

AN INSIGHT INTO THE CHEMICAL AND NATURAL HEPATOPROTECTIVE AGENTS

Abstract

The most significant organ that is vital to the preservation of the body's many physiological functions is the liver. It is involved in metabolism, secretion, and storage, among other essential processes. It is involved in metabolism, secretion, and storage, among other essential processes. It is essential for the excretion and detoxification of numerous endogenous and exogenous substances. Liver damage or dysfunction is a serious health issue that affects the pharmaceutical industry, drug regulatory organizations, and medical professionals alike. One important source of hepatoprotective medications is medicinal herbs. Preparations made of single or multiple herbs have been used to treat liver diseases. Over 700 herbal preparations, both mono and poly, in the form of decoctions, tinctures, tablets, and capsules derived from over 100 plants are reportedly in clinical use. A total of 178 medicinal plants are said to have hepatoprotective properties based on the literature review. Numerous hepatoprotective herbs have been documented in the literature. For many years, liver disease has been treated with herbal remedies. The goal of the current study is to gather information on phytochemicals from hepatoprotective herbs that show promise.

Keywords: Liver disease, management, hepatoprotective, phytochemicals

Authors

Nadim Siddique

Goel Institute of
Pharmaceutical Sciences
Lucknow, India.

Amit K Nigam

Goel Institute of Pharmacy
and Sciences
Lucknow, India.

Karuna S Shukla

Goel Institute of
Pharmaceutical Sciences
Lucknow, India.

Dr Akash Ved

Faculty of Pharmacy
Dr APJ Abdul Kalam Technical
University
Lucknow, Uttar Pradesh, India.

Krishna Kumar

Goel Institute of
Pharmaceutical Sciences
Lucknow, India.

Monu Kashyap

Goel Institute of
Pharmaceutical Sciences
Lucknow, India.

Awadhesh Kumar

Goel Institute of
Pharmaceutical Sciences
Lucknow, India.

I. INTRODUCTION

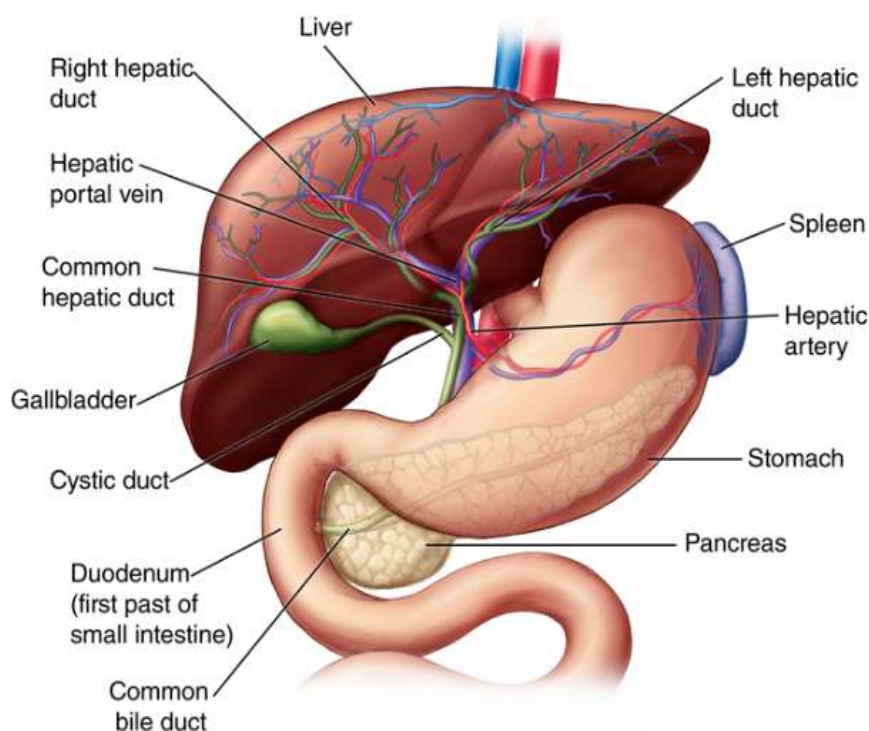
The region in the upper right quadrant of the abdomen encompasses a large organ known as the liver [1]. It is a multipurpose auxiliary organ of the digestive system that carries out several vital tasks, including bile generation, detoxification, protein synthesis, and nutrition storage. It makes up about 2% of our total weight and is the most significant gland in the human body, weighing around 1.5 kg [2]. It supports fundamental homeostatic systems and functions in synchrony with several other organs.

The liver is enveloped by the visceral peritoneum, except for a specific region known as the naked area, where it directly interfaces with the diaphragm [3].

The liver receives blood from two separate sources, which are as follows:

- The hepatic artery is responsible for the passage of oxygenated blood into the liver.
- The hepatic portal vein facilitates the transportation of blood rich in nutrients.

The liver retains around one pint, or 13% of the total blood volume inside the human body at any moment. The liver is comprised of two main lobes [4]. Both entities consist of 1,000 lobules, smaller lobes, further subdivided into 8 segments. The common hepatic duct is generated by amalgamation of lobules and small ducts, which merge with larger ones. The common hepatic duct uses the common bile duct as a conduit for transporting hepatic bile, synthesised by hepatocytes, to the gallbladder and the duodenum, the first portion of the small intestine [5,6].



II. FUNCTIONS OF THE LIVER

After the skin, the liver is the second largest organ in the body. It is located just below the ribs on the right side and is about the size of a football. The liver separates nutrients and waste throughout the meal digestion process. It also produces bile, which aids digestion and flushes the body of impurities [7].

The liver is responsible for regulating the majority of chemicals present in the bloodstream, in addition to its role in the excretion of bile. This process facilitates the elimination of waste from the liver [8]. The liver processes all blood that exits the stomach and intestines. When the liver processes this blood, it breaks down, produces, and balances nutrients. It also metabolizes medicines into harmless, simplerharmless, or simpler forms for the rest of the body to utilize. The liver is involved in over 500 essential processes. Among the most popular features are the following ones [9, 10]

1. The production of bile, which is beneficial to the small intestine in terms of both waste elimination and fat breakdown.
2. The synthesis of certain proteins for utilisation in blood plasma
3. The conversion of spare sugar into glycogen for storage (glycogen may subsequently be metabolized back to glucose for energy), as well as the maintenance of a stable glucose level and the production of glucose when required.
4. Maintenance of the amounts of amino acids in the blood, which are the fundamental components of proteins.
5. Transformation of harmful ammonia to urea (urea is an end product of protein synthesis and is eliminated in the urine).
6. Eliminating medicines and other potentially harmful chemicals from the blood
7. Clotting of the blood and its regulation.
8. Protecting oneself against diseases by producing immunological factors and clearing the circulation of bacteria
9. Eliminating bilirubin, including its removal from red blood cells, is a significant process. Jaundice manifests when there is an excessive buildup of bilirubin, resulting in the yellowing of the skin and eyes.

The bile or blood contains the waste products the liver excretes after breaking down harmful substances. Bile byproducts exit the body as faeces after passing through the stomach. The kidneys filter out waste from the body and excrete them as urine.

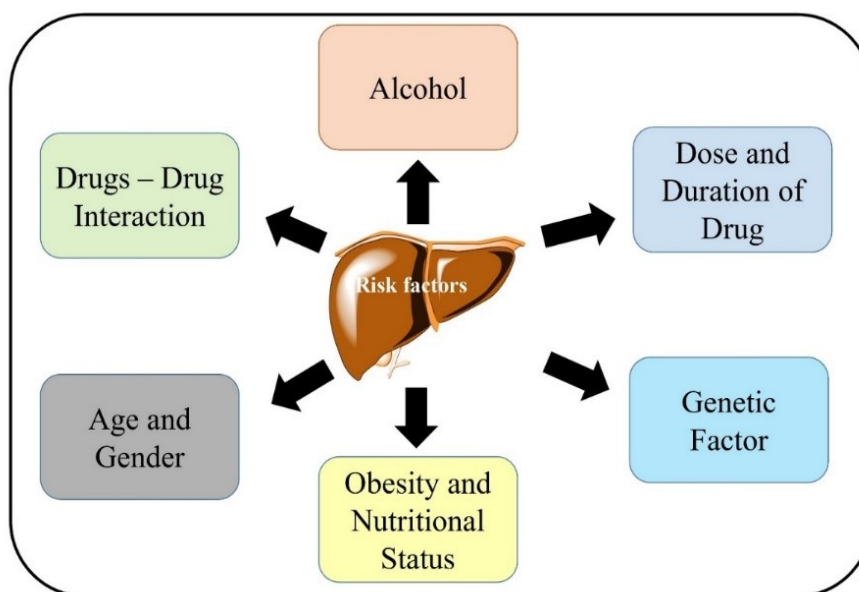
It involves many vital functions, including metabolism, storage, and secretion. It is necessary for the removal and detoxification of several internal and external toxins. Consequently, any harm done to it or impairment of its function has detrimental effects on the affected individual's health. Even though viral infection is one of the main causes of hepatic impairment, hepatitis-related liver cirrhosis is responsible for around 18,000 fatalities annually. Metals, proteins, glycogen, and other vitamins are stored there. It also helps regulate blood volume and supports the immune system by transporting blood from the portal to the systemic circulation and its reticuloendothelial system [11]. The human body recognizes almost all drugs as foreign substances (xenobiotics), and they undergo a series of chemical events, including metabolism, to be ready for excretion. It takes chemical alterations to: (a) reduce fat solubility; and (b) modify biological activity. Although nearly

every tissue in the body is capable of metabolizing chemicals to some degree, the smooth endoplasmic reticulum in the liver functions as the principal "metabolic clearing house" for both endogenous chemicals (such as cholesterol, steroid hormones, fatty acids, and proteins) and foreign compounds (such as medications) [12]. Owing to its essential role in removing and altering chemicals, the liver is susceptible to damage from medications.

Because it is the site of drug metabolism and biotransformation, the liver is the body's defense against toxic foreign chemicals. This leads to the liver being exposed to different amounts of drugs, chemicals, and other xenobiotics, eventually damaging the liver. Every year, liver problems claim the lives of around 2 million people globally. Of these, 1 million are associated with complications from cirrhosis, while the other half are believed to be due to liver cancer and viral hepatitis. Currently, the leading causes of mortality are cirrhosis (ranked 11th with 1.16 million deaths) and liver cancer (ranked 16th with 788,000 fatalities), contributing to 3.5% of global mortality. Worldwide, excessive alcohol use is the main factor contributing to liver impairment. Approximately half, or 75 million, of the projected 2 billion alcohol drinkers worldwide have been diagnosed with alcohol-related illnesses, notably liver diseases associated with alcohol intake, according to World Health Organization research [13].

III. RISK FACTORS

Hepatic diseases may arise from a variety of etiologies. The bacteria that cause the most serious types of hepatic illness include cytomegalovirus, Epstein-Barr virus, yellow fever virus, hepatitis viruses A, B, and C. Metabolic syndrome, xenobiotics (drugs, alcohol, and chemicals), autoimmune illnesses and liver malignancies are other variables that contribute to the condition.



Risk factors for liver disorders

IV. LIVER DISORDERS

The phrase "hepatic disease" encompasses a diverse array of disorders that have the potential to impact and impair the functionality of the liver. The progression of a liver illness may ultimately lead to the development of fibrosis or cirrhosis. When the replacement of healthy liver tissue by scar tissue exceeds a certain threshold, the liver's normal functioning becomes compromised. If liver sickness remains untreated, it might potentially result in liver failure and liver cancer [14].

1. Causes

Many types of liver disease are caused by various factors [15, 16, 17].

- **Viral infections:** Infectious diseases caused by viruses, such as hepatitis A, hepatitis B, and hepatitis C, are pathological conditions resulting from viral infections.
- **Issues pertaining to the immune system:** When the immune system erroneously targets the liver, autoimmune liver disorders may arise. Primary biliary cholangitis and autoimmune hepatitis are two examples of illnesses that an autoimmune response in the liver may cause.
- **Inherited disorders:** Includes a subset of liver disorders that arise due to a hereditary abnormality passed down from one's parents. Wilson's disease and hemochromatosis are two instances of liver diseases that may be passed down from generation to generation.
- **Cancer:** It refers to the pathological condition characterized by the uncontrolled proliferation of aberrant cells inside the liver, potentially leading to the formation of tumors. The tumors in question have the potential to be either benign, indicating a noncancerous nature, or malignant, indicating the presence of liver cancer.
- **Excessive ingestion of toxic substances:** A condition known as alcohol-related fatty liver disease may develop as a direct result of consuming alcohol.
- **Non-alcohol-related fatty liver disease (NAFLD):** It is a consequence of excessive fat consumption. Non-alcoholic fatty liver disease, often known as NAFLD, is becoming more common at the same time as obesity and diabetes are becoming more common in the general population.
- **Manifestation or clinical indicators:** Certain forms of liver disease, such as non-alcoholic fatty liver disease, have a low incidence of symptomatic manifestations. In the case of several medical disorders, the predominant manifestation is jaundice, characterized by the discoloration of the skin and sclerae, resulting in a yellowish appearance. The condition of jaundice arises due to impaired hepatic clearance of bilirubin [18].
- **Other signs of liver disease**
 - Abdominal discomfort, particularly on the right side.
 - Easy to bruise.
 - Discoloration of urine and stool.
 - Fatigue.
 - Symptoms of nausea or vomiting.
 - Arm or leg swelling (edema)

2. Types of liver disease ^[19, 4, 20, 6]

- **Hepatitis:** The liver inflammation is most often brought on by illnesses caused by viruses. There are several distinct forms of viral hepatitis, including Hepatitis A, Hepatitis, Hepatitis C, Hepatitis D, and Hepatitis E.
- **Alcoholic Liver Disease:** Consumption of alcohol in large quantities and over an extended period is the root cause of this condition, which manifests as inflammation, accumulation of fat, and finally, liver cirrhosis.
- **Non-Alcoholic Fatty Liver Disease (NAFLD):** A condition characterized by the deposition of adipose in liver cells and often related to diabetes, overweight, and a metabolic syndrome.
- **Cirrhosis:** The last stage of many liver illnesses, is characterized by the replacement of healthy hepatic tissue by scar tissue, which ultimately results in an impairment of liver physiology. Cirrhosis is a condition that has a number of potential causes, the most common of which are excessive alcohol use, viral hepatitis, and fatty liver disease.
- **Liver Fibrosis:** The early stage of scarring in the liver, often preceding cirrhosis. It can result from various chronic liver diseases.
- **Autoimmune Hepatitis:** A condition in which the body's immune system mistakenly attacks the liver cells, leading to inflammation and liver damage.
- **Primary Biliary Cholangitis (PBC):** This is a description of a kind of autoimmune disorder that particularly targets the bile ducts located in the liver, resulting in inflammation and subsequent destruction.
- **Primary Sclerosing Cholangitis (PSC):** Another autoimmune disorder that causes inflammation and scarring in the bile ducts both inside and outside the liver.
- **Hemochromatosis:** A genetic disorder that causes the body to absorb and store too much iron, which can lead to iron accumulation in the liver and other organs.
- **Wilson's Disease:** A genetic disorder that causes copper to accumulate in various organs, particularly the liver and brain.
- **Gilbert's Syndrome:** A benign genetic condition that leads to intermittent bilirubin elevations in the blood, causing mild jaundice.
- **Liver Cancer (Hepatocellular Carcinoma):** Cancer that originates in the liver, often as a complication of underlying chronic liver disease.
- **Budd-Chiari Syndrome:** A rare condition where blood flow out of the liver is blocked, usually due to a clot in the hepatic veins.
- **Acute Liver Failure:** Sudden and severe impairment of liver function, often resulting from viral hepatitis, drug-induced liver injury, or other acute causes.
- **Alpha-1 Antitrypsin Deficiency:** A genetic disorder that can lead to liver and lung problems due to the buildup of abnormal proteins

It's important to note that some liver diseases can be preventable or manageable through lifestyle changes, medications, and medical interventions. If you suspect you have a liver condition or are at risk, it's best to consult a healthcare professional for proper diagnosis and guidance.

V. HEPATOPROTECTIVE AGENTS

Hepatoprotective medicines are a class of pharmaceutical agents that have the potential to boost hepatic function, stimulate the regeneration of liver cells, and facilitate liver detoxification. However, it is important to note that there is currently no consensus about categorizing these drugs. Based on their distinct modes of action, these medications may be categorized as detoxification agents (such as NAC and GSH), anti-inflammatory agents (such as preparations containing Glycyrrhizic acid), hepatocyte membrane protectors (such as PPC), and antioxidant agents (such as Bicyclol and Silymarin) [23, 24].

The therapeutic importance of allopathic medications in the treatment of liver disorders:

The frequency of medication review has increased as a result of recent breakthroughs, which include the use of evidence-based approaches, standard pharmacopeia, and randomized placebo control clinical studies to assess the clinical effectiveness of contemporary medicine [25]. Therapeutic interventions developed with artificial targets and lead compounds, guided by conventional medicine concepts, are associated with a significant risk-benefit ratio, often entailing high costs and demonstrating diminished effectiveness. The following table presents many liver-protective medications and their corresponding harmful effects [26, 27].

Table 1: Commonly used allopathic medicine for liver protection with clinical application

S. no	Modern medicine	Disease condition	Mechanism of action	Clinical outcomes	References
1	Corticosteroids	The objective is to decrease the production of cytokines and exhibit antifibrotic properties.	Many activated inflammatory genes may be successfully deactivated by inhibiting histone acetyltransferase (HAT) and recruiting histone deacetylase 2 (HDAC2) activity to the transcription complex.	Recent research findings indicate that the impact of this drug has diminished in contemporary times, and its potential as a hepatoprotective agent in the future is likewise receiving less recognition.	[28]
2	Interferons	Antiviral and antifibrotic	The replication of hepatitis B and C viruses is hindered by the reduction of RNA transcription, which is a result of the presence of covalently closed circular DNA.	The treatment of hepatitis B and C is possible. The antifibrotic action has yet to be evaluated and substantiated in human subjects. Adverse effects seen at therapeutic dosage levels include symptoms such as sadness, anxiety, agitation, suicidal thoughts, and maybe even suicide.	[29]
3	Lamivudine	Hepatitis B and cirrhosis	Intracellular metabolism of the chemical yields its	It is possible that prolonged use will lead to the rise of hepatitis B virus resistance.	[30]

			triphosphate derivative, which then faces competition from cytosine triphosphate for incorporation into the developing viral DNA strand.		
4	Propylthiouracil	Alcohol-related disorders of the liver	The individual's response involves interacting with certain oxidising agents produced during the respiratory burst in neutrophils, which afterwards function as antioxidants. This interaction leads to the inhibition of alcohol-induced liver necrosis.	Induce a state of hypothyroidism in people with reduced metabolism.	[31]
5	Colchicine	In opposition to the occurrence of gout, the use of antifibrotic agents has been proposed.	The breakdown of tubulin results in the subsequent down-regulation of many channels of inflammation and the control of innate immune responses.	Recently, there has been a lack of evidence to support the beneficial characteristics. At elevated concentrations, the substance exhibits significant toxicity.	[32]
6	Pentoxifylline	Alcohol-related severe hepatitis	Prevents the production of TNF-alpha and inflammation	The remarkable safety profile of this treatment has significant therapeutic implications for hepatorenal syndrome. It is recommended that those who exhibit hypersensitivity to xanthine should refrain from using pentoxifylline.	[33]
7	Ursodeoxycholic acid	Non-alcoholic fatty liver disease (NAFLD)	This substance hinders the process of DNA repair and the functioning of coenzyme A, cyclic AMP, p53, phagocytosis, and the stimulation of nitric oxide synthetase.	The use of this medication has shown efficacy in improving liver histology, enzymatic activity, and mitigating oxidative stress, hence proving its utility in the management of hepatobiliary illnesses. Prolonged administration of ursodeoxycholic acid in human subjects may lead to a depletion of taurine levels.	[34]

8	Rosiglitazone	Non-alcoholic fatty liver disease (NAFLD)	A member of the peroxisome proliferator-activated receptor (PPAR) family of intracellular receptors (PPAR) is activated.	Raised possibility of a cardiac arrest	[35]
---	---------------	---	--	--	------

Natural hepatoprotective agents

1. **Silymarin (family: Asteraceae):** Silymarin, an ingredient of *Silybum marianum* (L.) Gaertn., or “milk thistle,” is one of the conventional liver-treating plants. Dried seeds contain four flavonolignan isomers—silybin, isosilybin, silydianin, and silychristin—which are important plant-based constituents. The intricate combination of these four flavonolignan isomers is silymarin. Silymarin protects the liver by modulating enzymatic and nonenzymatic hepatic biochemical markers via inducing Nrf2 expression. Numerous hepatic injury studies have shown silymarin's anti-inflammatory effects. Silymarin reduced NF- κ B, IL-6, MMP-2, MMP-13, TGF- β 1, Krueppel-like factor, collagen α 1, and PDGF signalling in rats with alcoholic fatty liver models. Similarly, silymarin inhibits HCV-infected cells by activating NF- κ B and nuclear translocation through TNF- α . Individuals tolerate silymarin well and safely. Silymarin-loaded solid nanoparticles improve its antioxidant and hepatoprotective effects by overcoming its poor dissolution in water [36].

2. **Glycyrrhizin (family: Leguminaceae):** The triterpenoid glycoside known as glycyrrhizin, which is obtained from the root of the liquorice plant, has historically been used in traditional medicinal practices in several nations including Nepal, India, and China, for the treatment of jaundice. The composition of the substance includes potassium and calcium salts of glycyrrhizinic acid, beta-sitosterol, hydroxycoumarins, and flavonoids. Glycyrrhizin has hepatoprotective effects via the augmentation of antioxidant defence mechanisms and the attenuation of inflammatory processes. Glycyrrhizin has been shown to have the capacity to inhibit or impede the binding of HMGB1 to the promoter region of GSTO1, hence mitigating the inflammatory response. In the context of liver fibrosis induced by CCl₄, it was shown that both glycyrrhizin and its metabolite, glycyrrhetic acid, had inhibitory effects on the expression of the collagen α 1(I) gene. Glycyrrhetic acid has been shown to induce hepatic cell DNA synthesis via its binding to the epithelial growth factor receptor (EGFR) and subsequent activation of extracellular signal-regulated kinases (ERK2), so promoting liver regeneration. In individuals diagnosed with hepatic illness, the administration of intravenous glycyrrhizin resulted in a significant decrease in blood alanine transaminase levels during a 12-week treatment period. Additionally, after 52 weeks of treatment, this intervention had beneficial benefits on inflammation-induced liver fibrosis and necrosis, especially in situations where IFN- α -based therapy had failed. In the elderly population, the prevention of liver cirrhosis linked to HCV infection has also shown effectiveness. Equine models with hepatic damage were used to study the effects of 18 β -glycyrrhetic acid on oxidative stress and inflammatory markers both in vitro and in vivo. As expected, the results showed that 18 β -glycyrrhetic acid successfully reduced oxidative stress and inflammatory markers. The up-regulation of Nrf2 target genes and the down-regulation of NF- κ B produced this result [37, 38].

- 3. Andrographolide and neoandrographolide (family: Acanthaceae):** Andrographolide and neoandrographolide are the primary bioactive compounds found in the perennial plant. *Andrographis paniculata* Nees, which is extensively referred to as the "king of bitters" because of its distinctive bitter taste. This plant is renowned for its efficacy in treating liver problems. The main bioactive ingredient is derived from the leaves and is a member of the diterpene lactone class. The components are specifically neoandrographolide, andrographolide, andrographine, panicoline, paniculide-A, paniculide-B, and paniculide-C, as well as 14-deoxy-11-dehydroandrographolide, 14-deoxy-11-oxoandrographolide, and deoxy-andrographolide. Andrographolide demonstrates the ability to impede inflammation, angiogenesis, and fibrosis in an animal model of chemically induced liver damage via its antioxidant and anti-inflammatory pathways. Andrographolide has been shown to counterbalance the upregulation of many proteins and genes involved in oxidative stress response, such as hypoxia-inducible factor-1 alpha, superoxide dismutase (SOD-1), heme oxygenase-1 (HO-1), and glutathione S-transferase (GST1). This compound effectively increases the nucleus concentration of Nrf2 and enhances its DNA-binding ability, hence mitigating oxidative stress-induced gene expression. Additionally, it has been shown that the p38 mitogen-activated protein kinase (MAPK)/Nrf2 pathway plays a role in the overexpression of HO-1, which exhibits anti-hepatitis C virus (HCV) action. Furthermore, andrographolide has been shown to contribute to the downregulation of hypoxia-inducible genes, including vascular endothelial growth factor (VEGF). It also has the ability to decrease the production of TNF- α and cyclooxygenase-2 (COX-2). As a result, andrographolide effectively lowers liver hypoxia and mitigates hepatic apoptosis and fibrosis in rats. The substance exhibits a reduction in blood levels of TNF- α and interleukin-1 beta (IL-1 β), as well as a drop in hepatic expression of TGF- β , cannabinoid receptor type 1 (CBR1), and Bax. The anticipated mechanism behind the reduction of serum levels of TNF- α and IL-1 β involves the downregulation of JNK and ERK phosphorylation. The findings of a research investigation involving mice subjected to a high-fat diet (HFD) and treated with andrographolide revealed a reduction in cellular lipid buildup [39, 40, 63].
- 4. Picroside I and kutkoside (family: Scrophulariaceae):** Picroside and kutkoside are the primary bioactive compounds found in the roots and rhizomes of *Picrorhiza kurroa* Royle, a plant popularly referred to as "Kutki" or "Kutaki." These compounds have been traditionally used for the treatment of hepatic disorders over an extended period of time. The primary bioactive compounds are kurkoside, apocynin, drosin, cucurbitacin glycoside, and iridoid glycosides such as picroside 1, 2, and 3. Kutkin is synthesised by the combination of picroside I and kutkoside in a proportionate ratio of 1:2. Picroside-I and kutkoside have been shown to have hepatoprotective characteristics via their ability to stabilise cell membranes, reduce lipid levels, and act as antioxidants. Additionally, these compounds have been seen to promote liver regeneration in rats by stimulating the creation of nucleic acids and proteins. Picroside-I and kutkoside have been identified as compounds with the ability to scavenge free radicals, namely the superoxide anion (O $_2^{\bullet}$), and have inhibitory effects on lipid peroxidation in liver tissue. Additionally, the study demonstrated the restoration of bilirubin levels and the activity of serum liver indicators including AST, ALT, ALP, and LDH in an animal model of acetaminophen-induced liver damage. This protective effect was shown via the prevention of hepatocyte injury, thereby confirming its hepatoprotective properties. Additionally, picroside has been shown to decrease lipid peroxidation, restore glutathione metabolism to normal levels, and suppress

hepatocarcinogenesis induced by N-nitrosodiethylamine in rats. This is achieved by an increase in the lifespan of rats with tumours. Paracetamol has been seen to decrease the expression of LDL receptors on the surface of cells. Conversely, it has been found to increase the levels of conjugated dienes in liver cells. Additionally, it has a role in maintaining the balance of oxidation and reduction processes, which is crucial for the overall health of the liver [41, 42].

- 5. Curcumin (family: Zingiberaceae):** Curcumin is the main curcuminoid in *Curcuma longa*, or "turmeric." Turmeric has long been used in traditional medicine to treat bilirubin-related liver illnesses such as jaundice and other hepatic issues. Curcuminoids are structurally related phenolic compounds found in turmeric rhizomes. Curcumin, demethoxycurcumin, and bisdemethoxycurcumin are the main curcuminoids in turmeric rhizomes. Curcumin is a diferuloylmethane, however it is typically found as keto-enol. This chemical fuses diferulic acid with methylene or another carbon group. Curcumin's antioxidant properties and activation of phase 2 detoxifying/antioxidant enzymes including HO-1, NADPH quinone oxidoreductase-1 (NQO1), and Nrf2/Keap1/ARE pathway may protect the liver. In addition, this chemical in food decreases oxidative stress, Cytochrome P450 2E1 (CYP2E1), and Prx1 expression while increasing Prx6 expression. Hepatotoxins cause oxidative stress, which activates MAPKs, NF- κ B, and STAT3. Several mechanisms may activate this. Curcumin reduces TLR2, TLR4, and HMGB1 synthesis in rats with fibrogenesis-associated ligand molecules, according to studies. The T-cell-mediated hepatitis caused by Concanavalin A was reduced by curcumin in mice. This was largely to avoid liver irritation. Curcumin also reduces liver damage from lipopolysaccharide (LPS)/D-galactosamine (D-GalN) by suppressing Sirtuin (silent mating type information regulation 2 homolog)-1 (SIRT1) mRNA levels. It also suppresses the expression of genes for receptors implicated in advanced glycation in hepatic stellate cells (HSCs) via enhancing PPAR activity and lowering oxidative stress. Curcumin also protects hepatocytes from paracetamol-induced mortality by decreasing Bax and caspase-3 and boosting antiapoptotic genes. The Bcl-2 mRNA gene is downregulated and the p53 protein gene is upregulated in thioacetamide-induced cytotoxicity by curcumin. This helps wounded cells die, reducing hepatic inflammatory gene expression and fibrogenesis. Curcumin's antioxidant, antiviral, and anti-inflammatory properties may protect mice against human cytomegalovirus [43, 44].
- 6. Phyllanthin and hypophyllanthin (family: Euphorbiaceae):** Phyllanthin is a powerful hepatoprotective lignan that may be extracted from the *Phyllanthus niruri* Linn plant. Herbal treatment for jaundice and other conditions related to the liver has been used for a very long time and is popularly known as "gale of the wind." Alkaloids, astragalin, brevifolin, ellagitannins, amariin, repandusinic acid, phyllanthusin D galocatechins, geraniin, hypophyllanthin, lignans, nirutin, phyllanthin, and phyllanthinol are the primary active chemical ingredients. Other compounds include lignans, geraniin, and hypophyllanthin. In terms of their chemical composition, phyllanthin and hypophyllanthin are lignans that have been extracted from the hexane extract. These lignans have been shown to be hepatoprotective agents. It has been shown that *Phyllanthus niruri* is a good treatment for infectious hepatitis as well as other forms of liver illness. This plant's ethanolic extract contains substantial hepatoprotective properties, both in vitro and in vivo research has shown this to be the case. Because of its ability to protect and purify the liver, it was traditionally used in India as a treatment for jaundice in children. According

to the findings of a research conducted in the United Kingdom, Phyllanthus extract has the potential to be a successful therapy for both acute and chronic forms of hepatitis in children. Both phyllanthin and hypophyllanthin have the ability to protect rat liver cells against cytotoxicity and toxicity caused by carbon tetrachloride. Phyllanthin is more potent than hypophyllanthin in this regard. Additionally, the "fatty liver" condition may be normalised by these lignans, which also protect the liver from harm caused by alcohol. It is via the mechanism of inhibiting superoxide and hydroxyl radicals as well as lipid peroxidation that phyllanthus lignin is able to exert its hepatoprotective properties [45].

- 7. Berberine (family: Berberidaceae):** Phyllanthin is a powerful hepatoprotective lignan that may be extracted from the Phyllanthus niruri Linn plant. Herbal treatment for jaundice and other conditions related to the liver has been used for a very long time and is popularly known as "gale of the wind." Alkaloids, astragalins, brevifolin, ellagitannins, amarillin, repandusinic acid, phyllanthusin D gallo catechins, geraniin, hypophyllanthin, lignans, nirutin, phyllanthin, and phyllanthinol are the primary active chemical ingredients. Other compounds include lignans, geraniin, and hypophyllanthin. In terms of their chemical composition, phyllanthin and hypophyllanthin are lignans that have been extracted from the hexane extract. These lignans have been shown to be hepatoprotective agents. It has been shown that Phyllanthus niruri is a good treatment for infectious hepatitis as well as other forms of liver illness. This plant's ethanolic extract contains substantial hepatoprotective properties, both in vitro and in vivo research has shown this to be the case. Because of its ability to protect and purify the liver, it was traditionally used in India as a treatment for jaundice in children. According to the findings of a research conducted in the United Kingdom, Phyllanthus extract has the potential to be a successful therapy for both acute and chronic forms of hepatitis in children. Both phyllanthin and hypophyllanthin have the ability to protect rat liver cells against cytotoxicity and toxicity caused by carbon tetrachloride. Phyllanthin is more potent than hypophyllanthin in this regard. Additionally, the "fatty liver" condition may be normalised by these lignans, which also protect the liver from harm caused by alcohol. It is via the mechanism of inhibiting superoxide and hydroxyl radicals as well as lipid peroxidation that phyllanthus lignin is able to exert its hepatoprotective properties [46].
- 8. Embelin (family: Myrsinaceae):** Embelin, scientifically referred to as "2,5-dihydroxy-3-undecyl-1,4-benzoquinone," is a bioactive compound found in the leaves of Embeliaribes Burm.f., a plant usually referred to as "false black pepper." It is recognised for its ability to scavenge free radicals and provide protection to the liver. The primary bioactive compounds included in the substance are embelin, christembin, quercitol, and resin. The primary mechanism through which embelin exhibits its hepatoprotective action is via its ability to scavenge free radicals and inhibit lipid peroxidation. The administration of embelin in carbon tetrachloride-treated rats has been shown to have regulatory effects on many liver indicators, including AST, ALT, ALP, LDH, bilirubin γ -glutamyltranspeptidase, and total protein levels. A study conducted on the mitochondria of rat liver shown that embelin had inhibitory effects on lipid peroxidation. Furthermore, the treatment of embelin was found to restore the impaired level of superoxide dismutase. In addition, the study aimed to investigate the extrapolation of the mechanism and reaction rate of embelin with hydroxyl radicals. This was achieved by using nanosecond pulse radiolysis, a method used to oxidise single electrons and generate a radical species known as "organohaloperoxyl." The redox potential of embelin was also assessed in the

research, which demonstrated that embelin has strong free radical scavenging activity under physiological settings [47].

- 9. Resveratrol:** Resveratrol, chemically known as "trans-3,5,4'-trihydroxystilbene," is a naturally occurring polyphenol compound with strong antioxidant properties found in *Vitis labrusca*, also known as "grapes," *Vaccinium myrtillus* L., "blueberries," and *Rubus idaeus* L., "raspberries." Microbial and fungal infections cause plants to generate resveratrol. Resveratrol reduces oxidative stress in the liver following hepatocyte injury via modifying Nrf2 and NF- κ B expression and downregulating HO-1 and iNOS gene expression. This boosts phase 2 enzyme free radical scavenging. In addition, it reduces proinflammatory cytokines such IL-2, IL-6, and TNF- α in concanavalin A-induced autoimmune hepatitis. Resveratrol protects the liver from excessive cholesterol by upregulating autophagy and downregulating Bax, caspase-3, and caspase-8. After that, resveratrol decreases isoniazid and rifampicin hepatotoxicity through altering mouse hepatic cell SIRT1 mRNA expression. This decreases liver oxidative stress, cytokine production, and PPAR γ gene expression. Resveratrol also prevents acetaminophen-induced hepatotoxicity by upregulating SIRT1 expression, downregulating p53 signalling, increasing cell nuclear antigen, promoting hepatic cell proliferation, improving liver regeneration, and increasing cyclin D1 and Cdk4 levels [48].

Table 2: Major Phytoconstituents with hepatoprotective activity

SNo	Phytoconstituents	Plant name	Hepatotoxicity-inducing agents	Finding of study	Mechanism of hepatoprotective activity	References
1	Acteoside: a phenylethanoid glycoside	<i>Plantago major</i> L	Carbon tetrachloride	The drug reduced blood ALT, AST, ALP, and GGT enzymes and total and direct bilirubin. The liver decreased LPO and increased GSH.	The compound effectively inhibits the P50-mediated bioactivation of CCL4 and demonstrates notable antioxidant properties by scavenging superoxide free radicals.	[49]
2	Alpha amyirin: Pentacyclitriterpene	<i>Alstoniascholaris</i> Linn	Carbon tetrachloride	AST, ALT, LDH, ALP, ACP, SDH, GDH, total bilirubin, and protein reduced. Higher levels of glutathione, ceruloplasmin, β -carotene, vitamin C, and vitamin E are seen. Elevated liver antioxidants including SOD,	Serum GGT, AST, ALT, LDH, ALP, ACP, SDH, GDH, and total bilirubin decreased in the research. However, glutathione, ceruloplasmin, β -carotene, vitamin C, and vitamin E levels were shown to be higher. Hepatic antioxidant enzymes including SOD, CAT, GPx, GR, and GST	[50]

				CAT, GPx, GR, and GST and oxidative stress indicators like LPO, 5'-ribonucleotidase, acid ribonuclease, and succinic dehydrogenase.	increased. LPO, 5'-ribonucleotidase, acid ribonuclease, and succinic dehydrogenase also increased.	
3	Triterpenoid: asiatic acid	<i>Potentillachinensis</i>	Lipopolysaccharide/Dgalactosamine	The liver pathology improved when ALT and AST values decreased.	The inhibition of MAPK and NF-κB is achieved by the partial stimulation of PDCD4 and the upregulation of Nrf2, which occurs in a manner reliant on the activation of the AMPK/GSK3β pathway. This leads to the suppression of oxidative stress and inflammation.	[51]
4	Pentacyclic triterpenoidsaponin: asiaticoside	<i>Centellaasiatica</i>	Lipopolysaccharide/D-galactosamine	The dose-dependent reduction in elevated blood ALT, hepatocyte apoptosis, and caspase-3 activity was observed.	Inhibits TNF alpha and MAPKs	[52]

				Additionally, hepatic pathological damage improved. The liver tissue also showed decreased phospho-p38 MAPK, phospho-JNK, phospho-ERK, and TNF-alpha mRNA expression.		
5	Saponin: cristatain	<i>Celosia cristata</i> L	CCl ₄ and N,N-dimethyl formamide	The serum values of AST, ALT, and ALP exhibited a notable decrease, and histopathological assessments showed a contrast with the control group.	The compound inhibits the activities of caspase-3 and caspase-8, hence suppressing apoptosis in liver cells. The compound has antioxidant properties by effectively scavenging hydroxyl and DPPH-free radicals.	[53]
6	Oleanolic acid saponins: celosin A and celosin B	<i>Semen celosiae</i>	Carbon tetrachloride	The intervention resulted in the suppression of serum levels of AST, ALT, and	Both compounds have notable hepatoprotective benefits as a result of their antioxidant	[54]

				ALP, while simultaneously enhancing the serum levels of GSH_PX, MDA, CAT, and SOD.	characteristics, which lead to a reduction in serum liver biochemical indicators and liver antioxidant enzymes.	
7	Sesquiterpeneglycoside: cichotyboside	<i>Cichoriumintybus</i>	Carbon tetrachloride	Significant hepatoprotective efficacy was shown by lowering high levels of liver enzymes such as AST and ALT	The administration of the substance results in a decrease in liver weight and liver protein levels. Additionally, it has an inhibitory effect on oxidative stress by enhancing the levels of reduced glutathione and reducing lipid peroxidation.	[55]
8	Flavonol glycoside: visconoside C	<i>Cleome viscosa</i> L	Carbon tetrachloride	The compound demonstrated a noteworthy hepatoprotective effect via its antioxidant mechanism, with quercetin serving as the standard reference.	Demonstrates the capacity to scavenge free radicals and restore damaged membrane function.	[56]

9	Dehydrocavidine	<i>Corydalis saxicola</i>	CCl ₄ liver fibrosis	Reduced serum levels of ALT, AST, ALP, and TB, while increasing SOD, CAT, and GPx.	The mitigation of liver damage is achieved by the reduction of fibrous septa development, decrease in the concentration of malondialdehyde (MDA), attenuation of oxidative stress, facilitation of collagenolysis, and regulation of genes associated with fibrosis.	[57]
10	Isoflavones: puerarin	Kudzu roots/ <i>Pueraria lobelia</i>	Chronic alcohol-related liver damage	ALT, AST, ALP, and intrahepatic ADH were reduced, but ALDH increased.	Reduces the endogenous enzyme functions of CYP2E1, CYP1A2, and CYP3A, which may contribute to the equilibrium of metabolic processes.	[58]
11	Rubiadin	<i>Rubiocordifolia</i> Linn	CCl ₄ -induced hepatic damage in rats	The blood values of ALT, AST, ALP, and GGT were normal. Glutathione S-transferase and reductase activity decreased.	The study demonstrates the role of glutathione in facilitating detoxification processes and its ability to scavenge free radicals.	[59]

12	Ursolic acid	<i>Hedyotis corymbosa</i> L	Paracetamol-induced liver injury	Reduced serum ALT, AST, ALP, and total bilirubin and normalised liver histology compared to paracetamol.	Reduces NF-κB activation, suppresses Cytochrome P4502E1 expression, boosts hepatic-glutathione regeneration, and increases metallothionein expression.	[60]
13	Coumarin: wedelolactone	<i>Eclipta prostrata</i> L	Concanavalin A-induced hepatitis in mice	Significantly decreased hepatic leukocyte infiltration and T-cell activation. Block nuclear factor-kappa B, tumour necrosis factor, interferon-gamma, and IL-6.	Reduces leukocyte infiltration into the liver via inhibiting NF-κB signalling.	[61]
14	Betulinic acid and ricinine	<i>Tetracarpidium conophorum</i>	CCl ₄ -induced hepatotoxicity	In vivo, betulinic acid and ricinine protected the liver in CCl ₄ rats. The active sites of hepatitis B virus DNA polymerase have strong attraction and interaction.	Enhanced tissue redox system, reduced lipid peroxidation, and antioxidant system maintenance.	[62]

15	Coumarin analogues: meranzin hydrate I	<i>Citrus grandis</i>	D- Galactosamine - induced cell survival inhibition in LO2 cells by MTT assay	Liver toxic model increased superoxide dismutase, glutathione peroxidase, and reduced malondialdehyde .	Improves free radical scavenging and cellular antioxidant pathway.	[63]
-----------	---	-----------------------	---	---	--	------

REFERENCES

- [1] Nosek, Thomas M. "Section 6/6ch2/s6ch2_30". *Essentials of Human Physiology*. Archived from the original on 2016-03-24.
- [2] Elias, H.; Bengelsdorf, H. (1 July 1952). "The Structure of the Liver in Vertebrates". *Cells Tissues Organs*. 14 (4): 297–337. doi:10.1159/000140715. PMID 14943381.
- [3] Abdel-Misih, Sherif R.Z.; Bloomston, Mark (2010). "Liver Anatomy". *Surgical Clinics of North America*. 90 (4): 643–653. doi:10.1016/j.suc.2010.04.017. PMC 4038911. PMID 20637938.
- [4] "Anatomy and physiology of the liver – Canadian Cancer Society". *Cancer.ca*. Archived from the original on 2015-06-26. Retrieved 2015-06-26.
- [5] Tortora, Gerard J.; Derrickson, Bryan H. (2008). *Principles of Anatomy and Physiology* (12th ed.). John Wiley & Sons. p. 945. ISBN 978-0-470-08471-7.
- [6] Maton, Anthea; Jean Hopkins; Charles William McLaughlin; Susan Johnson; MaryannaQuon Warner; David LaHart; Jill D. Wright (1993). *Human Biology and Health*. Englewood Cliffs, New Jersey, USA: Prentice Hall. ISBN 978-0-13-981176-0. OCLC 32308337.
- [7] Zakim, David; Boyer, Thomas D. (2002). *Hepatology: A Textbook of Liver Disease* (4th ed.). ISBN 9780721690513.
- [8] Liver Anatomy at eMedicine
- [9] Cotran, Ramzi S.; Kumar, Vinay; Fausto, Nelson; Nelso Fausto; Robbins, Stanley L.; Abbas, Abul K. (2005). *Robbins and Cotran pathologic basis of disease* (7th ed.). St. Louis, MO: Elsevier Saunders. p. 878. ISBN 978-0-7216-0187-8.
- [10] "Enlarged liver". Mayo Clinic. Archived from the original on 2017-03-21. Retrieved 2017-03-29.
- [11] Molina, D. Kimberley; DiMaio, Vincent J.M. (2012). "Normal Organ Weights in Men". *The American Journal of Forensic Medicine and Pathology*. 33 (4): 368–372. doi:10.1097/PAF.0b013e31823d29ad. ISSN 0195-7910. PMID 22182984. S2CID 32174574.
- [12] Molina, D. Kimberley; DiMaio, Vincent J. M. (2015). "Normal Organ Weights in Women". *The American Journal of Forensic Medicine and Pathology*. 36 (3): 182–187. doi:10.1097/PAF.0000000000000175. ISSN 0195-7910. PMID 26108038. S2CID 25319215.
- [13] "Etymology online hepatic". Archived from the original on December 15, 2013. Retrieved December 12, 2013.
- [14] "Anatomy of the Liver". *Liver.co.uk*. Archived from the original on 2015-06-27. Retrieved 2015-06-26.
- [15] Renz, John F.; Kinkhabwala, Milan (2014). "Surgical Anatomy of the Liver". In Busuttill, Ronald W.; Klintmalm, Göran B. (eds.). *Transplantation of the Liver*. Elsevier. pp. 23–39. ISBN 978-1-4557-5383-3.
- [16] "Cantlie's line | Radiology Reference Article". *Radiopaedia.org*. Archived from the original on 2015-06-27. Retrieved 2015-06-26.
- [17] Kuntz, Erwin; Kuntz, Hans-Dieter (2009). "Liver resection". *Hepatology: Textbook and Atlas* (3rd ed.). Springer. pp. 900–903. ISBN 978-3-540-76839-5.
- [18] Singh, Inderbir (2008). "The Liver Pancreas and Spleen". *Textbook of Anatomy with Colour Atlas*. Jaypee Brothers. pp. 592–606. ISBN 978-81-8061-833-8.[permanent dead link]
- [19] McMinn, R.M.H. (2003). "Liver and Biliary Tract". *Last's Anatomy: Regional and Applied*. Elsevier. pp. 342–351. ISBN 978-0-7295-3752-0.
- [20] Skandalakis, Lee J.; Skandalakis, John E.; Skandalakis, Panajiotis N. (2009). "Liver". *Surgical Anatomy and Technique: A Pocket Manual*. pp. 497–531. doi:10.1007/978-0-387-09515-8_13. ISBN 978-0-387-09515-8.
- [21] Ahmad A, Ahmad R (2014) Resveratrol mitigate structural changes and hepatic stellate cell activation in N^o-nitrosodimethylamine-induced liver fibrosis via restraining oxidative damage. *ChemBiol Interact* 221:1–12
- [22] Al-Amarat W, Abukhalil MH, Alruhaimi RS, Alqhtani HA, Aldawood N, Alfwuaires MA, Althunibat OY, Aladaileh SH, Algefare AI, Alanezi AA (2022) Upregulation of Nrf2/HO-1 signaling and attenuation of oxidative stress, inflammation, and cell death mediate the protective effect of apigenin against cyclophosphamide hepatotoxicity. *Metabolites* 12:648
- [23] Al-Asmari AK, Al-Elaiwi AM, Athar MT, Tariq M, Al Eid A, Al-Asmary SM (2014) A review of hepatoprotective plants used in Saudi traditional medicine. *Ev-Based Complement Altern Med* 2014:1-22
- [24] Al-Snai A, Mousa H, Majid WJ (2019) Medicinal plants possessed hepatoprotective activity. *IOSR J Pharmacy* 9:26–56
- [25] Ambade A, Mandrekar P (2012) Oxidative stress and inflammation: essential partners in alcoholic liver disease. *Int J Hepatol* 853175:1

- [26] Antarkar D (1980) A double-blind clinical trial of Arogya-wardhani-an Ayurvedic drug-in acute viral hepatitis. *Indian J Med Res* 72:588–593
- [27] Antunes C, Arbo MD, Konrath EL (2022) Hepatoprotective native plants documented in Brazilian traditional medicine literature: current knowl- edge and prospects. *ChemBiodivers* 19:e202100933
- [28] Arteel G, Marsano L, Mendez C, Bentley F, McClain CJ (2003) Advances in alcoholic liver disease. *Best Pract Res ClinGastroenterol* 17:625–647
- [29] Ahmad A, Ahmad R (2014) Resveratrol mitigate structural changes and hepatic stellate cell activation in N'-nitrosodimethylamine-induced liver fibrosis via restraining oxidative damage. *ChemBiol Interact* 221:1–12
- [30] Al-Amarat W, Abukhalil MH, Alruhaimi RS, Alqhtani HA, Aldawood N, Alfwuaires MA, Althunibat OY, Aladaileh SH, Algefare AI, Alanezi AA (2022) Upregulation of Nrf2/HO-1 signaling and attenuation of oxidative stress, inflammation, and cell death mediate the protective effect of apigenin against cyclophosphamide hepatotoxicity. *Metabolites* 12:648
- [31] Al-Asmari AK, Al-Elaiwi AM, Athar MT, Tariq M, Al Eid A, Al-Asmary SM (2014) A review of hepatoprotective plants used in Saudi traditional medicine. *Ev-Based Complement Altern Med* 2014:1-22
- [32] Al-Snai A, Mousa H, Majid WJ (2019) Medicinal plants possessed hepatoprotective activity. *IOSR J Pharmacy* 9:26–56
- [33] Ambade A, Mandrekar P (2012) Oxidative stress and inflammation: essential partners in alcoholic liver disease. *Int J Hepatol* 853175:1
- [34] Antarkar D (1980) A double-blind clinical trial of Arogya-wardhani-an Ayurvedic drug-in acute viral hepatitis. *Indian J Med Res* 72:588–593
- [35] Antunes C, Arbo MD, Konrath EL (2022) Hepatoprotective native plants documented in Brazilian traditional medicine literature: current knowl- edge and prospects. *ChemBiodivers* 19:e202100933
- [36] Arteel G, Marsano L, Mendez C, Bentley F, McClain CJ (2003) Advances in alcoholic liver disease. *Best Pract Res ClinGastroenterol* 17:625–647
- [37] Eldesoky AH, Abdel-Rahman RF, Ahmed OK, Soliman GA, Saeedan AS, Elzorba HY, Elansary AA, Hattori M (2018) Antioxidant and hepatoprotective potential of *Plantago major* growing in Egypt and its major phenylethanoid glycoside, acteoside. *J Food Biochem* 42:e12567
- [38] Eugenio-Pérez D, Montes De Oca-Solano HA, Pedraza-Chaverri J (2016) Role of food-derived antioxidant agents against acetaminophen-induced hepatotoxicity. *Pharm Biol* 54:2340–2352
- [39] Ezhilarasan D (2018) Oxidative stress is bane in chronic liver diseases: clinical and experimental perspective. *Arab J Gastroenterol* 19:56–64
- [40] Farombi EO, Shrotriya S, Na HK, Kim SH, Surh YJ (2008) Curcumin attenuates dimethylnitrosamine-induced liver injury in rats through Nrf2-mediated induction of heme oxygenase-1. *Food Chem Toxicol* 46:1279–1287
- [41] Federico A, Trappoliere M, Loguercio C (2006) Treatment of patients with non-alcoholic fatty liver disease: current views and perspectives. *Dig Liver Dis* 38:789–801
- [42] Feher J, Deák G, Múzes G, Lang I, Niederland V, Nekam K, Kartesz M (1989) Liver-protective action of silymarin therapy in chronic alcoholic liver diseases. *Orv Hetil* 130:2723–2727
- [43] Ferenci P, Dragosics B, Dittrich H, Frank H, Benda L, Lochs H, Meryn S, Base W, Schneider B (1989) Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. *J Hepatol* 9:105–113
- [44] Flora K, Hahn M, Rosen H, Benner K (1998) Milk thistle (*Silybummarianum*) for the therapy of liver disease. *Am J Gastroenterol* 93:139–143
- [45] García-Niño WR, Pedraza-Chaverri J (2014) Protective effect of curcumin against heavy metals-induced liver damage. *Food Chem Toxicol* 69:182–201
- [46] George A, Udani JK, Yusof A (2019) Effects of *Phyllanthusamarus* PHYLLPROTM leaves on hangover symptoms: a randomized, double-blind, placebo-controlled crossover study. *Pharm Biol* 57:145–153
- [47] Ghosh N, Ghosh R, Mandal V, Mandal SC (2011) Recent advances in herbal medicine for treatment of liver diseases. *Pharm Biol* 49:970–988
- [48] Graebin CS (2018) The pharmacological activities of glycyrrhizic acid (“glycyrrhizin”) and glycyrrhetic acid. *Sweeteners* 2018:245-261
- [49] Gutiérrez-Rebolledo GA, Siordia-Reyes AG, Meckes-Fischer M, Jiménez-Arellanes A (2016) Hepatoprotective properties of oleanolic and ursolic acids in antitubercular drug-induced liver damage. *Asian Pac J Trop Med* 9:644–651
- [50] Guyton AC, Hall JE (2006) Medical physiology. Gökhan N, Çavuşoğlu H (Çeviren). 3.
- [51] Handa S (1986) Natural products and plants as liver protecting drugs. *Fitoterapia*. 57:307–351

- [52] Harish R, Shivanandappa T (2006) Antioxidant activity and hepatoprotective potential of *Phyllanthus niruri*. *Food Chem* 95:180–185
- [53] Hasan S, Khan R, Ali N, Khan A, Rehman M, Tahir M, Lateef A, Nafees S, Mehdi S, Rashid S (2015) 18- β Glycyrrhetic acid alleviates
- [54] 2-acetylaminofluorene-induced hepatotoxicity in Wistar rats: role in hyperproliferation, inflammation and oxidative stress. *Hum Exp Toxicol* 34:628–641
- [55] Lee T-Y, Lee K-C, Chang H-H (2010) Modulation of the cannabinoid receptors by andrographolide attenuates hepatic apoptosis following bile duct ligation in rats with fibrosis. *Apoptosis* 15:904–914
- [56] Li G, Chen JB, Wang C, Xu Z, Nie H, Qin XY, Chen XM, Gong Q (2013) Curcumin protects against acetaminophen-induced apoptosis in hepatic injury. *World J Gastroenterol* 19:7440–7446
- [57] Li H, Sureda A, Devkota HP, Pittalà V, Barreca D, Silva AS, Tewari D, Xu S, Nabavi SM (2020) Curcumin, the golden spice in treating cardiovascular diseases. *Biotechnol Adv* 38:1
- [58] Li J, Pan Y, Kan M, Xiao X, Wang Y, Guan F, Zhang X, Chen L (2014) Hepatoprotective effects of berberine on liver fibrosis via activation of AMP-activated protein kinase. *Life Sci* 98:24–30
- [59] Li M, Liu L, Zhou Q, Huang L, Shi Y, Hou J, Lu H, Yu B, Chen W, Guo Z (2023) *Phyllanthus niruri* L. Applications of herbal medicine to control chronic kidney disease: volume II. *Frontiers in Pharmacology* 13:1-236
- [60] Li R, Liang T, He Q, Guo C, Xu L, Zhang K, Duan X (2013) Puerarin, isolated from Kudzu root (Willd.), attenuates hepatocellular cytotoxicity and regulates the GSK-3 β /NF- κ B pathway for exerting the hepatoprotection against chronic alcohol-induced liver injury in rats. *Int Immunopharmacol* 17:71–78
- [61] Marjani M, Baghaei P, Dizaji MK, Bayani PG, Fahimi F, Tabarsi P, Velayati AA (2016) Evaluation of hepatoprotective effect of silymarin among under treatment tuberculosis patients: a randomized clinical trial. *Iranian J Pharmaceut Res* 15:247
- [62] Martinou E, Pericleous M, Stefanova I, Kaur V, Angelidi AM (2022) Diagnostic modalities of non-alcoholic fatty liver disease: from biochemical biomarkers to multi-omics non-invasive approaches. *Diagnostics* 12:407
- [63] Masood M, Arshad M, Rahmatullah Q, Sabir S, Shoaib M, Amjad HQ, Tahir ZJP, Biology A (2021) 02. *Picrorhizakurroa*: an ethnopharmacologically important plant species of Himalayan region. *Pure Appl Biol* 4:407–417