Pharmacogn. Res., 2024; 16(4):706-717.
https://www.phcogres.com

Review Article

Exploring the Mechanisms and Dosages of Herbal Hepatoprotective Agents

Rajendra Prasad Menasagere Rajappa[1,2], Paramakrishnan Nallupillai[1,*] , Kamsagara Linganna Krishna[3], Manoj Madanahalli Ramesh[4], Annegowda Hardur Venkatappa[4]

[1]Department of Pharmacognosy, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Bannimantap, Mysuru, Karnataka, INDIA.
[2]Department of Pharmacognosy, Farooqia College of Pharmacy, Mysore, Karnataka, INDIA.
[3]Department of Pharmacology, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Bannimantap, Mysuru, Karnataka, INDIA.
[4]Department of Pharmacognosy, Sri Adichunchanagiri College of Pharmacy, Faculty of Pharmacy, Adichunchanagiri University, BG Nagara, Mandya, Karnataka, INDIA.

ABSTRACT

Herbal hepatoprotective drugs are important for managing liver health because they provide complementary or alternative treatments for the various disorders of the liver. This review provides a thorough analysis of the numerous herbal hepatoprotective drugs' studied during the recent years, including their modes of action, suggested dosages, market trends, status of clinical trials and patents. The hepatoprotective properties of these herbal medicinal products are partly attributed to their mechanisms of actions such as antioxidant, anti-inflammatory, enzyme-modulating actions, and regeneration of hepatocytes. The recommended dosages differ based on the particular plant and ailment, highlighting the necessity for individualized treatment plans and more research to achieve the best possible therapeutic results. Patented compositions and polyherbal formulations provide novel treatments with synergistic effects that improve medicinal efficacy. The increased demand for natural treatments and their potential applications in pharmaceutical and nutraceutical fields has resulted in a considerable and expanding market for herbal hepatoprotective agents. Notwithstanding their possible advantages, more investigation is required to clarify mechanisms of action, assess long-term safety and efficacy, and provide uniform standards for clinical application. In general, herbal hepatoprotective drugs are promising approaches to manage liver health; nonetheless, their use necessitates regulatory oversight, quality control procedures, and evidence-based practice.

Keywords: Herbal Drugs, Hepatoprotective Agents, Mechanism, Dosage, Patents, Market Size.

Correspondence:
Paramakrishnan Nallupillai
Associate Professor, Department of Pharmacognosy, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Bannimantap, Mysuru-570015, Karnataka, INDIA.
Email: nparamakrishnan@jssuni.edu.in

Received: 05-07-2024;
Revised: 10-07-2024;
Accepted: 04-09-2024.

INTRODUCTION

Liver is a vital organ in human body and hence maintaining liver health is crucial because liver illnesses have a significant impact on public health. Chronic liver illnesses, such as hepatitis C and alcoholic liver disease, can have a major impact on quality of life and result in consequences such liver transplantation and encephalopathy.[1] Recent researches revealed the existence of a connection between gut health, liver health, and sleep quality.[2,3] Understanding how the gut and liver interact is essential for reducing systemic inflammation and preserving the general health of the liver.[3] Therefore, maintaining liver function and overall well-being requires implementing interventions that focus on lifestyle variables and appropriate management of liver disease.[4] Though there exists only few synthetics drugs used in the treatment of liver diseases, the side effects of treating liver illnesses with them encourages the exploration of complementary therapies like herbal remedies and even they are occasionally insufficient to prevent drug-induced liver damage.[5] The need for preventive measures is highlighted by the ongoing research to develop synthetic substances that may provide liver protection against adverse reactions to medical preparations.[6] Because of the drawbacks of synthetic medications, it is even more crucial to investigate natural remedies and novel strategies for liver protection in order to lessen the risks involved.

As mentioned earlier a promising treatment option for liver health management without side effects is the use of herbal hepatoprotective substances. These substances are made from traditionally employed medicinal plants, are being investigated for their ability to either protect or rejuvanate the liver without endangering it. Since the herbal medicinal ingredients are

DOI: 10.5530/pres.16.4.82

Publishing Partner : Manuscript Technomedia. [www.mstechnomedia.com]

found to be poorly absorbed when taken orally, they lowers the possibility of side effects.[7] Researchers want to offer non-toxic and therapeutically safe solutions for liver protection by applying traditional knowledge and creating plant-based hepatoprotective medications.[8,9] According to Rajaratnam M, *et al.*,[10] combining different hepatoprotective herbs may have a synergistic impact that provides antioxidant, antifibrotic, antiviral, immunomodulatory, and anti-inflammatory properties for all-encompassing liver support. Silymarin (milk thistle), Liv-52, *Camellia sinensis* (green tea), *Glycyrrhiza glabra* (licorice), *Fuzheng Huayu, Crocus sativus, Pistacia lentiscus*, and *Cinnamomum* spp. are hepatoprotective herbal medicinal products as well as herbs that are helpful in treating liver ailments. The traditional uses of these plants are being investigated for their potential liver-protective qualities without causing negative side effects.[10,11] Though herbal therapies may have advantages but few of them must also be used with caution since they may cause liver damage. Herbs with such properties include *Teucrium, Atractylis gummifera, Callilepsis laureola*, pyrrolizidine alkaloids, and senna glycosides.[12] It is essential to comprehend the safety and efficiency profiles of hepatoprotective herbs in order to properly incorporate them into the management of liver illness.

Several herbs that have been identified as hepatoprotective, including Silymarin derived from *Silybum marianum*, Liv-52, *Camellia sinensis, Glycyrrhiza glabra, Fuzheng huayu, Crocus sativus, Pistacia lentiscus*, and *Cinnamomum* species work by scavenging free radicals, reducing lipid peroxidation, and boosting antioxidant defenses. According to,[13] these herbs may shield liver cells from oxidative stress, promoting liver health. In order to ensure safety and efficacy, it is imperative to adhere to recommended parameters supplied by healthcare professionals or thorough instructions on product labels. The dosage of these herbs varies depending on the particular herb and formulation.[14] In order to maximize the benefits of hepatoprotective herbs in treating liver illnesses while limiting potential hazards, it is crucial to understand their mode of action and optimum dosages.

Understanding herbs and their products for treating liver diseases is crucial due to their potential hepatoprotective properties and minimal adverse effects.[15] Herbal remedies like milk thistle (silymarin) have shown efficacy in reducing liver injury caused by various factors.[16] These medicinal plants offer hepatoprotective activities, making them valuable in managing liver conditions.[13] Incorporating herbal medicines into liver disease treatment can provide long-lasting curative effects with minimal side

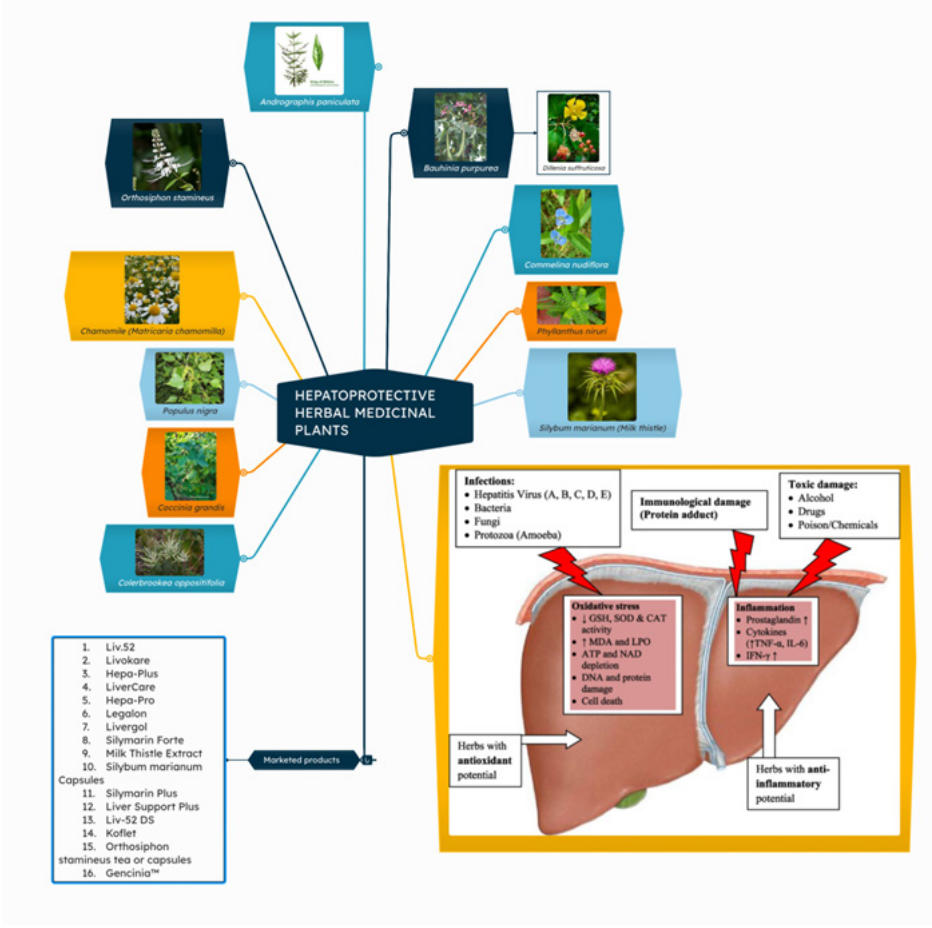

Figure 1: Hepatoprotective herbal medicinal plants, their marketed products and mechanisms of liver damage and how these herbs offer protection through antioxidant and anti-inflammatory properties.

effects, making them a promising alternative or complementary approach. However, rigorous clinical trials are necessary to establish the safety and efficacy of herbal treatments for liver diseases before widespread use can be recommended.[17] Figure 1 illustrates various herbal medicinal plants known for their hepatoprotective properties. These plants include *Andrographis paniculata, Bauhinia purpurea, Dillenia suffruticosa, Orthosiphon stamineus, Commelina nudiflora, Phyllanthus niruri, Silybum marianum* (Milk thistle), *Chamomile* (*Matricaria chamomilla*), *Populus nigra, Coccinia grandis*, and *Colebrookea oppositifolia*. The abstract highlights the marketed products derived from these herbs, such as Liv.52, Livokare, Hepo-Plus, LiverCare, Hego-Pro, Legalon, Livparmi, Silymarin Forte, Milk Thistle Extract, *Silybum marianum*, and various capsules. The diagram also categorizes the mechanisms of liver damage (infections, immunological damage, toxic damage) and shows how these herbs can counteract liver damage through their antioxidant and anti-inflammatory potentials.

The present review aims to provide a comprehensive overview of herbal hepatoprotective agents, including their mechanisms of action, recommended dosages, patented compositions, and market trends. The collected and articulated information of the review derived from scientific studies, patents, and market reports enhance understanding of herbal remedies for liver health management and informs healthcare professionals, researchers, and consumers about their potential benefits and challenges.

Liver Disease

When a health condition affects the liver's structure or function, this constitutes liver disease. Depending on whether or not the symptoms continue over time, such illnesses are known as either "acute" or "chronic". Acute liver disease occurs from when symptoms last less than six months, whereas Chronic Liver Disease (CLD) refers to symptoms continued beyond that length of time amounting to permanent structural changes within the challenged old liver.[18]

Alcohol use, viral infections such as hepatitis B and C, Non-Alcoholic Fatty Liver Disease (NAFLD), genetic factors (such as inheritances that result in a high prevalence of the dreaded type O negative blood group), and autoimmune disease conditions are the main causes of liver disease. Alcoholic liver disease, which primarily affects those with severe alcoholic use disorders, can take many various forms, from alcoholic fatty liver to alcoholic hepatitis to full-blown cirrhosis of the liver. In addition, NAFLD can progress to non-alcoholic steatohepatitis followed by fibrosis. Chronic viral hepatitis (B, C and D) infections are common causes of CLD, especially in East Asia and Sub-Saharan Africa. Genetic bases such as alpha-1 antitrypsin deficiency or inherited hemochromatosis can also bring on CLD. Autoimmune hepatitis and primary biliary cirrhosis are rare autoimmune conditions that cause liver damage.[19] Hence, the better way to protect the liver is to adopt better lifestyle management. Figure 2 illustrates the progression of liver disease, starting from a healthy liver and leading to various stages of liver damage. It highlights factors contributing to liver disease, such as viral infections (Hepatitis B and C), excessive alcohol consumption, fatty liver disease, autoimmune conditions, genetic factors, certain medications, and exposure to toxins. The progression depicted includes fatty liver, fatty liver disease, liver with cirrhosis, and liver with hepatocellular carcinoma. An anatomical diagram shows the liver's location in the male body.

Early diagnosis and intervention are crucial in the treatment of liver disease, as most cases are preventable and reversible.

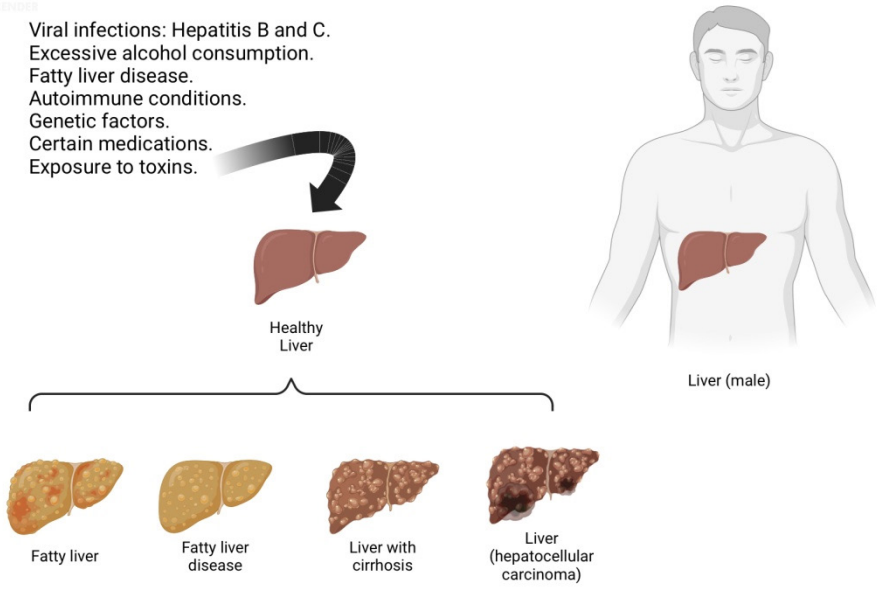

Figure 2: Factors and stages in the progression of liver disease.

Non-invasive scoring systems, such as the FIB-4 index for Fibrosis-4 congealed into counting score, enhanced liver fibrosis test and elastography to detect/stage liver fibrosis, can be performed to evaluate whether cells are undergoing death or on the opposite about rejuvenation.[20] Recently, genetic therapies, including gene silencing methods and CRISPR/Cas9-associated systems, are being researched to tackle liver diseases.[21]

Herbs with Hepatoprotective activity

Since centuries various herbs are therapeutically used for the treatment of different ailments exists among human as well as animals. Various herbs with traditional claims are still used effectively by traditional healers. However, plenty of herbs with traditional claims are exploited scientifically to provide the scientific evidence. This has led to the success in few cases as it is found to be difficult for the scientific world to mimic the method of treatment adopted by herbal healers. Still based on these traditional claims few herbs are studied and extensive studies led to the isolation of potential biologically active chemical constituents from the plants. Since these medicinal herbs are time tested and used since longtime, the extracts, bioactive compounds isolated from them or their semisynthetic as well as synthetic derivates may be therapeutically potent with least adverse effects.[22]

Herbs with hepatoprotective activity are natural plants that have been traditionally used for their ability to protect the liver from damage and promote its health. These herbs contain bioactive compounds that exhibit protective effects on the liver, aiding in detoxification, regeneration, reducing oxidative stress as well as overall liver function. Researchers around the globe are involved in the systematic scientific studies using crude drugs, their extracts or their isolated compounds to find a better treatment option for liver disorders. Results of these studies indicate that extracts of leaves and plants extracts of some medicinal plants have good potentials for use in hepatic disease. The present review emphasizes the evidential exploration of the mechanism of action of medicinal plants, their extracts, isolated compounds and their formulation against experimentally induced hepatotoxicity in different animal models, giving many links to develop future trials.[23] Table 1 highlights the various Herbal extracts, their bioactive compounds, and marketed products used in the hepatoprotective activity.

Mechanism of action of hepatoprotective herbs

Andrographis paniculata

The bioactive compound andrographolide, which has significant cytotoxic activity against cancer cells, induces apoptosis, possesses anti-inflammatory and anti-angiogenic properties, and has the potential to be chemoprotective towards normal cells, is responsible for the hepatoprotective effects of *A. paniculata*. The aqueous extract of *A. paniculata* has been shown to significantly reduce liver tissue abnormalities and liver enzymes in ethanol-induced hepatotoxicity in albino Wistar rats. The ethanolic leaf extract of *A. paniculata* has also been found to have hepatoprotective effects on thioacetamide-induced hepatotoxicity in rats, reducing liver damage and preventing the progression of liver cirrhosis. Andrographolide inhibits NF-κB-mediated MMP-9 expression, which in turn inhibits Matrix Metalloproteinase (MMP)-9 expression and activity, which plays an important role in liver pathology, particularly in cases of alcohol- and toxicity-induced liver disease.[36]

Dosage: Recommended doses for hepatoprotective activity:

- *A. paniculata*: 400 mg/kg
- *A. paniculata* or *Swertia chirayita* extract: 100-200 mg/kg
- *A. paniculata* crude extract: 10 mg/kg and 100 mg/kg
- Andrographolide: 800 mg/kg.[37]

Bauhinia purpurea

The antioxidant action of *B. purpurea* has been linked to its hepatoprotective properties. In rats with paracetamol-induced liver injury, the Chloroform Extract of *B. purpurea* (CEBP)leaves has been demonstrated to exhibit hepatoprotective activity. This is demonstrated by the notable reversal of the toxic effect of paracetamol on serum levels of AST and ALT, as well as the activity of endogenous Catalase (CAT) and Superoxide Dismutase (SOD). The Oxygen Radical Absorbance Capacity (ORAC) experiment indicates that the CEBP has a strong antioxidant capacity. Additionally, flavonoids were detected in CEBP by UHPLC-ESI-MS analysis.[38]

It has also been demonstrated that *B. purpurea* leaf Methanolic Extract (MEBP) exhibits strong anti-inflammatory and antioxidant properties. Additionally, MEBP may have hepatoprotective effects, which may be related in part to its high phenolic content and antioxidant activity.[39] Rats with PCM-induced liver injury were used to synthesize the extract in various partitions and test it for hepatoprotective bioactive components in MEBP. After the Aqueous Partition (AQBP) and the Petroleum Ether Partition (PEBP), the ethylacetate partition of MEBP (EABP) had a high Total Phenolic Content (TPC) value and showed impressive antioxidant activity. Low anti-inflammatory action was also demonstrated by all partitions through the Xanthine Oxidase (XO) and Lipooxygenase (LOX) pathways. The hepatoprotective activity of *B. purpurea* may be due to the synergistic action of a mixture of polar and non-polar compounds with the intermediate polarity, as suggested by the fact that EABP, at all tested doses, were able to reduce the serum enzymes' level, which had previously been increased by the overdose PCM.[40]

Dosage: The hepatoprotective ability of *B. purpurea* leaf Methanol Extract (MEBP) against paracetamol-induced liver damage in rats led to a study that recommended 50, 250, or 500 mg/kg of *Bauhinia purpurea* for hepatoprotective action (Yahya

Table 1: Herbs with hepatoprotective activity.

Sl. No	Name of the herb	Extract	Bioactive compound	Marketed products
1	*Andrographis paniculata*	Ethanol leaves extract.[23]	Andrographolide	Polyherbal formulations like Liver Care and Ayurvedic formulation like Livokare contains *A. paniculata** and other herbs, used for liver disorders and to maintain liver health. Hepa-Plus and Hepa-Pro are herbal supplements containing *A. paniculata* and other herbs, used for liver support and detoxification.
2	*Bauhinia purpurea*	Methanol leaf extract.	The antioxidant potential of *B. purpurea* is attributed to the presence of specific compounds such as flavonoids, phenolic content, carotenoids, alkaloids, tannins, saponins, and glutathione (GSH).[24]	
3	*Commelina nudiflora*	Methanol leaf extract.	The bioactive compounds responsible for the hepatoprotective activity in carbon tetrachloride-induced hepatotoxicity by reducing oxidative stress and inflammation of *Commelina nudiflora* include phenol (0.71%), benzyl alcohol (1.62%), eugenol (0.64%), and phenol,2,4-bis(1).[25]	
4	*Dillenia suffruticosa*	Methanol root extract.	The methanol extract of *D. suffruticosa* leaves contains various bioactive compounds, including saponins, triterpenes, sterols, and polyphenolic compounds, which contribute to its hepatoprotective activity.[26]	
5	*Phyllanthus niruri*	Aerial parts of aqueous extract.	The bioactive compounds responsible for the hepatoprotective activity of *P. niruri* includes corilagin, isocorilagin, brevifolin, quercetin, kaempferol rhamnoside, gallic acid, and brevifolin carboxylic acid.[26]	
6	*Silybum marianum* (Milk thistle)	Acetone seeds and fruits extract.[27,28]	Silymarin is composed of four major isomers: silybin, isosilybin, silydianin, and silychristin, with silybin being the most active and major component, representing about 60-70% of silymarin. (Mahli et al., 2015).[29]	Legalon, Livergol, Silymarin Forte, Liver Care, Milk Thistle Extract, *Silybum marianum* Capsules, Silymarin Plus and Liver Support Plus.

Sl. No	Name of the herb	Extract	Bioactive compound	Marketed products
7	*Orthosiphon stamineus*	Methanolic extract of *Orthosiphon stamineus* leaves.	The hepatoprotective bioactive compounds of *O. stamineus* are rosmarinic acid, sinensetin, eupatorin, and 3'-hydroxy-5, 6, 7, 4'-tetramethoxyflavone.[29]	Liv.52 and Liv-52DS are herbal supplement manufactured by Himalaya Herbal Healthcare, which contains a blend of herbs including *O. stamineus, Capparis spinosa*, and *Terminalia arjuna*, among others. * *O. stamineus* tea or capsules, which are marketed as a natural remedy for liver health and other health benefits.
8	Chamomile (*Matricaria chamomilla*)	Aqueous ethanol leavs extract.	The chemical composition of the hepatoprotective solvent extract of chamomile contains polyphenols (chamazulene and bisabolol oxides), flavonoids, and condensed tannins, and exhibits antioxidant activity. The essential oil consists of bisabolol, chamazulene, cyclic sesquiterpenes, bisabolol oxides, and other azulenes and terpenes may contribute to the hepatoprotective effects of chamomile extract.[30]	-
9	*Populus nigra*	Ethanol extract of resinous exudate of buds of poplar trees.[32]	The most known compound among salicylic compounds is salicin (salicyl alcohol glucoside).[31,32]	
10	*Coccinia grandis*	Methanolic leaf extract of *Coccinia grandis* demonstrated hepatoprotective activity.[33]	The bioactive compounds responsible for the hepatoprotective activity in *C. grandis* leaves include phenolic compounds, flavonoids (rutin, quercetin-3-O-neohesperidoside, kaempferol-3-O-rutinoside, kaempferol-3-O-neohesperidoside, kaempferol-3-O-glucoside, kaempferol-hexoside), saponins, tannins, thiamine, riboflavin, niacin, etc.[33,34]	Gencinia™
11	*Colerbrookea oppositifolia*	Petroleum ether extract of the plant leaves.	Steroidal compounds like sitosterol, n-triacontane, hydroxydotriacontyl ferulate, acetyl alcohol, and 3,7,4,2-tetramethoxyflavones are found to possess hepatoprotective activity.[35]	

et al., 2013).38 The research discovered that MEBP demonstrated notable hepatoprotective effect over PCM-induced liver damage at dosages of 50, 250, and 500 mg/kg. In a different investigation, it was discovered that *B. purpurea* leaf Chloroform Extract (CEBP) at doses of 50, 250, and 500 mg/kg significantly protected rats' livers against damage caused by PCM. In rats with liver damage brought on by PCM, the study discovered that CEBP dramatically lowered the levels of the liver enzymes ALT and AST. Consequently, *B. purpurea's* MEBP and CEBP have both demonstrated encouraging hepatoprotective action, giving them viable options for the treatment of liver disease.[38]

Dillenia suffruticosa

In rats, *Dillenia suffruticosa* was found to block carbon tetrachloride-induced liver damage through the modulation of inflammatory markers and oxidative stress pathways. This therapeutic mechanism, in turn, involves enlargement of hepatic antioxidant enzymes such as superoxide dismutase,

catalase, glutathione peroxidase and glutathione S-trase which are vital in defending the liver from oxidative damage. These enzymes' activity is increased by the methanol extract of leaves of *Dillenia suffruticosa* making them more effective at breaking down peroxide lipids and keeping the liver from suffering from oxidative stress in general. The extract was also found to adjust stage two metabolic enzymes in rats, including quinone reductase and glutathione-S-transferase, which are involved in the liver is socially harmful substances detoxification. It is believed that the active compounds responsible for these protective effects found in *D. siffreticoa* are saponins, triterpenes, steroids, and polyphenolic compounds, all of which are parts of its ingredients. These constituents have been identified as potential causes of the extract's cytotoxic activity, indicating their potential role in causing apoptosis and also halting cancer-cell growth in animal experiments.[41]

Dosage: The recommended dose for *Dillenia suffruticosa* for hepatoprotective activity is 200, 300, and 400 mg/kg body weight once daily for 14 days, as reported in a study where rats were pretreated with the methanol extract of *D. suffruticosa* leaves.[41]

This dosage showed significant depletion of elevated enzymatic levels and reduced the extent of malondialdehyde production, indicating its potential in protecting the liver from carbon tetrachloride (CCl_4)-induced oxidative injury.

Phyllanthus niruri

The mechanism of *P. niruri* liver protection is on the grounds that it can keep glutathione in a reduced state, which is an important antioxidant enzyme to prevent oxidative stress of liver cells. This means that the aqueous extract of *P. niruri* can significantly reduce levels of ALT and AST, as well as restore reduced activities for such natural antioxidants as GSH and SOD responsive to CCl4 induced liver damage in rats. According to a study carried out by,[41] the AE of *P. niruri* has been identified as an inhibitor for HBV replication and at the same time it has good safety. *P. niruri* possess some clinical effects in treating chronic hepatitis patients who praise from it's high efficacy during recovery.[42] The bioactive compounds in *P. niruri*, such as corilagin and isocorilagin, have strong hepatoprotective activity against CCl_4-induced liver injury in clone-9 and HepG2 cells (brevifolin, quercetin kaempferol rhamnoside, gallic acid, brevifolin carboxylic acid). It is possible that these substances play a part in killing cells at the same time as inducing apoptosis or inhibiting proliferation of cancer cells.[43] Liver protection of *P. niruri* is including repairing the liver cells, reducing serum markers back to their normal levels and restoring hepatocyte function.

Dosage: It is not specifically specified how much *Phyllanthus niruri* should be taken to protect the liver. However, a trial conducted over a 12-month period indicated that a daily dose of 3,000 mg (12 capsules) of *P. niruri*, given in two divided doses, did not significantly lower liver enzyme levels and the CAP score in individuals with mild-to-moderate NAFLD.[44] Another study discovered that giving individuals with alcoholic hepatitis *P. niruri* for four weeks greatly increased their appetite and antioxidant levels.[45] Only at a dose of 1,000 mg daily did a pilot research employing a standardized extract of *P. niruri* demonstrate improvements in liver histology and a decrease in visceral adipose tissue weight. According to a study, giving mice a 20% aqueous extract of *P. niruri* at a dose of 10 g/kg body weight is both safe and efficacious.[46] According to a network pharmacology study, *P. niruri* has an excellent safety profile, potential therapeutic benefits, including its efficacy in treating hepatitis, and may play a role in blocking the reproduction of the HBV.[47] Therefore, further research is needed to determine the optimal dosage for liver protection.

Silybum marianum

The mechanism of action of *Silybum marianum* (milk thistle) for hepatoprotective activity involves multiple beneficial effects attributed to silymarin, a key component of *Silybum marianum*. Silymarin exhibits antioxidant activities, anti-inflammatory properties, and anti-fibrotic effects, which collectively contribute to its hepatoprotective action.[48] Studies have shown that silymarin can scavenge free radicals, reduce liver inflammation, and prevent fibrosis, particularly in conditions like carbon tetrachloride (CCl4)-induced hepatotoxicity.[49,50] Additionally, silymarin has been reported to lower blood lipids, exhibit antioxidant effects, prevent diabetes, and inhibit various signaling pathways associated with liver diseases like Nonalcoholic Fatty Liver Disease (NAFLD).[49] The molecular docking analysis of silymarin with key targets involved in liver protection showed an average docking affinity of -6.77 kcal/mol, indicating its potential efficacy in interacting with these targets. Furthermore, silymarin has been found to inhibit the expression of pro-inflammatory and pro-fibrogenic genes in hepatic stellate cells, which play a crucial role in liver fibrosis.[50] Overall, the hepatoprotective mechanism of *Silybum marianum* involves a combination of antioxidant, anti-inflammatory, and anti-fibrotic actions mediated by silymarin, making it a valuable natural remedy for liver health.

Dosage: The hepatoprotective activity of *Silybum marianum*, also known as milk thistle, is attributed to its active compound silymarin. Silymarin has been shown to inhibit free radicals, protect cellular membranes, enhance hepatic glutathione, and increase protein synthesis in hepatocytes.[51] Human studies have used silymarin dosages of up to 2100 mg/day, indicating its safety and potential for treating liver diseases. The European Union has approved silymarin for treating liver disease, with a recommended dosage of 140-175 mg three times daily.[52] However, the optimal dosage may vary depending on the specific liver condition and the individual's response.

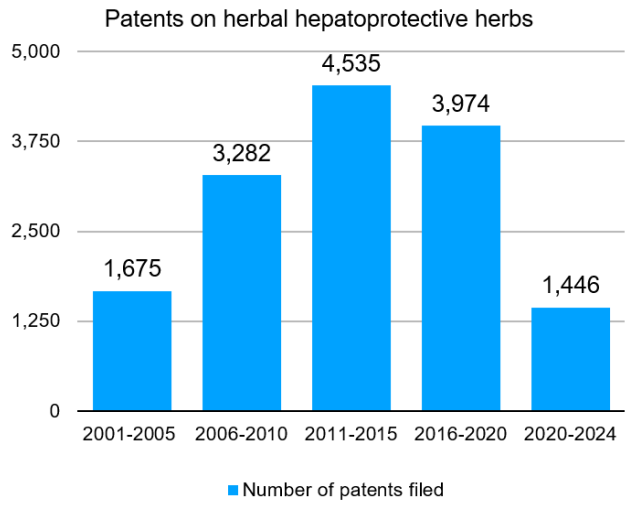

Figure 3: Number of Patents Filed on Herbal Hepatoprotective Herbs Over Different Periods.

Orthosiphon stamineus

Orthosiphon stamineus known for its hepatoprotective properties, exerts its effects on Non-Alcoholic Fatty Liver Disease (NAFLD) through various mechanisms. The plant modulates cellular processes like oxidative stress, mitochondrial β-oxidation, and inflammation, all crucial in the pathogenesis of NAFLD.[53] By targeting these pathways, *O. stamineus* helps reduce liver injury, prevent necrotic changes, and restore liver function parameters towards normal levels. Additionally, its antioxidant and free radical scavenging properties play a significant role in protecting liver cells from damage and maintaining liver health.[54,55] These combined actions make *Orthosiphon stamineus* a promising natural remedy for liver disorders, particularly NAFLD.

Dosage: A study mentioned that the hepatoprotective effect of *O. stamineus* extract was observed in rats treated with different doses of 250, 500, and 1000mg/kg. Another study used a dose of 200mg/kg of methanol extract of *O. stamineus* leaves for hepatoprotective activity in rats.[56] It is important to note that these dosages are for experimental purposes and may not be directly applicable to humans. The appropriate dosage for human consumption should be determined by a healthcare professional, taking into account factors such as age, weight, and overall health.

Chamomile (*Matricaria chamomilla*)

Chamomile extract has been found to have hepatoprotective effects against liver damage, possibly due to its antioxidant and anti-inflammatory properties. The mechanisms of action include decreasing oxidative stress, treating liver histopathological changes, improving the antioxidant defense system, and inhibiting free radicals.[57,58] The extract has been shown to decrease the levels of liver enzymes such as AST and ALT, indicating reduced liver injury. The antioxidant activity of chamomile extract may be due to the presence of polyphenols and flavonoids, which scavenge free radicals and inhibit lipid peroxidation. The anti-inflammatory activity of the extract may be due to the inhibition of COX-2 and iNOS, which are involved in the inflammatory response. The extract has also been found to have antiproliferative effects, which may contribute to its hepatoprotective activity by reducing liver cell proliferation and inflammation.[57] Overall, chamomile extract has potential therapeutic benefits for liver damage, and further research is needed to fully understand its mechanisms of action and therapeutic potential.

Dosage: The doses of Chamomile (*M. chamomilla*) extract for hepatoprotective activity vary based on the study. In one study, the aqueous ethanolic extract of chamomile was administered at doses of 5, 10, and 25 mg/kg to evaluate its hepatoprotective effects.[58] Another study mentioned the pretreatment with chamomile extract at 500 mg/kg, which was found to be as effective as silymarin with negligible liver toxicity, indicating significant hepatoprotective potential.[59] These doses highlight the range of concentrations used in research to assess the hepatoprotective properties of chamomile extract.

Populus nigra

The components of propolis secreted by poplar tree buds house phenolic glycosides, also known as salicylic compounds, with varying pharmacological impacts. These compounds predominantly originate from trees and shrubs like those belonging to the Salicaceae family including short rotation plants. According to,[60,61] the ethanol extract of propolis has demonstrated potent hepatoprotective properties owing to its antioxidant characteristics. Propolis' antioxidant attributes mitigate free radical scavenging that can induce harmful impacts on the liver. The hepatoprotective effects of propolis depend on dosage as it was shown to substantially decrease serum ALT levels in rodents with liver harm induced by hepatotoxic medications. Likewise, the decrease in serum enzymes signifying ALT liver injury and the reduction in liver cell degeneration scores and inflammatory reaction in rodents pretreated with propolis supports propolis' hepatoprotective impact. Furthermore, the assessment of serum bilirubin levels, which can diagnose or monitor liver diseases for example cirrhosis, hepatitis or biliary obstruction, demonstrated that propolis did not induce hepatotoxicity.[62]

Dosage: The doses of propolis used in studies for liver diseases are:

* 250 mg twice daily for 4 months for nonalcoholic fatty liver disease (NAFLD).[63]

* 510 mg per day for 8 weeks for obese patients with NAFLD.[64]

* 100 mg/kg for rats with NAFLD.[65]

It is important to note that the safe and effective doses of propolis for liver diseases may vary depending on the formulation, the specific liver condition, and individual patient characteristics.

Coccinia grandis

C. grandis leaves are known to have hepatoprotective properties because of their capacity to reduce bilirubin levels and the activities of blood enzymes that are signs of liver injury, including SGOT, SGPT, and ALP.[66,67] Similar to the common hepatoprotective medication silymarin, it has been demonstrated that the diethyl ether extract of C. grandis leaves has hepatoprotective efficacy against liver damage induced by carbon tetrachloride in rats.[68] The mechanism of action of *C. grandis* leaves in protecting the liver is not explicitly stated in the search results, but it is suggested that the plant extract may contain flavonoids, which are known to have hepatoprotective properties.[69] These flavonoids may be responsible for reducing serum AST, ALT, and ALP levels, indicating a protective effect on the liver.

Dosage: The doses for the hepatoprotective activity of *C. grandis* leaves are as follows:

* The leaf powder of *C. grandis* was administered at doses of 0.5, 1, and 2 g/kg body weight.

* The methanol extract of *C. grandis* leaves was administered at a dose of 2 g/kg body weight.

* The methanolic extract of leaves of *C. grandis* exhibited the antipyretic activity at the doses of 100 and 200 mg/kg.[68]

Polyherbal Herbal hepatoprotective products

Liv.52

The active compounds in Liv.52 that contribute to its hepatoprotective effects include *Capparis spinosa* (65 mg), *Solanum nigrum* (32 mg), *Cichorium intybus* (16 mg), *Terminalia arjuna* (16 mg), *Cassia occidentalis* (8 mg), *Achillea millefolium* (8 mg), *Tamarix gallica* (8 mg), and *Mandur bhasma* (33 mg). These constituents work synergistically to provide hepatoprotective benefits and support liver health.

The active ingredients in Liv.52 work by preventing lipid peroxidation, enhancing the activity of antioxidant enzymes like glutathione peroxidase and superoxide dismutase, and inhibiting glutathione depletion in HepG2 cells, all of which contribute to the compound's hepatoprotective effects. Furthermore, in tert-butyl hydroperoxide-induced hepatotoxicity, Liv.52 has been demonstrated to inhibit elevated levels of MDA, a marker of lipid peroxidation, and SOD, which eliminates intracellular free radicals. It has also been shown to inhibit elevated levels of MDA and SOD in ischemia-reperfusion (I/R) injury and lower liver enzymes to levels comparable to the control group in liver damage caused by different hepatotoxins. Additionally, in a toxicity investigation, Liv.52 was demonstrated to reduce the inflammatory response in the injured liver tissue brought on by I/R injury and to raise the amount of glutathione (GSH), a potent antioxidant that shields cells from the harm caused by free radicals produced by I/R.[70]

Liverin

Liverin, a commercial hepatoprotective polyherbal formulation available in the Indian market, contains active ingredients such as Silymarin Milk Thistle, Kalmegh, Bhringraj, Punarnava, Kadu, Chicory, Turmeric, Shankhpushpi, Henna, Kakamachi, Dandelion, Amla, Bhumiamla, Tulsi, and Giloy.[71]

These ingredients work synergistically to protect the liver from damage caused by toxins, alcohol, drugs, and other harmful substances, thereby supporting liver function and health.

Patents on herbs having hepatoprotective

Patents on herbs having hepatoprotective action are numerous, indicating high interest in this field.

Examples of patents in this field:

A hepatoprotective herbal composition using *Rheum emodi* Wall, *Phyllanthus amarus* Linn., *Eclipta alba* Hassk., *Andrographis paniculate* Nees., and *Picrorhiza kurroa* is described in WO2011074001A2. *Fumaria officinalis, Royle* ex Benth., *Terminalia chebula* Retz., *Tinospora cordifolia* Miers., *Cichoriu intybus* Linn., *Teplirosea purpurea* Linn., and *Boerhaavia diffusa.* This mixture is used to treat hepatoprotective medications for liver viral infections, including animal hepadnavirus and acute Hepatitis E and B.

A liver-protective herbal soft drink composed of *Glycyrrhiza glabra, Vitis vinifera, Withania somnifera, Boerhaavia diffusa, Tinospora cordifolia, Elettaria cardamomum*, and *Cinnomomum* sps is described in Indian Patent application 2939/DELNP/2004.

Herbosomes containing andrographolide and their formulations for the treatment of acute or chronic liver diseases are described in Indian patent IN 234595. Indian patent application 1782/DEL/2007 describes the usage of jatamansi, post turanj, haldi, and trikatu in the treatment of liver cirrhosis.

Extracts of Cichorium intybus seeds and/or all of the components of *Eclipta prostrata* are included in the hepatoprotective herbal composition WO2011080721A2. This natural herbal combination can be used by humans to treat cirrhosis, non-alcoholic fatty liver disease, and other liver diseases brought on by chemotherapy and infection.

Indian Patent Application 623/DEL/1996 makes use of the following: *Rheum emodi* Wall, *Phyllanthus amarus* Linn., *Eclipta alba* Hassk., *Andrographis paniculata* Nees., *Picrorhiza kurroa* Royle ex Benth., *Fumaria officinalis, Tinospora cordifolia* Miers., *Terminalia chebula* Retz., *Cichoriu intybus* Linn., *Teplirosea purpurea* Linn., and *Boerhaavia diffusa* Linn. These illustrations demonstrate the range and volume of study that goes into creating hepatoprotective herbal remedies that are both secure and efficient.

The Figure 3 shows the number of patents filed on herbal hepatoprotective herbs in five-year intervals from 2001 to 2024. The numbers increased significantly from 1,675 patents in 2001-2005 to a peak of 4,535 patents in 2011-2015. There was a slight decline to 3,974 patents in 2016-2020, followed by a more pronounced drop to 1,446 patents in 2020-2024 (Google Patents).

Market size for herbal hepatoprotective agents

The market size for herbal hepatoprotective agents is significant and growing. According to a report by SkyQuest Technology, the global herbal medicine market size was valued at USD 151.91 billion in 2021 and is poised to grow to USD 437.59 billion by 2030, with a CAGR of 11.16% from 2022 to 2030. This growth is driven by the increasing demand for herbal products in the pharmaceutical and nutraceutical industries, as well as the rising demand for natural medicine from growing countries.

Herbal hepatoprotective drugs have a sizable and expanding market. The size of the global market for herbal medicines was estimated by SkyQuest Technologies to be USD 151.91 billion in 2021 and is expected to increase to USD 437.59 billion by 2030, with a Compound Annual Growth Rate (CAGR) of 11.16% from 2022 to 2030. The expanding demand for natural medicine from developing nations and the expanding need for herbal products in the pharmaceutical and nutraceutical industries are the main drivers of this expansion.

Silymarin, a single herbal medication formulation used in liver illnesses, is valued at approximately 240 million US dollars in Germany alone when it comes to specific herbal hepatoprotective compounds. Due to their widespread availability in the global market, tablets and capsules hold a significant share of the herbal medicine market. The market is segmented by form, application, product type, source, and distribution channel (Herbal Medicine Market Size, Share, Growth Analysis, by Form, Application, Product Type, Source, Distribution Channel - Industry Forecast 2022-2028, n.d.). The substantial market share of the pharmaceutical and nutraceutical segments can be attributed to the elevated demand for herbal products within these respective industries.

Even though the market for herbal hepatoprotective drugs is expanding, more study is still required to determine the specific hepatoprotective potentials of these agents as well as the phytoconstituents from these plants that have hepatoprotective properties. Herbs and herbal remedies have long been used to treat liver disorders, and the Natural Health Product Regulations of Canada support the use of contemporary technologies for plant-based products in healthcare.[72,73]

CONCLUSION

In conclusion, the diverse array of herbal hepatoprotective agents, including single herbs, polyherbal formulations, and patented compositions, provides promising opportunities for supporting liver health. These agents exert their effects through mechanisms such as antioxidant activity, anti-inflammatory properties, and modulation of liver enzymes, contributing to their hepatoprotective potential. The dosages of these agents vary greatly, underscoring the importance of tailored therapeutic approaches and further investigation to optimize efficacy. The growing marketplace for herbal hepatoprotective agents reflects expanding public interest in natural remedies for liver health. However, continuous study into the relative effectiveness and safety profiles of these agents is essential to harness their full healing power and meet the evolving needs of individuals seeking support for liver health. All in all, herbal medicine presents a compelling avenue for managing liver health, with the ability to complement conventional treatment modalities and improve patient outcomes.

ACKNOWLEDGEMENT

We extend our heartfelt thanks to all those who contributed to this review. Our appreciation goes out to the researchers, colleagues, institutions, and individuals whose support and insights were invaluable. We also acknowledge the role of our families in providing unwavering encourage

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ALT: Alanine Aminotransferase; **AST:** Aspartate Aminotransferase; **ALP:** Alkaline Phosphatase; **GSH:** Glutathione; **SOD:** Superoxide Dismutase; **CAT:** Catalase; **MDA:** Malondialdehyde; **NAFLD:** Non-Alcoholic Fatty Liver Disease; **HBV:** Hepatitis B Virus; **HCV:** Hepatitis C Virus; **CCl4:** Carbon Tetrachloride; **AE:** Aqueous Extract; **PCM:** Paracetamol; **CEBP:** Chloroform Extract of Bauhinia Purpurea; **MEBP:** Methanol Extract of Bauhinia Purpurea.

REFERENCES

1. Spiegel BMR, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: A systematic review and quantitative assessment. *Hepatology*. 2005;41:790-800.
2. Guan Y-S, He Q. Plants Consumption and Liver Health. *Evidence-based Complementary and Alternative Medicine*. 2015; 2015:1-10.
3. Park B, Lee H, Lee Y. Alcoholic liver disease: focus on prodromal gut health. *Journal of Digestive Diseases* 2016;17:493-500.
4. Javed S, Ahsan W, Kohli K. Pharmacological influences of natural products as bioenhancers of silymarin against carbon tetrachloride-induced hepatotoxicity in rats. *Clinical Phytoscience*. 2018;4. doi:10.1186/s40816-018-0079-6.
5. Cheong AM, Koh JXJ, Patrick NO, Tan CP, Nyam KL. Hypocholesterolemic Effects of Kenaf Seed Oil, Macroemulsion, and Nanoemulsion in High-Cholesterol Diet Induced Rats. *Journal of Food Science*. 2018;83:854-63.

6. Mahmoudi F, Elyasi S. None Herbal Agents as Preventive and Therapeutic Measures for Doxorubicin Induced Hepatotoxicity: A Comprehensive Review. *Journal of Pharmaceutical Care*. 2022. doi:10.18502/jpc.v10i3.10796.
7. Farghali H, Canová NK, Zakhari S. Hepatoprotective properties of extensively studied medicinal plant active constituents: Possible common mechanisms. *Pharmaceutical Biology*. 2014;53:781-91.
8. Yadav UCS, Baquer NZ. Pharmacological effects of *Trigonella foenum-graecum* L. in health and disease. *Pharmaceutical Biology*. 2013;52:243-54.
9. Girish C, Pradhan SC. Indian herbal medicines in the treatment of liver diseases: problems and promises. *Fundamental and Clinical Pharmacology*. 2011;26:180-9.
10. Rajaratnam M, Prystupa A, Lachowska-Kotowska P, Załuska W, Filip R. Herbal medicine for treatment and prevention of liver diseases. *Journal of Pre-Clinical and Clinical Research*. 2015;8:55-60.
11. Shamsi-Baghbanan H, Sharifiyan A, Esmaeili S, Minaei B. Hepatoprotective Herbs, Avicenna Viewpoint. *Iranian Red Crescent Medical Journal*. 2014;16. doi:10.5812/ircmj.12313.
12. Del Prete A, Scalera A, Iadevaia MD, Miranda A, Zulli C, Gaeta L *et al.* Herbal Products: Benefits, Limits, and Applications in Chronic Liver Disease. *Evidence-based Complementary and Alternative Medicine*. 2012; 2012:1-19.
13. Ali SA, Sharief NH, Mohamed YS. Hepatoprotective Activity of Some Medicinal Plants in Sudan. *Evidence-based Complementary and Alternative Medicine*. 2019; 2019:1-16.
14. Danan G, Teschke R. RUCAM in Drug and Herb Induced Liver Injury: The Update. *International Journal of Molecular Sciences*. 2015;17:14.
15. Hong M, Li S, Tan HY, Wang N, Tsao S-W, Feng Y. Current Status of Herbal Medicines in Chronic Liver Disease Therapy: The Biological Effects, Molecular Targets and Future Prospects. *International Journal of Molecular Sciences*. 2015;16:28705-45.
16. Abenavoli L, Capasso R, Milic N, Capasso F. Milk thistle in liver diseases: past, present, future. *PTR Phytotherapy Research/Phytotherapy Research*. 2010;24:1423-32.
17. Perumpail B, Li A, Iqbal U, Sallam S, Shah N, Kwong W *et al.* Potential Therapeutic Benefits of Herbs and Supplements in Patients with NAFLD. *Diseases*. 2018;6:80.
18. Wlodzimirow KA, Eslami S, Abu-Hanna A, Nieuwoudt M, Chamuleau R a. FM. Systematic review: acute liver failure – one disease, more than 40 definitions. *Alimentary Pharmacology and Therapeutics*. 2012;35:1245-56.
19. Ginès P, Kamath PS, Arroyo V. *Chronic Liver Failure*. Springer Science and Business Media, 2010http://books.google.ie/books?id=FIK2vk7_3PgC&printsec=frontcover&dq=Chronic+Liver+Disease&hl=&cd=1&source=gbs_api.
20. Macpherson I, Abeysekera KWM, Harris R, Mansour D, McPherson S, Rowe I, *et al.* Identification of liver disease: why and how. *Frontline Gastroenterology*. 2022;13:367-73.
21. Ray G. Management of liver diseases: Current perspectives. *World Journal of Gastroenterology*. 2022;28:5818-26.
22. Chaughule RS, Barve RS. Role of herbal medicines in the treatment of infectious diseases. *Vegetos/Vegetos - International Journal of Plant Research*. 2023;37:41-51.
23. Subramanian R, Asmawi MZ, Sadikun A. Effect of Andrographolide and Ethanol Extract of *Andrographis paniculataon* Liver Glycolytic, Gluconeogenic, and Lipogenic Enzymes in a Type 2 Diabetic Rat Model. *Pharmaceutical Biology*. 2008;46:772-80.
24. H S. Antioxidants from Bauhinia and Future Research Gap. *Annals of Experimental and Molecular Biology*. 2023;5:1-8.
25. Shah MD, D'Souza UJA, Iqbal M. The potential protective effect of *Commelina nudiflora* L. against carbon tetrachloride (CCl4)-induced hepatotoxicity in rats, mediated by suppression of oxidative stress and inflammation. *Environmental Health and Preventive Medicine*. 2017;22. doi:10.1186/s12199-017-0673-0.
26. Armania N, Yazan LS, Musa SN, Ismail IS, Foo JB, Chan KW, et al. *Dillenia suffruticosa* exhibited antioxidant and cytotoxic activity through induction of apoptosis and G2/M cell cycle arrest. *Journal of Ethnopharmacology*. 2013;146:525-35.
27. Bahmani M, Shirzad H, Rafieian S, Rafieian-Kopaei M. *Silybum marianum*: Beyond Hepatoprotection. *Journal of Evidence-based Complementary and Alternative Medicine*. 2015;20:292-301.
28. Wianowska D, Niewski MW. Simplified Procedure of Silymarin Extraction from *Silybum marianum* L. Gaertner. *Journal of Chromatographic Science*. 2014;53:366-72.
29. Alshawsh MA, Abdulla MA, Ismail S, Amin ZA. Hepatoprotective Effects of *Orthosiphon stamineus* Extract on Thioacetamide-Induced Liver Cirrhosis in Rats. *Evidence-based Complementary and Alternative Medicine*. 2011; 2011:1-6.
30. Sebai H, Jabri M-A, Souli A, Hosni K, Rtibi K, Tebourbi O, *et al.* Chemical composition, antioxidant properties and hepatoprotective effects of chamomile (*Matricaria recutita* L.) decoction extract against alcohol-induced oxidative stress in rat. *General Physiology and Biophysics*. 2015;34:263-75.
31. Tyśkiewicz K, Konkol M, Kowalski R, Rój E, Warmiński K, Krzyżaniak M, *et al.* Characterization of bioactive compounds in the biomass of black locust, poplar and willow. *Trees*. 2019;33:1235-63.
32. Woźniak M, Mrówczyńska L, Kwaśniewska-Sip P, Waśkiewicz A, Nowak P, Ratajczak I. Effect of the Solvent on Propolis Phenolic Profile and its Antifungal, Antioxidant, and *in vitro* Cytoprotective Activity in Human Erythrocytes Under Oxidative Stress. *Molecules/Molecules Online/Molecules Annual*. 2020;25:4266.
33. Namchaiw P, Jaisin Y, Niwaspragrit C, Malaniyom K, Auvuchanon A, Ratanachamnong P. The Leaf Extract of *Coccinia grandis* (L.) Voigt Accelerated *in vitro* Wound Healing by Reducing Oxidative Stress Injury. *Oxidative Medicine and Cellular Longevity*. 2021; 2021:1-10.
34. Sunilson JAJ, Muthappan M, Das A, Suraj R, Varatharaj R, Promwichit P. Hepatoprotective Activity of *Coccinia grandis* Leaves Against Carbon Tetrachloride Induced Hepatic Injury in Rats. *International Journal of Pharmacology*. 2009;5:222-7.
35. Kumar D, Singla RK, Sharma R, Sharma P, Kumar L, Kaur N, *et al.* Phytochemistry and Polypharmacological Potential of *Colebrookea oppositifolia* Smith. *Current Topics in Medicinal Chemistry*. 2023;23:334-48.
36. Cai Q, Zhang W, Sun Y, Xu L, Wang M, Wang X, *et al.* Study on the mechanism of andrographolide activation. *Frontiers in Neuroscience*. 2022;16. doi:10.3389/fnins.2022.977376.
37. Nagalekshmi R, Menon A, Chandrasekharan DK, Nair CKK. Hepatoprotective activity of *Andrographis Paniculata* and *Swertia Chirayita*. *Food and Chemical Toxicology*. 2011;49:3367-73.
38. Zakaria ZA, Yahya F, Mamat SS, Mahmood ND, Mohtarrudin N, Taher M, *et al.* Hepatoprotective action of various partitions of methanol extract of *Bauhinia purpurea* leaves against paracetamol-induced liver toxicity: involvement of the antioxidant mechanisms. *BMC Complementary and Alternative Medicine*. 2016;16. doi:10.1186/s12906-016-1110-4.
39. Yahya F, Mamat SS, Kamarolzaman MFF, Seyedan AA, Jakius KF, Mahmood ND, *et al.* Hepatoprotective Activity of Methanolic Extract of *Bauhinia purpurea* Leaves against Paracetamol-Induced Hepatic Damage in Rats. *Evidence-based Complementary and Alternative Medicine*. 2013; 2013:1-10.
40. Zakaria ZA, Sahmat A, Azmi AH, Zainol ASN, Omar MH, Balan T, *et al.* Liver protective effect of chloroform extract of *Bauhinia purpurea* leaves is attributed partly to its antioxidant action and the presence of flavonoids. *Pharmaceutical Biology*. 2023;61:1152-61.
41. Shah MD, Gnanaraj C, Khan MS, Iqbal M. Dillenia suffruticosa L. Impedes Carbon Tetrachloride-Induced Hepatic Damage by Modulating Oxidative Stress and Inflammatory Markers in Rats. *Journal of Environmental Pathology, Toxicology and Oncology/Journal of Environmental Pathology, Toxicology, and Oncology*. 2015;34:133-52.
42. Ezzat MI, Okba MM, Ahmed SH, El-Banna HA, Prince A, Mohamed SO, *et al.* In-depth hepatoprotective mechanistic study of *Phyllanthus niruri*: *In vitro* and *in vivo* studies and its chemical characterization. *PloS One*. 2020;15:e0226185.
43. Tan S, Yulandi A, Tjandrawinata RR. Network pharmacology study of *Phyllanthus niruri*: Potential target proteins and their hepatoprotective activities. *Journal of Applied Pharmaceutical Science*. 2023. doi:10.7324/japs.2023.146937.
44. Kodoli RS, Galatage ST, Killedar SG, Pishwikar SA, Habbu PV, Bhagwat DA. Hepatoprotective activity of *Phyllanthus niruri* Linn. endophytes. *Future Journal of Pharmaceutical Sciences*. 2021;7. doi:10.1186/s43094-021-00243-1.
45. Zarzour RHA, Ahmad M, Asmawi MohdZ, Kaur G, Saeed MAA, Al-Mansoub MA, et al. *Phyllanthus niruri* Standardized Extract Alleviates the Progression of Non-Alcoholic Fatty Liver Disease and Decreases Atherosclerotic Risk in Sprague–Dawley Rats. *Nutrients*. 2017;9:766.
46. Hassan MRA, Said RHM, Zainuddin Z, Omar H, Ali SMM, Aris SA, *et al.* Effects of one-year supplementation with *Phyllanthus niruri* on fibrosis score and metabolic markers in patients with non-alcoholic fatty liver disease: A randomized, double-blind, placebo-controlled trial. *Heliyon*. 2023;9:e16652.
47. Thyagarajan S, Jayaram S, Gopalakrishnan V, Hari R, Jeyakumar P, Sripathi. Herbal medicines for liver diseases in India. *Journal of Gastroenterology and Hepatology*. 2002;17. doi:10.1046/j.1440-1746.17.s3.30.x.
48. Saeed M, Babazadeh D, Arif M, Arain MA, Bhutto ZA, Shar AH *et al.* Silymarin: a potent hepatoprotective agent in poultry industry. *World's Poultry Science Journal*. 2017;73:483-92.
49. Jiang G, Sun C, Wang X, Mei J, Li C, Zhan H, *et al.* Hepatoprotective mechanism of *Silybum marianum* on nonalcoholic fatty liver disease based on network pharmacology and experimental verification. *Bioengineered*. 2022;13:5216-35.
50. Mahli A, Koch A, Czech B, Peterburs P, Lechner A, Haunschild J, *et al.* Hepatoprotective effect of oral application of a silymarin extract in carbon tetrachloride-induced hepatotoxicity in rats. *Clinical Phytoscience*. 2015;1. doi:10.1186/s40816-015-0006-z.
51. Vargas-Mendoza N. Hepatoprotective effect of silymarin. *World Journal of Hepatology*. 2014;6:144.
52. Gillessen A, Schmidt HH -j. Silymarin as Supportive Treatment in Liver Diseases: A Narrative Review. *Advances in Therapy*. 2020;37:1279-301.
53. Alshehade SA, Zarzour RHA, Mathai M, Giribabu N, Seyedan A, Kaur G et al. *Orthosiphon aristatus* (Blume) Miq Alleviates Non-Alcoholic Fatty Liver Disease via Antioxidant Activities in C57BL/6 Obese Mice and Palmitic–Oleic Acid-Induced Steatosis in HepG2 Cells. *Pharmaceuticals*. 2023;16:109.
54. Alshehade SA, Zarzour RHA, Murugaiyah V, Lim SYM, El-Refae HG, Alshawsh MA. Mechanism of action of *Orthosiphon stamineus* against non-alcoholic fatty liver disease: Insights from systems pharmacology and molecular docking approaches. *Saudi Pharmaceutical Journal*. 2022;30:1572-88.
55. Ashraf K, Sultan S, Adam A. *Orthosiphon stamineus* Benth. is an outstanding food medicine: Review of phytochemical and pharmacological activities. *Journal of Pharmacy and Bioallied Sciences*. 2018;10:109.
56. Li Z, Qu B, Zhou L, Chen H, Wang J, Zhang W, *et al.* A New Strategy to Investigate the Efficacy Markers Underlying the Medicinal Potentials of *Orthosiphon stamineus* Benth. *Frontiers in Pharmacology*. 2021;12. doi:10.3389/fphar.2021.748684.
57. Afarani MS, Mohammadi M, Shokri MM, Mohammadzadeh S. Investigation of Protective Effect of *Matricaria chamomilla* L. Extract on Methotrexate-Induced

Hepatotoxicity in Wistar Rat. *Brazilian Archives of Biology and Technology*. 2020;63. doi:10.1590/1678-4324-2020180626.

58. Shebbo S, Joumaa ME, Kawach R, Borjac J. Hepatoprotective effect of *Matricaria chamomilla* aqueous extract against 1,2-Dimethylhydrazine-induced carcinogenic hepatic damage in mice. *Heliyon*. 2020;6:e04082.
59. ????
60. Madrigal-Santillán E, Madrigal-Bujaidar E, Álvarez-González I, Sumaya-Martínez MT, Gutiérrez-Salinas J, Bautista M, *et al.* Review of natural products with hepatoprotective effects. *World Journal of Gastroenterology*. 2014;20:14787.
61. Ullah R, Alsaid MS, Shahat AA, Naser AA, Al-Mishari AA, Adnan M, *et al.* Antioxidant and Hepatoprotective Effects of Methanolic Extracts of *Zilla spinosa* and *Hammada elegans* against Carbon Tetrachloride induced Hepatotoxicity in Rats. *Open Chemistry*. 2018;16:133-40.
62. Silva JB, Paiva KAR, Costa KMFM, Viana GA, Júnior HNA, Bezerra LS, *et al.* Hepatoprotective and antineoplastic potencial of red propolis produced by the bees Apis mellifera in the semiarid of Rio Grande do Norte, Brazil. *Pesquisa Veterinária Brasileira*. 2019;39:744-56.
63. Mahani N, B NG a O, Wulandari NE, Sulaeman NA, Hardinsyah N, Nurjanah NN. Study of Hepatoprotective Activity of Stingless Bee Propolis againts Toxicity of Drugs. *Asian Journal of Pharmaceutical and Clinical Research*. 2021;86-92.
64. Soleimani D, Rezaie M, Rajabzadeh F, Navashenaq JG, Abbaspour M, Miryan M, *et al.* Protective effects of propolis on hepatic steatosis and fibrosis among patients with nonalcoholic fatty liver disease (NAFLD) evaluated by real-time two-dimensional shear wave elastography: A randomized clinical trial. *PTR Phytotherapy Research/ Phytotherapy Research*. 2020;35:1669-79.
65. Nikbaf-Shandiz M, Tutunchi H, Khoshbaten M, Bonab HN, Ebrahimi-Mameghani M. Propolis supplementation in obese patients with non-alcoholic fatty liver disease: Effects on glucose homeostasis, lipid profile, liver function, anthropometric indices and meta-inflammation. *Food and Function*. 2022. doi:10.1039/d2fo01280d.
66. Kismet K, Ozcan C, Kuru S, Celemli OG, Celepli P, Senes M, *et al.* Does propolis have any effect on non-alcoholic fatty liver disease? *Biomedicine and Pharmacotherapy*. 2017;90:863-71.
67. Delgado-Montemayor C, Cordero-Pérez P, Salazar-Aranda R, Waksman-Minsky N. Models of hepatoprotective activity assessment. *Medicina Universitaria/Medina Universitaria*. 2015;17:222-8.
68. Meharie BG, Amare GG, Belayneh YM. Evaluation of Hepatoprotective Activity of the Crude Extract and Solvent Fractions of *Clutia abyssinica* (*Euphorbiaceae*) Leaf Against CCl4-Induced Hepatotoxicity in Mice *Journal of Experimental Pharmacology*. 2020;12:137-50.
69. Lobo JA, S S. Pharmacological Review on *Coccinia grandis* Leaves. *International Journal of Pharmaceutical Sciences Review and Research*. 2022;96-9.
70. Su N, Cc M, Kc M. Ameliorative effect of aqueous seed extract of *Delonix regia* on hyperglycemia, liver function and lipid profile levels in Streptozotocin induced Diabetic Male wistar rats. *Pharmacy and Pharmacology International Journal*. 2019;7. doi:10.15406/ppij.2019.07.00242.
71. Dhanasekar JJ, Ganapathy M. Hepatoprotective Effect of Cassia auriculata L. Leaf Extract on Carbon Tetrachloride Intoxicated Liver Damage in Wister Albino Rats. *Asian Journal of Biochemistry*. 2010;6:104-12.
72. Girish C, Pradhan SC. Indian herbal medicines in the treatment of liver diseases: problems and promises. *Fundamental and Clinical Pharmacology*. 2011;26:180-9.
73. Ilyas U, Katare DP, Aeri V, Naseef PP. A review on hepatoprotective and immunomodulatory herbal plants. *Pharmacognosy Reviews/Bioinformatics Trends/ Pharmacognosy Review*. 2016;10:66.

Cite this article: Rajappa RPM, Nallupillai P, Krishna KL, Ramesh MM, Venkatappa AH. Exploring the Mechanisms and Dosages of Herbal Hepatoprotective Agents. Pharmacog Res. 2024;16(4):706-17.