable source of therapeutic substances, offering a wide range of therapeutic plants that produce advantageous phytochemicals. Liver illness is a severe condition, and the situation is made worse by the absence of specific treatment plans. The treatments for liver diseases that are now available are inappropriate, and systemic toxicity prevents their long-term usage. Since medicinal herbs seem to have a reduced toxicity level, they have been utilized historically for ages to treat liver problems. Numerous therapeutic plants and their phytoconstituents have been shown to have strong hepatoprotective properties with no systemic side effects, which may restrict their long-term application. Since medicinal herbs seem to have a reduced toxicity level, they have been utilized historically for ages to treat liver problems. Numerous therapeutic plants and their phytoconstituents have been shown to have strong hepatoprotective properties with no systemic side effects, which may restrict their long-term application. Research has shown that the primary mechanism by which phytoconstituents reduce various disease pathways is through their antioxidant qualities, which include boosting the cells' antioxidant defense system, scavenging free radicals, lowering lipid peroxidation, enhancing their anti-inflammatory potential, and further preventing hepatic cell damage. In conclusion, this study highlights the significance of additional research to examine the effectiveness and safety of these natural medicines for a variety of liver illnesses by compiling the knowledge on medicinal plants and their possibly hepatoprotective bioactive phytoconstituents.

Keywords: Hepatoprotective Activity, Medicinal Plant**,** Phytoconstituents, Traditional Medicine.

1. Introduction

A fully developed adult's liver weighs over 1.5 kg, making it the biggest organ in the human body and accounting for 2% of total body weight [1]. Since the liver is where drugs are metabolized and biotransformed, it serves as the body's defense against harmful foreign chemicals. Additionally, the liver plays a role in the metabolism of glucose, fatty acids, and amino acids—byproducts of the breakdown of proteins, carbs, and lipids [2]. A variety of essential substances, including iron, minerals, vitamins, hormones, glycogen, and more, are stored in the liver [3]. The GI tract also sends toxins and other foreign substances to the liver,

where they are detoxified and eliminated through urine and bile [4]. Apart from this, the liver is the primary organ responsible for the metabolism of medications. Enzymes comprising cytochrome P-450 help transform them there into either active or inactive metabolites. It serves as the primary physiological location for nearly all of the body's metabolic processes, such as the distribution and storage of energy and nutrients, the production and control of hormones and enzymes, the breakdown of xenobiotics, and the neutralization of infections and toxins. Additionally, the liver plays a crucial role in the digestive system by supplying the bile juice in the duodenum and other digestive enzymes at certain locations, which facilitate the digestion of proteins and fats [5]. To aid in the digestion of fats, the liver produces bile, which is temporarily held in the gall bladder before being released into the duodenum. The bulk of the biliary content is composed of bile salts, which function as a detergent and help the extremely hydrophilic and acidified digestive content dissolve highly hydrophobic substances including oils, fats, long-chain fatty compounds, and fat-soluble vitamins. Bile salts also facilitate the removal of cholesterol and other fat-soluble hazardous compounds, including xenobiotics, medicines, carcinogens, and toxic metabolites, by a similar mechanism [6]. Additionally, most prodrugs that are administered in their inactive forms to reduce toxicity or increase bioavailability need to be activated by hepatic enzymes in order to have their respective therapeutic effects [7]. Because of this, a functioning liver is essential to preserving equilibrium and good health. Worldwide, liver disorders claim the lives of millions of individuals every year. Each year, more than 20 lakh people die from liver disorders (10 lacs from liver cirrhosis, 10 lacs from viral hepatitis, and 10 lacs from liver cancer) [8]. Despite tremendous progress in contemporary medicine, no safe drugs now exist that may boost liver function, offer total liver protection, or multiply liver cells [9]. Although there are vaccines and some drugs, including steroids and antivirals, to prevent and treat liver diseases, they are not only costly but also have unfavorable side effects [10–11]. Data clearly indicate that medicinal plants and their phytoconstituents can be used to cure and manage liver diseases [12–13]. The identification of medicinal plants that can both prevent and treat liver problems has therefore been the subject of much research.

In addition to acute or chronic inflammation of the liver, liver disorders encompass a range of pathological abnormalities such as hepatosis, hepatic adenoma, or liver cancer [14]. Allopathic drugs such oral contraceptives, ciprofloxacin, paracetamol, diclofenac, fluconazole, amoxicillin, and chlorpromazine can induce liver damage. These drugs may result in intense inflammation of the liver, hepatic vein obstruction, liver cell death, and innocuous neoplasms. Among the dangerous chemicals that can also injure the liver are carbon tetrachloride, alcohol, and aflatoxin [15]. Nearly 20 million individuals die each year from hepatic cirrhosis, hepatocellular cancer, and viral hepatitis. Liver cancer is the sixteenth most prevalent cause of tumor-related deaths worldwide [5, 16, 17]. It has been demonstrated that medications, obesity, viral infections, and excessive alcohol use can all cause liver disease to worsen and change over time. Approximately 75 million of the 2 billion alcohol users worldwide are known to suffer from alcohol-related issues, such as alcoholism-associated hepatic impairment [16]. An increased risk of hepatic damage, such as hepatocellular carcinoma and nonalcoholic fatty liver disease, is associated with obesity and diabetes, which afflict about 2 million and 400 million people globally, respectively [17]. Further increasing the risk of liver illnesses include acute hepatitis and other hepatitis B and C virus infections [18-20]. These compounds, together with hepatotoxic chemicals that generate reactive oxygen species (ROS), cause oxidative stress. By increasing lipid peroxidation and oxidative damage to liver cells, an excess of ROS can cause cirrhosis, chronic hepatitis, hepatic steatosis, and hepatocellular carcinoma. These lead to the liver

being subjected to various amounts of medications, chemicals, and other xenobiotics, which ultimately causes liver damage. The causes of hepatic disorders are many and number in the hundreds. At the moment, a number of illnesses are being treated with phytochemicals derived from natural resources. Despite significant progress in contemporary medicine, there is still a persistent problem with a lack of suitable and effective hepatoprotective drugs [21]. Due to reports of drug-induced liver damage (DILI), some drugs have been taken off the market. Severe liver dysfunction might result in death or necessitate liver transplantation [22]. Plant-based medicines are the main treatment for liver ailments, and modern medications don't do much to alleviate them. But there aren't many medications on the market right now to treat liver diseases 23]. Nearly 2 million individuals worldwide are dying each year from hepatic complications, of which 1 million are cirrhosis-related complications and the remaining half are related to liver cancer and viral hepatitis [24, 25]. Currently, liver cancer ranks 16 (788,000 deaths) and cirrhosis ranks 11 (1.16 million deaths) among the leading causes of mortality, together accounting for 3.5% of all human fatalities globally [26, 27]. In a worldwide setting, the primary cause of liver disease is excessive use of alcoholic beverages [28]. According to a World Health Organization report, somewhat less than half, or 75 million, of the world's estimated 2 billion alcohol users have been diagnosed with conditions linked to alcohol use, particularly various alcohol-associated liver diseases [29, 30]. The number of fatalities from viral hepatitis-related illness in 2015 was 1.34 million, which was comparable to the amount from TB (1.37 million) and greater than the deaths from HIV (1.06 million) and malaria (0.44 million) combined [31]. The cirrhosis complication and the proliferation of liver cancer are the primary causes of the hepatitis B virus (66%) and hepatitis C virus (30%), which together account for 96% of the morbidity caused by viral hepatitis [32]. One of the main issues in treating a number of acute and chronic medical diseases is drug-induced liver damage (DILI). Studies have shown that histamine antagonists (cimetidine), penicillin antibiotics (amoxicillin), antitubercular medicines (isoniazid), antipsychotics (chlorpromazine), analgesics and antipyretics (acetaminophen), and HMG-CoA reductase inhibitors (statins) are the main medications that cause DILI [33]. While combination antitubercular drug-induced liver injury is more severe in the east [34], amoxicillin/clavulanic acid-induced liver injury affects 1 in 2350 people in the west [35]. India and Nigeria have the greatest rates of DILI among them, followed by China and South Korea, where liver damage from herbal and alternative medicines is the most common cause [36], according to the WHO. Around the world, antimicrobial drugs are thought to be the primary cause of idiosyncratic DILI [37-39]. According to the most recent statistics above, the prevalence of liver illness has grown over time, having a significant impact on public life globally. Traditional medicine is widely used worldwide and is particularly beneficial for individuals in underdeveloped nations in terms of both prevention and treatment [40]. The World Health Organization defines "traditional medicine as diverse health practices, approaches, expertise, and customs incorporating plant, animal, and/or mineral based medicine, spiritual therapies, manual techniques, and exercises applied singly or in conjunction to sustain good health, in addition to for the purpose of treating, diagnosing, or avoiding illness" [41].

Natural products made from plants have been widely employed for their therapeutic qualities since ancient times. They are also often used as components in food and as dietary supplements. Plant materials have made substantial contributions to the food, pharmaceutical, and nutraceutical sectors because of their wide range of nutritional benefits, which include vitamins, minerals, phenolics, antioxidants, and enzymes. The treatment of hepatic disorders is significantly impacted by traditional medicine derived from natural sources. While several

natural phytoconstituents are said to have hepatoprotective and hepatocurative activities, many others have been shown to be effective hepatoprotective agents. Although phytoconstituents derived from natural products are thought to be the best and most proven source for creating new therapeutic agents, their widespread use for therapeutic purposes is still limited by their poor absorption, distribution, metabolism, and elimination as well as their limited toxicological characteristics. Researchers and scientists have been more motivated in recent decades to identify more viable hepatoprotective compounds derived from plants in order to create innovative, contemporary medications for various liver diseases [42, 43].

Phytoconstituents with Hepatoprotective Potentials

Compounds extracted from distinct plant species that differ in structure but have the same therapeutic effect serve as active ingredients in the treatment of a wide range of illnesses. There have been reports of several phytomolecules derived from different plant sources, such as flavonoids, alkaloids, glycosides, and saponins, being strong hepatoprotective agents [44]. Numerous substances with antioxidant properties may be found in plant tissues. Carotenoids, lignans, terpenes, nitrogen compounds (alkaloids, chlorophyll derivatives, amino acids, and amines), and phenolic compounds (flavonoids and phenolic acids) have all been shown to have antioxidative properties that inhibit the start or spread of chain reactions [45].

Biologically Active Phytoconstituents

Due primarily to their anti-inflammatory and antioxidant qualities, natural product small molecules (NPSMs) or active fractions containing these molecules have recently attracted more attention as a means of treating liver illnesses [46]. Since they contain a variety of phytoconstituents, including phenolics, flavonoids, coumarins, alkaloids, essential oils, glycosides, xanthenes, carotenoids, organic acids, lignins, and monoterpenes, it has been investigated if a variety of plants and fruits can preserve liver function [47]. From plants, a large number of hepatoprotective phytoconstituents from various chemical classes have been identified and extracted (Figure 1).

Flavonoids

The following flavonoids have hepatoprotective properties: procyanidin B2, orientin, isoorientin, luteolin, rutin, baicalein, baicalin, wogonin, silymarin, epicatechin, and anastatin A and B. Certain fruits and leaves of Anacardium occidentale and Annona crassiflora contain catechin. Through two different mechanisms, silymarin (Silybum marianum) has hepatoprotective and regenerative qualities. It functions by reducing the production of free radicals (FR), which are produced by toxins that harm cell membranes, particularly lipid peroxidation (LPO) [15, 48-51].

Phenolics Compound

Phenolics are a prominent component of hepatoprotective plants, and several studies have demonstrated that these plants' hepatoprotective effect is caused by their active phenolics, which include caffeic acid, gallic acid, phyllanthin, hypophyllanthin, and chlorogenic acid. Liver fibrosis can be fought using phyllanthin, a protective substance that comes from the plants Phyllanthus amarus, Phyllanthus emblica, Phyllanthus niruri, and Phyllanthus polyphyllus. It was shown that via blocking ALK5 and Smad2 and 3, phyllanthin inhibits the TGF signaling pathway [15, 52].

Terpenoids

α, β, and δ-amyrins, ursolic acid, andrographolide, hautriwaic acid, onitin, glycyrrhizin, and asiatic acid are examples of terpenoids. Andrographolide, which is found in Andrographis paniculata [15, 53), works in a variety of ways. Its immunomodulatory, anti-inflammatory, and antioxidant qualities have been demonstrated to support its hepatoprotective action. A variety of plants including the Malvaceae family member Adansonia digitata, contain ursolic acid. Its advantageous qualities, including as anti-inflammatory, anti-oxidant, anti-apoptotic, and anticarcinogenic qualities, make it useful [15, 54].

Glycosides

Plants frequently contain them, and they may have therapeutic benefits. The nature of their active glycosides, several plants, including amburoside A, caffeoyl-glucoside, kinsenoside, saikosaponins, kaempferol-3-O-rutinoside, ononitol monohydrate, picroside, kutkoside, and brasoside, have hepatoprotective properties. Picrorhiza kurroa (Scrophulariaceae) contains a compound called picroside II, which may prevent cholestasis by activating the FXR, which regulates the pathways and enzymes necessary to keep a proper equilibrium of bile acids [15, 55].

Alkaloids

Because of their active alkaloids, certain plants have hepatoprotective properties, including lycorine, sarmentosin, and protopine [15].

Sulfur-Containing Compounds

Allicin, S-allyl-cysteine (SAC), and S-allylmercaptocysteine are active chemicals found in plants that have hepatoprotective properties. Because allicin (Allium sativum) significantly inhibited NLRP3 inflammasome activation, caspase-1 and IL-1 levels were lowered. The hepatoprotective effects of allicin against APAP-induced liver damage are accomplished via lowering oxidative stress, blocking the inflammasome pathway, and promoting apoptosis [15, 56, 57].

Others

Furan (5-hydroxymethylfurfural), p-Benzoquinone (thymoquinone), anthraquinone (rubiadin), coumestans (wedelolactone and demethylwedelolactone), steroid (β-sitosterol), and carbohydrates (fucoidan) [15].

Andrographolide

India and Sri Lanka are the natural habitats of the herbaceous plant Andrographis paniculata Nees. (Acanthaceae). Because of its very bitter flavor, Andrographis is known as the "king of bitters." The majority of uses for the roots and leaves are medicinal. The main ingredients include panicoline, paniculide-A, paniculide-B, and paniculide-C, as well as 14-deoxy-11-dehydroandrographolide, 14-deoxy-11-oxoandrographolide, andrographolide, andrographine, neoandrographolide, andrographolide, andrograph. The primary component isolated from the plant's leaves, andrographolide, is a bitter lactone that dissolves in water and gives A. paniculata its hepatoprotective properties [1, 15, 58-61]. Through antioxidant and anti-inflammatory pathways, andrographolide prevents inflammation, angiogenesis, and fibrosis in an animal model of chemically induced liver damage [60, 61]. Andrographolide demonstrated a strong dose-dependent protective effect on isolated rat hepatocytes against acetaminophen-induced damage. It was examined if the diterpenes andrographolide, andrographiside, and neoandrographolide might prevent the hepatotoxicity that

tertbutylhydroperoxide (tBHP) poisoning caused in mice. In rats, andrographolide also serves to decrease liver hypoxia and attenuate hepatic apoptosis and fibrosis by downregulating hypoxia-inducible genes such vascular endothelial growth factor (VEGF), reducing TNF-α, and decreasing the production of cycloxygenase-2 (COX-2) [62, 63-65]. The substance lowers hepatic expression of TGF-β, cannabinoid receptor type 1 (CBR1), and Bax as well as blood levels of TNF-α and interleukin-1 beta (IL-1β).

Acteoside

Syringa vulgaris L. (Oleaceae) and Cistanche tubulosa (Schrenk) Wight (Orobanchaceae) are the sources of acteoside, a phenylethanoid glycoside. Acteoside's preventive benefits against CCl_4-induced hepatotoxicity were examined in one research, along with potential mechanisms of action. The protective effects of acteoside against CCl_4-induced hepatotoxicity and the potential mechanisms behind these benefits were examined in one research. The main isozyme implicated in CCl_4 bioactivation, cytochrome P450 2E1, was also examined in relation to acteoside. Aniline hydroxylation and P450 2E1-dependent p-nitrophenol were significantly reduced in mice treated with acteoside in a dose-dependent manner. The amount of CYP2El protein was decreased. Acteoside showed antioxidant effects on superoxide radical scavenging activity and FeCl2-ascorbate-induced LPO in a mouse liver homogenate. These findings imply that acteoside may have protective effects against CCl4-induced hepatotoxicity through processes including its capacity to inhibit P450-mediated CCl4 bioactivation and its capacity to scavenge free radicals [15, 47, 66].

Asiatic Acid

Among the triterpenoid components of Terminalia catappa L. (Combretaceae) is Asiatic acid (AA), which possesses hepatoprotective, anti-inflammatory, and antioxidant properties. To ascertain the mechanism behind Terminalia's influence on hepatotoxicity, the effects of AA on mitochondria and free radicals were studied. Pretreatment with 50 and 100 mg/kg extract of T. catappa prevented the hepatotoxicity caused by CCl_4 [47, 67]. The pretreatment with 0.05, 0.1, and 0.5 g/l T. catappa extract prevented the elevated ALT and AST levels in the medium of primary cultured hepatocytes caused by d-GalN. Moreover, AA prevented the enlargement of the mitochondria caused by Ca2+. AA demonstrated dose-dependent superoxide anion and hydroxyl radical scavenging activities at doses between 50 and 500 Mm [68].

Curcumin

The main curcuminoid found in turmeric, a popular spice in India and a member of the ginger family (Curcuma longa L.; Zingiberaceae), is curcumin. Beyond its culinary applications, turmeric has been used in traditional medicine to treat a variety of skin conditions, parasite infections, ulcers, joint inflammation, jaundice, and other liver ailments. The rhizomes of turmeric contain a combination of numerous structurally similar phenolic chemicals called curcuminoids. Curcumin accounts for 60–80% of curcuminoids, followed by demethoxycurcumin (10–20%) and bisdemethoxycurcumin (5–10%). In terms of chemistry, curcumin is a diferuloylmethane containing a part of diferulic acid fused with either a methylene or another carbon atom. Its methylene-1, 3-diketo group exhibits keto-enol tautomerism as a result of hydrogen bonding stabilization. Instead of being in a diketo form, curcumin is mostly found in keto-enol form. Curcumin's antioxidant activity and activation of phase 2 detoxifying/antioxidant enzymes, including HO-1 and NADPH quinone oxidoreductase-1 (NQO1) and Nrf2/Keap1/antioxidant-responsive element (ARE) pathway, may be the cause of its hepatoprotective mechanism [1, 47, 69-72]. Furthermore, dietary

treatment of this substance lowers oxidative stress, decreases the expression of Cytochrome P450 2E1 (CYP2E1) and paired-related homeobox 1 (Prx1), and increases the expression of paired-related homeobox 6 (Prx6) [73]. Hepatotoxin-induced oxidative stress is intimately linked to the activation of many inflammatory mediators, including MAPKs, NF-κB, and signal transducer and activator of transcription-3 (STAT3), through several pathways [74].

Berberine

An alkaloid known as berberine is extracted from Berberis aristata L. (Berberidaceae). South Asian traditional medicine uses this plant, which is edible, and its fruits are utilized as a tonic for the heart and liver. Berberis aristata has several active chemical compounds, including aromoline, karachine, oxycanthine, berberamine, oxyberberine, and berberine. Hepatoprotective phytoconstituents berberine, karachine, and oxycanthine have been demonstrated in experiments [1, 47, 75, 76]. The main active ingredient is berberine, an isoquinoline alkaloid. Hepatoprotective effects of berberine have been demonstrated in experiments [77]. Acetaminophen-induced increases in blood levels of ALP, AST, and ALT were inhibited in mice pretreated with berberine (4 mg/kg; taken orally twice daily for two days), suggesting hepatoprotection. Animals receiving a single oral dosage of berberine (4 mg/kg) as a pretreatment caused the pentobarbital (60 mg/kg, i.p.) to be prolonged increased strychnine (0.3 mg/kg; i.p.) and induced sleep time.-induced toxicity, indicating a potential inhibitory impact on cytochrome P450s (CYPs), which are microsomal drug metabolizing enzymes. Berberine's effects on isolated rat hepatocytes' ion channels have been investigated. In a concentration-dependent manner, berberine 1–300 μmol/l decreased both Ca++ release-activated Ca++ currents and delayed outward potassium currents. Therefore, it was determined that berberine inhibits calcium and potassium currents in rat hepatocytes that have been isolated, perhaps contributing to hepatoprotection [78].

By increasing the ratio of Bcl-2/Bax in ischemia/reperfusion-injured rat livers and preventing caspase-3 cleavage in the liver, berberine exhibits antioxidant activity that may reduce oxidative stress and attenuate apoptosis [79]. It works by inhibiting the expression of mTOR and upregulating Akt [80]. Additionally, berberine had a hepatoprotective effect in hepatic ischemia by restoring hepatocyte nuclear factor-4 alpha and PPARα/peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α). Berberine shields the liver against ethanol-induced oxidative stress, according to an experiment conducted on mice with ethanol-induced steatosis [81]. In a mouse model of LPS-induced hepatotoxicity, berberine inhibits the expression of hepatic proprotein convertase subtilisin/kexin type 9 (PCSK9), a regulator of cholesterol homeostasis, and lowers levels of IFN-γ, TNF-α, IL-1α, and 8-isoprostane [82].

Embelin

The big scandent shrub Embelia ribes Burm.f. (Myrsinaceae) has elliptic-lanceolate, gland-dotted leaves and slender stems. The plant includes quercitol, christembine, embelin, and resins. Due to its anthelmintic, analgesic, antifertility, hepatoprotective, and antitumor qualities, this plant is frequently utilized. The primary active ingredient that gives it its hepatoprotective and antioxidant properties is embelin [1, 15, 47, 82, 83]. Chemically, 2,5-dihydroxy-3-undecyl-1,4-benzoquinone is embelin. Embelin's hepatoprotective effects are mostly attributed to its lipid peroxidation route and ability to scavenge free radicals. In rats given carbon tetrachloride, embelin can regulate the levels of bilirubin γ-glutamyl transpeptidase, AST, ALT, ALP, LDH, and total protein [1, 84]. An investigation in the rat

liver's mitochondria revealed that embelin may prevent lipid peroxidation and that administering embelin restored the lowered level of superoxide dismutase.

Glycyrrhizin

The triterpenoid glycoside glycyrrhizin (family: Leguminacae), which was extracted from the root of Glycyrrhiza glabra L., sometimes referred to as liquorice root, has been used to cure jaundice in traditional medical systems in China, India, Nepal, and other nations [80, 81]. Glycyrrhizinic acid is a potassium and calcium salt, and it contains flavonoids, β-sitosterol, hydroxycoumarins, and glycyrrhetinic acid as well as other phytoconstituents [1, 15, 85]. Glycyrrhizin has a hepatoprotective effect by inducing an increase in antioxidant defense in hepatic cells and by functioning as an anti-inflammatory agent [86, 87]. In order for glycyrrhizin to exhibit an anti-inflammatory action, high-mobility group protein box (HMGB1) is either reduced or prevented from binding to the glutathione S-transferase omega-1 (GSTO1) promoter region [88, 89]. In liver fibrosis brought on by CCl4, the expression of the collagen αI(I) gene was suppressed not only by glycyrrhizin, its metabolite, and glycyrrhetinic acid [88]. By binding to the epithelial growth factor receptor (EGFR) and promoting DNA synthesis in liver cells via the extracellular signal-regulated kinases (ERK2)-mediated pathway, glycyrrhetinic acid also aids in liver cell proliferation and aids in liver regeneration [89, 90]. When interferon alpha (IFN-α)-based therapy failed, intravenous glycyrrhizin significantly reduced serum alanine transaminase levels after 12 weeks of treatment and improved inflammatory liver fibrosis and necrosis in hepatic disease patients after 52 weeks of treatment [1, 15, 47, 82, 91].

Picroside I And Kutkoside

A popular plant in Ayurvedic medicine, Picrorhiza kurroa Royle Benth. (Scrophulariaceae) has long been used to cure upper respiratory tract and liver diseases, lower fevers, and treat chronic diarrhea, dyspepsia, and scorpion stings. The Himalayan area is home to this little perennial plant, which belongs to the Scrophulariaceae family. Often referred to as "Kutki" or "Kutaki," Picrorhiza kurroa Royle's roots and rhizomes contain the active chemical components picroside and kutkoside [1, 47, 82, 92]. In rats, kutkoside and picroside-I exhibit hepatoprotective effects through membrane stabilization, hypolipidemic and antioxidant qualities, and ultimately a liver regeneration impact through the promotion of protein and nucleic acid production [93]. Inhibiting lipid peroxidation in liver tissue, picroside-I and kutkoside are free radical scavengers (superoxide anion O2•) [94, 95]. Additionally, by shielding injured hepatocytes, it demonstrated a hepatoprotective impact by restoring bilirubin and the activity of blood liver indicators AST, ALT, ALP, and LDH against an animal model of acetaminophen-induced liver damage [96]. Additionally, by extending the lifespan of tumor-bearing animals, picroside lowers lipid peroxidation, restores glutathione metabolism, and prevents hepatocarcinogenesis brought on by N-nitrosodiethylamine in rats [97]. It counteracts paracetamol's decreased expression of the LDL receptor on the cell surface, increases conjugated dienes in liver cells, and preserves the oxidation-reduction balance necessary for a healthy liver [98, 99].

Phyllanthin

A strong hepatoprotective lignan, phyllanthin is derived from Phyllanthus niruri L. (Euphorbiaceae). This popular Ayurvedic plant, sometimes referred to as "gale of the wind," has long been used as a natural treatment for jaundice and other liver conditions. Phyllanthusiin D gallocatechins, geraniin, hypophylanthis, lignans, nirutin, phyllanthin, phyllanthenol, astragalin, brevifolin, ellagitannins, amariin, repandusinic acid, and alkaloids

are the primary active chemical components. Phyllanthin and hypophyllanthin are lignans that were chemically separated from the hexane extract and have been shown to have hepatoprotective properties (Figure 1). Fresh leaves, fruits, and the entire plant are used to cure a variety of illnesses, including hepatitis. This plant has demonstrated strong hepatoprotective and antioxidant properties. Infectious hepatitis and other liver diseases can be effectively treated with Phyllanthus niruri [1, 15, 47, 82, 100]. This plant's ethanolic extract exhibits strong hepatoprotective properties in both in vitro and in vivo settings. Because of its liver-protective and detoxifying properties, it was used to cure childhood jaundice in India [101, 102]. Phyllanthus extract may be useful in treating children's acute and chronic hepatitis, according to a UK research [103,104]. Rat liver can be shielded by both phytollanthin and hypophyllanthin against galactosamine-induced cytotoxicity and carbon tetrachloride-induced toxicity [105]. In addition to normalizing a "fatty liver" state, these lignans guard against alcohol-induced liver damage. Lipid peroxidation, superoxide, and hydroxyl radicals are inhibited by phyllanthus lignin to provide its hepatoprotective properties [106-108].

Resveratrol

Resveratrol is a polyphenol that occurs naturally and has a variety of positive health benefits, such as anti-aging, anti-inflammatory, antioxidant, cardioprotective, and neuroprotective properties. When bacteria or fungus attack plants, a phytoalexin called resveratrol is created. Red grapes, eucalyptus, spruce, blueberries, mulberries, peanuts, and giant knotweed are just a few of the foods and plants that contain resveratrol (Figure 1). It is also plentiful in red wine. Resveratrol, also known as "trans-3,5,4-trihydroxystilbene," is a naturally occurring polyphenol compound with strong antioxidant qualities that is found in Vitis labrusca, also known as "grapes," Vaccinium myrtillus L., also known as "blueberries," and Rubus idaeus L., also known as "raspberries." Through altering the expression of nuclear transcription factors Nrf2 and NF-κB and down regulating the expression of HO-1 and iONS genes, resveratrol protects the liver by reducing oxidative stress during hepatocyte damage [1, 15, 47, 82, 109]. Both phase 2 enzymes and free radical scavenging capabilities are improved by this [107]. In addition, it even suppresses proinflammatory cytokines including TNF-α, IL-2, and IL-6 in autoimmune hepatitis caused by concanavalin A [110]. The protective effect of resveratrol in liver damage caused by elevated cholesterol is mediated by the upregulation of proapoptotic proteins including Bax and caspase-3 and caspase-8 and the activation of autophagy [111]. Next, resveratrol reduces hepatotoxicity from isoniazid and rifampicin by modifying the expression of SIRT1 mRNA in mouse liver cells. This, in turn, reduces hepatic oxidative stress in the liver, cytokine production, and the expression of the PPARγ gene [112-113]. Additionally, resveratrol inhibits hepatotoxicity brought on by increased acetaminophen consumption by increasing SIRT1 expression, decreasing p53 signaling, boosting cell nuclear antigen expression, encouraging hepatic cell proliferation, improving liver regeneration, and raising cyclin D1 and Cdk4 levels [114].

Silymarin

One of the oldest and most extensively studied herbs for the treatment of liver disorders is silymarin, which is extracted from Silybum marianum (L.) Gaertn. (Asteraceae/Compositae), the plant usually referred to as "milk thistle." Active phytoconstituents, which include the four flavonolignan isomers silybin, isosilybin, silydianin, and silychristin, are mostly found in dried seeds. The complex combination of these four isomers of flavonolignans is called silymarin [115, 116]. It has been frequently utilized as a comparison benchmark for test

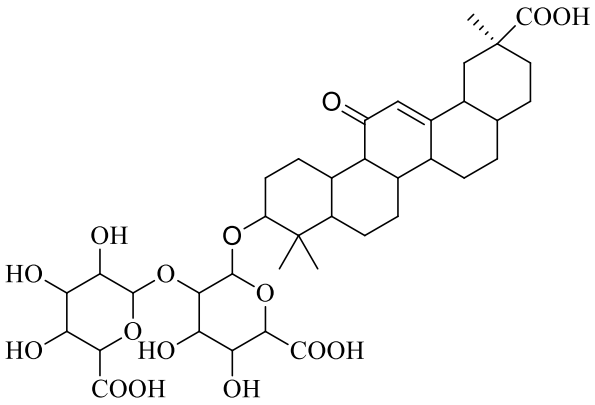
medications in preclinical investigations and is considered the gold standard of hepatoprotective agents. It is a polyphenolic flavonoid with cytoprotective, anti-inflammatory, and anti-carcinogenic properties (Figure 1). Silymarin's pharmacological profile is well established, and both in vitro and in vivo studies have examined its hepatoprotective qualities. Antioxidant and free radical scavenging qualities have been shown in experimental investigations. Silymarin exhibits strong antifibrotic properties as well. The plant's active ingredients, which include four flavonolignans together referred to as silymarin, are extracted from the dried seeds, where they are found in greater amounts. With the empirical formula $C_{25}H_{22}O_{10}$, silymarin is a complex combination of four flavonolignan isomers: silybin, isosilybin, silydianin, and silychristin. It is thought that silymarin's facilitation of protein synthesis is due to its structural resemblance to steroid hormones [117]. Silybin, which makes up around 60–70% of the isomers, is the main and most active component. It is followed by silychristin (20%), silydianin (10%), and isosilybin (5%). Most of its hepatoprotective properties are attributed to silybin [1, 15, 47, 82, 118-122].

Sauchinone

In Chinese traditional medicine, Saururus chinensis (Lour.) Bail. (Saururaceae) has been used to cure a number of illnesses, including gonorrhea, edema, jaundice, and painkillers. Cytoprotective and antioxidant properties are exhibited by the diastereomeric lignan sauchinone, the active ingredient in Saururus chinensis (Figure 1). It extract's hepatoprotective and antifibrotic properties have been assessed in rats with CCl4-induced liver fibrosis [123]. The effectiveness of sauchinone as a hepatic HO-1 inducer and its protective benefits in HepG2 cells were examined in one research. Sauchinone treatment of the cells resulted in concentration- and time-dependent increases in HO activity and HO-1 expression. Cytoprotection against oxidative damage brought on by tBHP was provided by this expression. Sauchinone-induced HO-1 expression also inhibited the production of ROS in HepG2 cells caused by tBHP. Furthermore, sauchine-induced HO-1 production and its protective effects were decreased when cells were treated with a p38 MAPK inhibitor (SB203580) [47, 124].

Solanine and Solasodine

Many people have used Solanum nigrum L. (Solanaceae) as an anti-inflammatory and hepatoprotective medication. Solanine, solasodine, solamargine-A, and solamargine-B are the main ingredients (Figure 1). Its antioxidant and hepatoprotective properties have been demonstrated experimentally in rats with chronic CCl4-induced hepatotoxicity [125, 126]. Oral administration of S. nigrum extract alleviated the hepatotoxicity produced by CCl4. Given that Solanum extract restored the decreased liver concentration and activity of GSH, SOD, and GST, this hepatoprotective effect may be attributed to its antioxidant properties. Solanum extract's effects on mice's liver fibrosis caused by TAA (0.2 g/kg, i.p., three times per week for 12 weeks) have been studied. Solanum extract treatment decreased TAA-induced TGF-β1 mRNA levels in the liver and the hepatic hydroxyproline levels of TAA-treated animals [127]. Significant increases in AOE activities were achieved by a single 150 kDa glycoprotein that was isolated from S. nigrum. Following treatment with the glycoprotein, there was an increase in the activity of SOD, catalase, and GPx. Lin et al. (2007) showed in one investigation that extracts from Solanum had a cytotoxic impact on HepG2 cells [127].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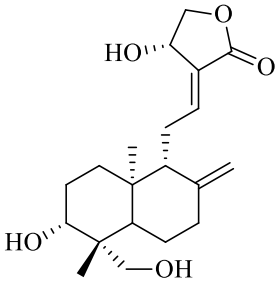
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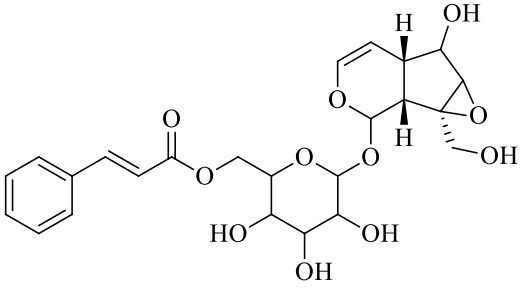
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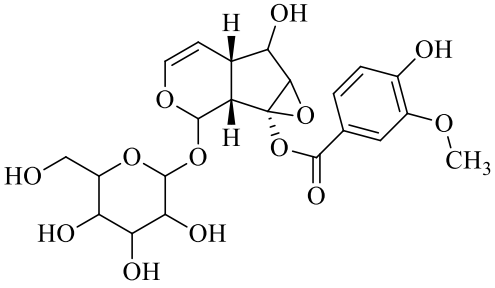
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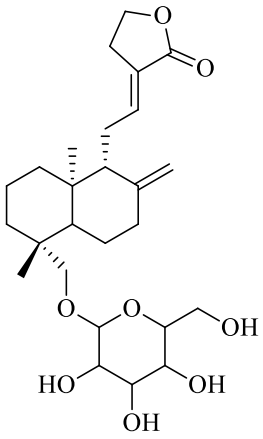
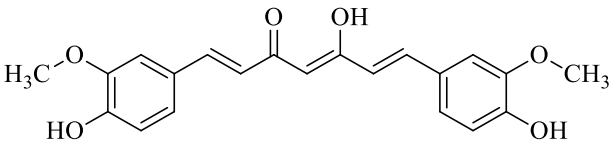

Neoandrographolide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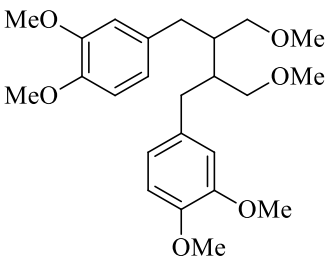
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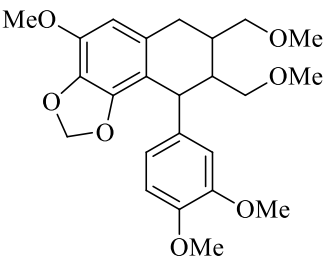
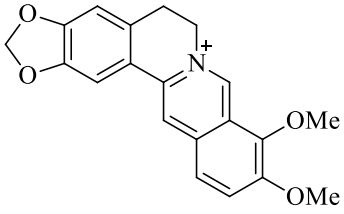

Hypophyllanthin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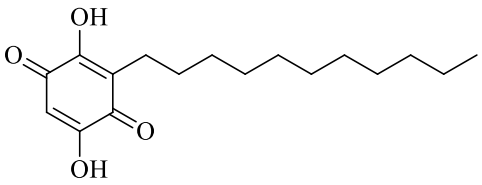
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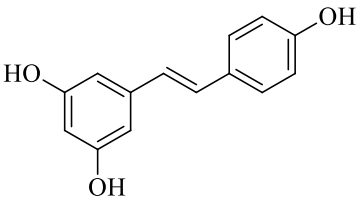
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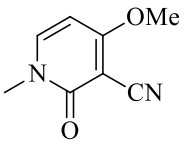
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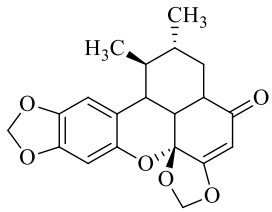
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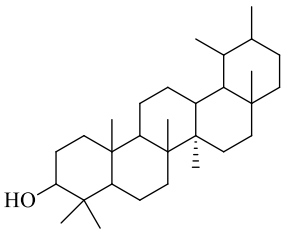
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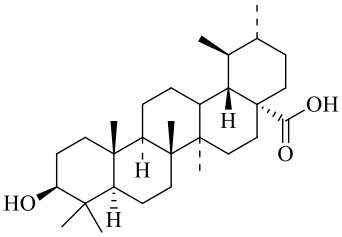
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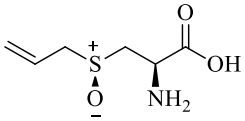
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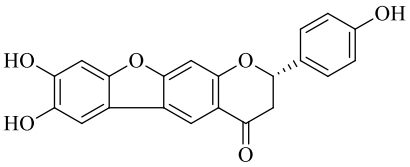
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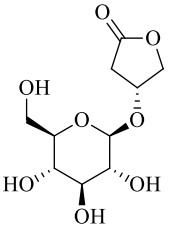
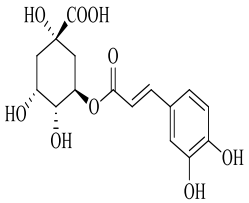
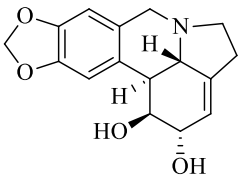

Kinsenoside


Chlorogenic acid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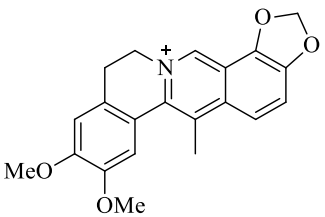
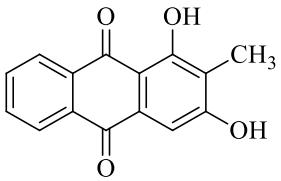

Dehydrocavadine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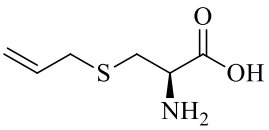
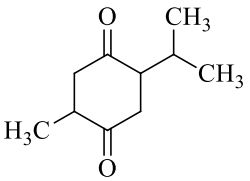
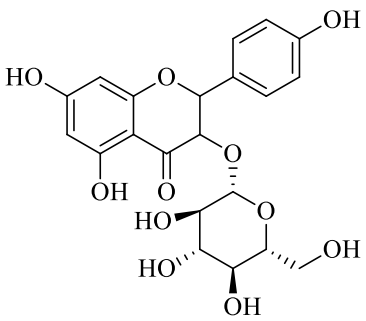
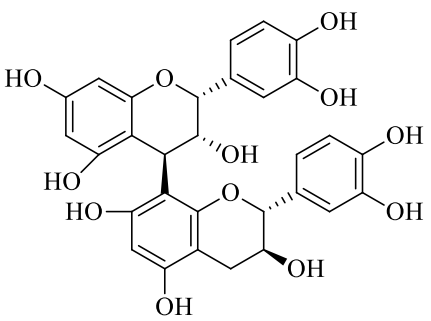
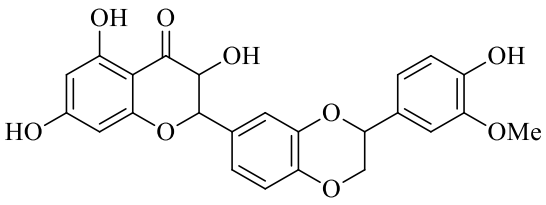

S-allyl Cysteine


Thymoquinone

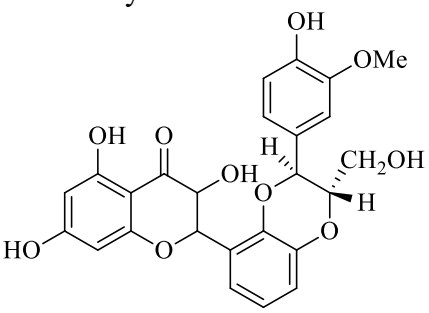




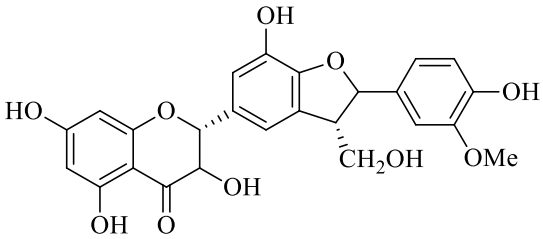
Kaempferol-3-o-glucoside



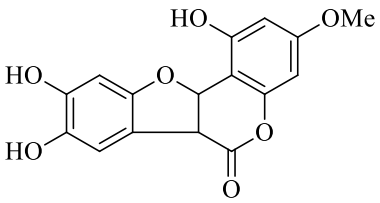
Procyanidin B2



Silymarin

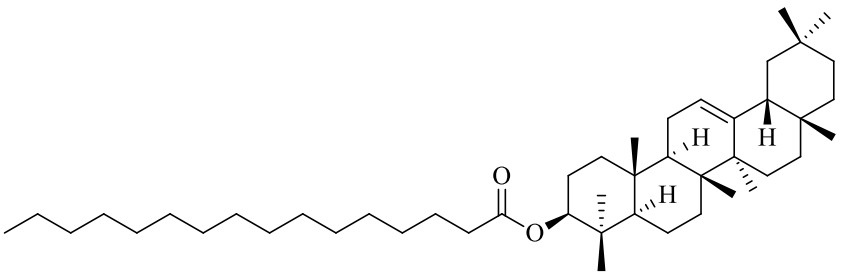


Silybin

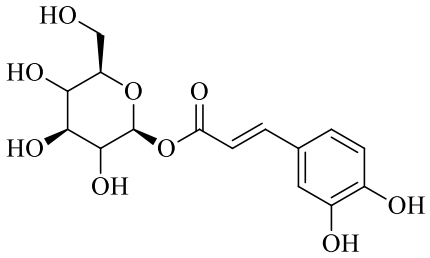


Silychristin

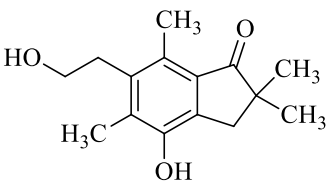
Wedealactone



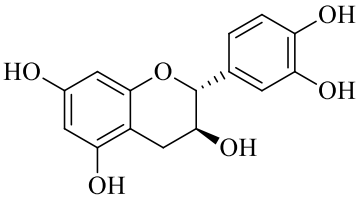
Beta-Amyrin palmitate



Caffeoyl glucoside



catechin



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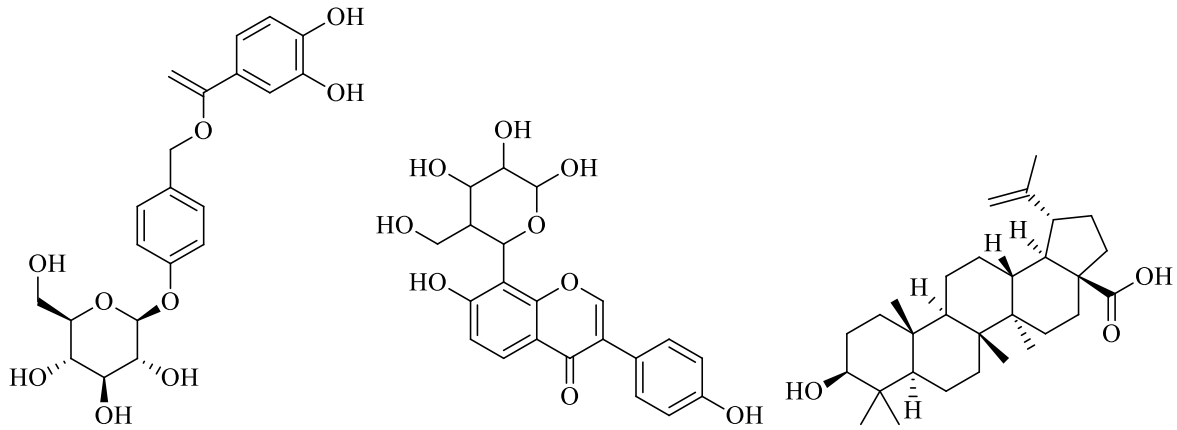

Amburoside A Puerarin Betilinic acid

Figure 1. Chemical structure of reported active bioactive phytoconstituents with hepatoprotective activity

Medicinal plants potentials with hepatoprotective activity

Human life has relied on plants to protect them against a variety of illnesses since the dawn of time. People still employ thousands of plants for medical purposes, even in spite of major advancements in modern medicine [Figure 2 (A-X)]. These plants include phytochemicals that exhibit a range of biological actions, including hepatoprotective, anti-inflammatory, anti-cancer, antioxidant, and antiulcerogenic qualities [128, 129]. Today, medicinal plants are the source of over 25% of pharmaceuticals [130].

Hygrophila auriculata (K. Schum) Heine

Hygrophila auriculata (K. Schum) Heine (synonym: Asteracantha longifolia Nees, Barleria auriculata Schum, Barleria longifolia Linn), is described in the Ayurvedic literature as Ikshura, Ikshagandha and Kokilasha having eyes like the kokila or the Indian cuckoo. It is classified in the Ayurvedic system of medicine as seethaveryam, mathuravipaka and is used for the treatment of a number of conditions including premeham (diabetes) and athisaram (dysentery) [Figure 2 (I)]. A methanolic extract of the seeds of H. auriculata at the dose of 200 mg/kg/p.o exhibited potent hepatoprotective activity against paracetamol and thioacetamide induced liver damage in rats [131, 132].

- Shanmugasundram et al., (2005) found that aqueous extract of the roots of H. auriculata at the dose of 150 mg/kg/p.o exhibited potent hepatoprotective activity-against carbon tetrachloride induced liver damage in rats [133].
- Hewawasam et al., (2003) to reported that the aqueous extract of A. longifolia was tested for hepatoprotective activity against carbon tetra chloride and paracetamol induced acute hepatotoxicity in mice. The plant exhibited significant hepatoprotective activity by reducing carbon-tetra chloride and paracetamol induced changes in biochemical parameters that were evident by enzymatic examination. The plant extract may interfere with free radical formation, which may conclude in hepatoprotective action. A. longifolia elicited significant hepatoprotective activity against carbon tetra chloride and paracetamol, comparable with standard drugs [134].
- The A. longifolia whole plant slurry was tested against carbon tetra chloride induced liver dysfunction in rats. The plant exhibited significant hepatoprotective activity by reducing carbon-tetra chloride induced changes in biochemical parameters that were evident by enzymatic examination. The whole plant slurry of A. longifolia showed significant

hepatoprotective efficacy against carbon tetra chloride, comparable with a known hepatoprotectant, silymarin [135-138].

Hedyotis corymbosa

The tiny plant Hedyotis corymbosa (Linn.) Lam., also known as khetpapra, has long been used to cure a variety of illnesses, including as inflammation, arthritis, and stomach discomfort [Figure 2]. According to a prior study, H. corymbosa has a strong hepatoprotective effect on liver damage caused by anti-tubercular medications in adult male rats weighing between 170g and 230g. [125]. Serum levels of ALT, AST, ALP, and serum bilirubin (SB) significantly rise after isoniazid and rifampicin (50 mg/kg) are administered, while albumin and total protein significantly decrease when compared to standard control (Silymarin), suggesting liver damage. Nevertheless, animals treated with 500 mg/kg of H. corymbosa ethanol extract before receiving rifampicin had their levels considerably returned to normal. It is evident that the plant extract and silymarin have potent hepatoprotective effects since the histopathological defects in rats treated with both isoniazid and rifampicin were nearly brought back to the levels of the control groups [139, 140].

Colocasia esculenta (L.) Schott

Due to its hepatoprotective qualities, which have been further confirmed by pharmacological research, C. esculenta has been acknowledged as a traditional remedy [Figure 2 (G)]. It has been reported that a methanol extract of the aerial parts of the plant significantly reverses iron-induced hepatotoxicity in Swiss albino mice, demonstrating its strong hepatoprotective qualities. In comparison to the standard desirox (20 mg/kg body weight), which suppressed the enzymes by 47.7% and 52.5%, respectively, the extract at a dose of 200 mg/kg body weight suppressed iron-induced elevated serum concentrations of alanine transaminase (ALT) and aspartate transaminase (AST) by 41.7% and 50.6%, respectively. The extract also potentiated hepatic antioxidants, which include superoxide dismutase (SOD), catalase, glutathione-S-transferase (GST), and reduced glutathione (GSH) by 289.6%, 103.8%, 144.1%, and 20.3%, respectively. Additionally, the extract's ability to detoxify iron by chelation and reduction was credited with its hepatoprotective properties [141-144].

Mangifera indica L.

A tropical tree, Mangifera indica belongs to the Anacardiaceae family. M. indica has been evaluated phytochemically and found to include terpenoids, polyphenols, microelements, fatty acids, and steroids [Figure 2 (T)]. Polyphenols include epicatechin, gallic acid propyl ester, 3,4,5-trihydroxybenzoic acid, 4-dihydroxybenzoic acid, mangoferin, benzoic acid, and methyl gallate. From the standpoint of ethnomedicine, M. indica is one of the most popular plants in South Asian rural regions due to its hepatoprotective qualities. According to studies on hepatoprotective effects of extracts of various plant parts, such as the stem, leaves, aerial parts, fruits, and pulps, against the synthetic compound silymarin, the aqueous extract of the fruits was able to reverse the oxidative stress-induced hepatotoxicity caused by cumene hydroperoxide in male Sprague-Dawley rats. Reduced rates of lipid peroxidation, hepatocyte lysis, reactive oxygen species (ROS) production, and intracellular glutathione depletion were demonstrated by further biochemical analysis [139, 141, 145-147].

Rosa damascene

Rosa damascena (Family: Rosaceae) is a kind of rose that contains flavonoids, carotenoids, tannin, pectin, citric acid, malic acid, and vitamins C, A, B1, B2, B3, and K. It has also been

found to have analgesic, anti-inflammatory, anti-headache, and muscle-relaxing properties [Figure 2 (O)]. AST, ALT, and ALP values in Swiss albino rats of either sex (weighing 120–140 g) show that R. damascene can prevent the liver damage caused by paracetamol. After taking 3 g/kg body weight of paracetamol, these enzyme levels rose. They were dramatically reversed when R. damascena crude extract was administered at dosages of 1.5 and 3 g/kg b.w. ($P < 0.05$), in a dose-dependent manner [139, 141, 148-152].

Trichosanthes dioica Roxb. (Cucurbitaceae)

It is a widely acknowledged perennial crop that is available for eight months of the year (February through September). When prepared in different ways, the fruit can be eaten on its own or combined with other meats or vegetables [Figure 2 (V)]. All of this plant's components have long been utilized for a variety of therapeutic reasons in India. Numerous trace elements, including magnesium, potassium, copper, sulfur, and chlorine, are present in it and are thought to be advantageous for human health. As per a different research, the female Long-Evans rats (weighing 180–200 g) treated with CCl4 showed considerably ($P<0.05$) higher blood AST and ALP activity. Treatment with 100 mg/kg, 200 mg/kg, and 400 mg/kg of TD peel extract decreased elevated AST and ALP activity in the plasma of rats given CCl4. When 100, 200, and 400 mg were administered, a significant dose–response interaction was seen. At a dose of 100 mg/kg, the TD extract significantly reduced plasma ALP in comparison to the effects of silymarin, a common medication. On the other hand, silymarin has been demonstrated to lower plasma AST levels more dramatically than TD extract [139, 141, 153-155].

Leucas aspera (Willd.)

The ethnomedical healers of Southeast Asia's Himalayan areas make considerable use of L. aspera, sometimes referred to as "Thumbai," for hepato-protection. It has also been professionally investigated for its hepatoprotective potential in addition to other biological activities [Figure 2 (K)]. The potential impact of L. aspera aqueous extract on D-galactosamine-induced hepatotoxicity in female Wistar albino rats was examined. In comparison to the conventional silymarin (100 mg/kg), which reduced the same indicators by 40.4%, 68.2%, 62.5%, and 61.9%, respectively, the extract at a dose of 400 mg/kg body weight suppressed pathological increase of ALT, AST, ALP, and total bilirubin by 35.5%, 60.9%, 54.5%, and 50.0%, respectively. Additionally, the extract and the standard diminished the rate of hepatic lipid peroxidation (50.4%, 46.0%, respectively) while increasing hepatic anti-oxidative enzymes such as SOD (256.0%, 238.8%, respectively), catalase (152.9%, 134.6%, respectively), and GPx (102.2%, 80.4%, respectively) [141, 156-159].

Moringa oleifera

The highly prized plant Moringa oleifera (Family: Moringaceae) is found in many tropical and subtropical nations and is linked to a remarkable number of high-nutritional therapeutic applications [Figure 2(N)] [139]. Islam and colleagues' investigation showed that after receiving 600 mg/kg body weight of paracetamol, the liver marker enzymes ALT, AST, and serum bilirubin levels were markedly elevated in Sprague Dawley rats of both sexes weighing 150–200g. Then pretreatment with the ethanolic M. oleifera (MO) extract of 250 and 500 mg/kg body weight significantly lowered the liver enzymes ($P < 0.001$) where Silymarin (100 mg/kg body weight) was given as standard. Through the reduction of serum ALP, AST, ALT, and SB levels, MO extracts show that they can preserve and protect the functional integrity of hepatic cells. Hepatobiliary dysfunction and severe disturbances in

hepatic function are indicated by an aberrant rise in SB levels. This result showed that MO extract guards against the hepatic harm that paracetamol causes [139, 141, 160-164].

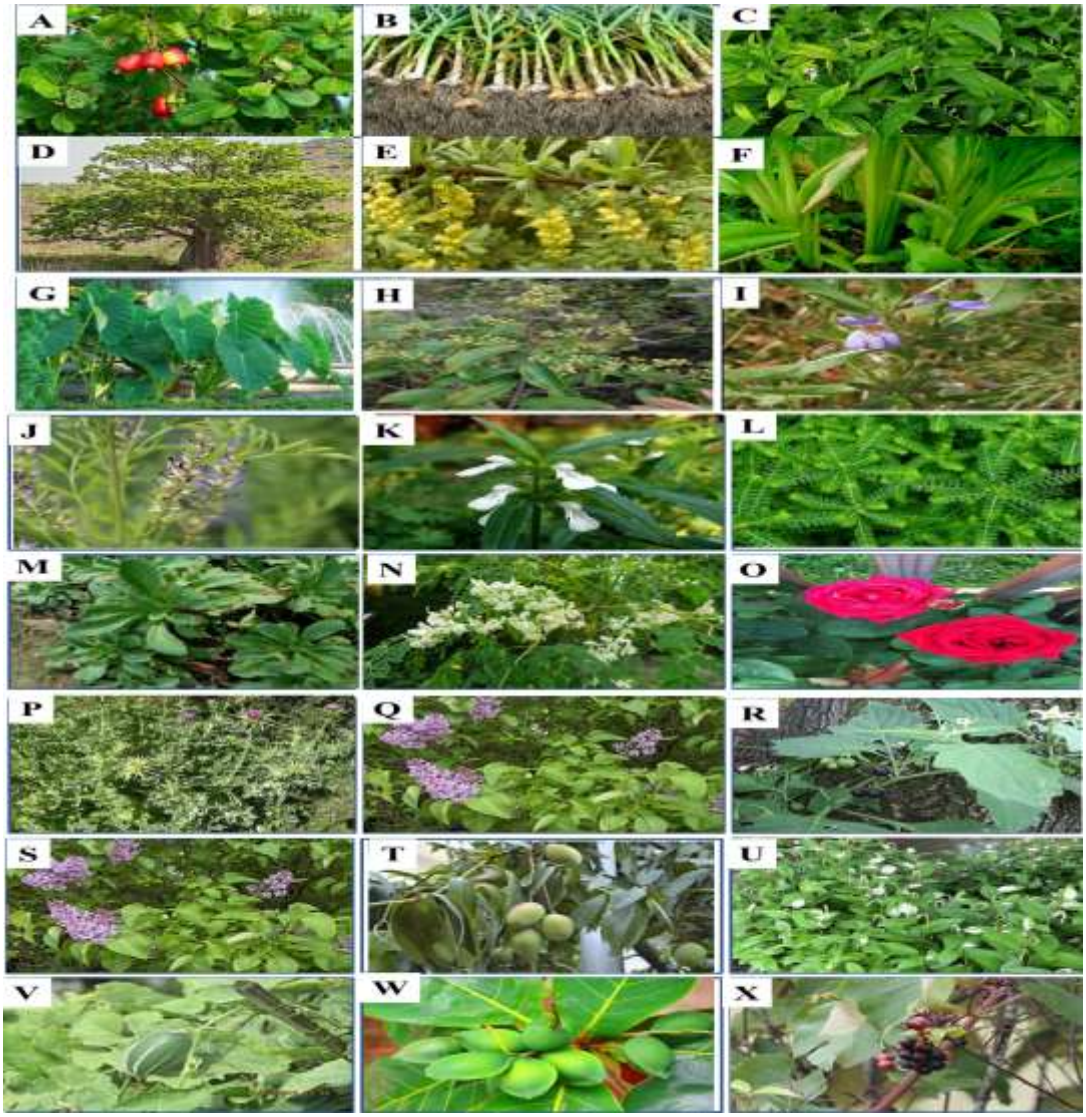

Figure 2. Traditional medicinal plants with hepatoprotective activity. (A) Anacardium occidentalis (B) Allium sativum (C) Andrographis paniculata (D) Adansonia digitata (E) Berberis aristata (F) Curcuma longa (G) Colocasia esculenta (H) Embelia ribes (I) Hygrophila auriculata K(Schum) Heine (J) Glycyrhiza glabra (K) Leucas aspera (L) Phyllanthus niruri Linn (M) Picrorhiza kurroa (N) Moringa oleifera (O) Rosa damascene (P) Silybanium (Q) Syringa vulgaris (R) Solanum nigrum (S) Terminalia catappa (T) Mangifera indica (U) Saururus chinensis (V) Trichosanthes dioica Roxb (W) Pachira aquatica (X) Vitis labrusca

2. Discussion

At least 25% of patients with liver illnesses employ natural phytoconstituents for disease therapy, and the usage of herb-based regimens is growing daily around the world. In order to unlock the secrets of medicinal plants, current research tactics are concentrated on

scientifically investigating herbal-based medicines for their safety and effectiveness through extensive preclinical investigations followed by clinical trials [1, 15]. In the end, these methods aid in identifying the true therapeutic lead and valuable pharmacotherapeutic candidate from natural sources, particularly plant origin, and standardize the dose schedule based on findings supported by science [139, 141]. These days, the majority of herbal products are promoted as ways to prevent ailments, promote health, alleviate symptoms, and treat various illnesses. The majority of these products are yet unproven pharmacologically and scientifically. The majority of experimental model studies on hepatotoxicity that used animals and cell cultures demonstrated that different plant extracts had curative and hepatoprotective properties, which help with clinical testing to find hepatoprotective leads. Most herbal-based formulations cannot be recommended for the treatment of liver illnesses due to a lack of scientifically supported pharmacological data [15, 47].

The present analysis makes it abundantly evident that herbal-based therapy may be quite effective in treating a variety of liver diseases and conditions that affect people. In a number of experimental animal models, a number of natural herbs and plant extracts exhibit quantifiable hepatoprotective effects. Alkaloids, flavonoids, phenolic compounds, tannins, lignins, and resin-based compounds are examples of secondary metabolites that are the main active phytocontituents with hepatoprotective effects [1]. This research also emphasized the biological process and scientific proof of hepatoprotection by botanical extracts that are crude. The most likely way that a number of plant extracts work is by scavenging dangerous free radicals that are produced during illnesses. Phenolic and flavonoid components of plant extracts have been demonstrated in several in vivo studies to improve protein secretion, reduce lipid peroxidation, increase the amount of blood glutathione, and improve free radical scavenging capabilities. Phytoconstituents also raise blood plasma levels of total bilirubin, lower levels of hepatic enzymes such as AST, ALT, ALP, and arginase, raise levels of antioxidative enzymes such as SOD, GPx, CAT, and GST, and lower levels of MDA [1. 15. 47, 42, 139, 141].

3. Conclusion and Future Perspective

Since many patients with liver disease use botanicals, the use of herbal medicines made from plant extracts to treat a wide range of clinical diseases is growing, and efforts are being made to clarify their mechanisms of action. The current review offers a thorough and up-to-date description of the most popular herbal medicines and herbal formulas used to treat chronic liver disease. By minimizing oxidative damage, reducing fibrogenesis, getting rid of viral infections, and stopping or slowing tumor growth, medicinal plants and phytochemicals have been shown to effectively cure chronic liver disease. It is still necessary to validate the active ingredients in certain therapeutic plants. To verify the therapeutic effectiveness of this herbal remedy in treating chronic liver disease, further randomized, placebo-controlled clinical studies are desperately needed. To distinguish between the genuine therapeutic benefit of these drugs and the unfounded expectations around them, future research will need to make significant methodological advancements. To allow for the logical clinical use of the agents, the active molecules must be separated, evaluated, and then randomized in placebo-controlled trials. Many of these identified lead compounds have the potential to develop into future hepatoprotective medications if they are thoroughly studied. Lastly, an attempt has been made in this research to gather the active phytoconstituents of hepatoprotective plants that have been reported worldwide. These plants are predicted to be identified for use in the

treatment of chronic liver disease in the future due to their considerable efficacy and safe performance.

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Conflicts of Interest- The authors affirm that they have no known financial or interpersonal conflicts that would have seemed to have an impact on the research presented in this study.

Author Contributions

Md. Shamim: Writing– review & editing, Writing– original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Monika Jain**: Writing– review & editing, Methodology, Conceptualization. **Md. Sarfaraj Hussain**: Writing– review & editing, Methodology, Formal analysis, Data curation, Validation, Methodology.

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