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REVIEW ARTICLE

The Protective and Therapeutic Effects of Herbal Medicines on Hepatic Disorders in Animals

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ABSTRACT

Liver is considered as the most important organ for metabolism, bile production, detoxification, and antioxidant defense in animals and humans. Liver diseases in animals represent major health and economic concerns because of their impact on productivity. Conventional hepatoprotective drugs are effective, but their use is constrained by adverse effects, antimicrobial resistance, and residue concern. These limitations of conventional hepatoprotective drugs make the scientists focus on new alternative treatments. Medicinal plants and their bioactive compounds are considered as the best among all the alternative strategies. The diverse biological activities of botanical compound make them suitable candidates to be used as hepatoprotectives. In this review, we will briefly discuss multiple hepatic diseases and detailed mechanisms of action of botanical compounds for better understandings to formulate new alternative products.

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INTRODUCTION

Liver is considered one of the most important and metabolically active body organs of animals (Hassani, 2022). Liver has multiple vital physiological roles, such as carbohydrate, lipid, and protein metabolism; bile synthesis and secretion; the retention of vitamins and minerals; detoxification of xenobiotics and immunomodulation (Mega *et al.*, 2021). Other significant functions of liver include important nutrient processing, hormonal metabolism, plasma protein synthesis, and immune defense functions in companion animals through Kupffer cell activity (Zaefarian *et al.*, 2019). However, in poultry birds, liver acts as the primary lipid metabolic and vitellogenic organ, where lipoproteins and yolk precursors essential to the formation of the egg are synthesized. It also plays a major role in thermoregulation during environmental stress. All these properties of the liver render irreplaceable in sustaining physiological homeostasis, development, and particularly the productivity of all animal species. Animals are prone to liver diseases caused by numerous factors, including infections, toxins, and nutritional or metabolic disorders. These diseases are common and economically costly, often worsened by exposure to chemical contaminants. Hepatic lipidosis, fascioliasis and clostridial infections, like infectious necrotic hepatitis (Black disease) are most common disease of liver (Ur Rehman *et al*., 2023; Tharwat *et al.*, 2025a). There are also several hepatic diseases in companion animals, including chronic hepatitis, cholangiohepatitis and copper related hepatopathies, which frequently result in chronic liver failure (Mitsui *et al.*, 2021). The synthetic drugs, antibiotics, antioxidants, and nutritional supplements are used as conventional therapeutic approaches used in treating liver diseases in animals. Though these treatments have drawbacks like expensive nature, side effects, resistance to the drugs and withdrawal in food-producing animals (Akram *et al*., 2023; Quintás *et al.*, 2023). The increased appeal of alternative and complementary therapies of natural origin has been stimulated by these restrictions. Herbal preparations and extracts feature in traditional medicine systems, including Ayurveda, Traditional Chinese Medicine, and Unani, and in veterinary medicine have received growing scientific interest over the past decades (Rizvi *et al.*, 2022).

Herbal medicines contain a diverse spectrum of bioactive compounds: flavonoids, alkaloids, terpenoids, phenolics, and glycosides are some of the bioactive compounds responsible for the hepatoprotective and therapeutic actions (Dar *et al.*, 2023; Hegazy *et al*., 2023). These phytochemicals have antioxidant, anti-inflammatory, anti-fibrotic, antiviral, immunomodulatory effects that have a comprehensive effect of protecting liver

cells against damage and leading to regeneration. However, some other biological properties of botanical compounds include enhancement in liver enzyme profiles, reinforcement of histological integrity and promote hepatocyte regeneration (Shawon *et al.*, 2024). These diverse properties of plant-based compounds make them suitable candidates for the development of new effective drugs against liver problems. Considering the increased incidence of liver diseases and the constraints of the available pharmacological treatment plans, there is an increased interest in the efforts to identify and confirm the effectiveness of herbal medicine as a hepatoprotective and curative agent on animals (Thilagavathi *et al.*, 2023).

The purpose of this review is to summarize the published knowledge of the protective and treatment effects of some of the herbal medicines on liver disease of the animals. It discusses the pathophysiology of hepatic diseases in various animal species, hepatoprotective mechanisms of herbal compounds, and the experimental and clinical support of their effects.

Major liver diseases of animals: Liver diseases are one of the major health issues in many animal species because of the centrality of liver in metabolism, detoxification, and general physiological regulation (Romeo *et al.*, 2025). The liver is a metabolic center and processes the nutrients that are absorbed along the digestive tract, producing the necessary biomolecules, controlling lipid and carbohydrate metabolism, and counteracting toxins and debris (Awuchi *et al.*, 2021). Because of its continuous contact with antigens in food, pathogens and toxins, as well as metabolic intermediates, the liver becomes especially susceptible to both structural and functional damage (Mega *et al.*, 2021). Animal hepatic diseases could be infectious, parasitic, toxic, metabolic, and nutritional in nature and their severity may be mild as subclinical disturbance, and acute and chronic hepatic failure (Al-Gheffari *et al*., 2024). Some major liver diseases in different animal species are discussed to better understand the mechanisms of botanical compounds to formulate new effective alternative treatments.

Liver diseases in bovines: Hepatic lipidosis, or fatty liver, is one of the most common metabolic liver diseases in high producing dairy cows, especially in the periparturient period (Melendez and Pinedo, 2024). It happens when the fat mobilization rate in adipose tissue surpasses the ability of the liver to oxidize or eliminate fatty acids like lipoproteins (Chandler *et al.*, 2023). This is usually occasioned by a negative energy imbalance after parturition, where the energy requirements that are needed to produce milk are increasing and feed consumption is decreasing. Overload of non-esterified fatty acids (NEFAs) into the liver results in triglycerides built up in hepatocytes, thereby causing hepatic dysfunction (Chen *et al.*, 2025). Clinically, cows with the disorder show anorexia, ketosis, low milk production and low fertility (Tufarelli *et al.*, 2024). Lab results are increased aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total bilirubin, and elevated NEFA and 2 -hydroxybutyrate. The liver seems enlarged, pale and greasy because of lipid destruction on histopathological examination (Agirca Tasan and Ozmen, 2022). The disorder impairs gluconeogenesis, detoxification and immune functions, which predispose the animals to secondary infections and metabolic diseases (Kour *et al.*, 2024).

Black disease or infectious necrotic hepatitis is an acute fatal toxemic infection of *Clostridium novyi* type B (Salvarani and Vieira, 2024). The disease is predominant in well-nourished grazing cattle and sheep and is usually a consequence of liver damage caused by ingested *Fasciola hepatica* larvae (Mostafa *et al*., 2023; Pramanik *et al.*, 2025). Such tracts resulting because of fluke cause a condition of the anaerobic environment that facilitates germination of spores and proliferation of bacteria. Some bacteria can produce powerful exotoxins, especially alpha toxin, which results in massive hepatic necrosis, systemic toxemia, and early death (Finnie and Uzal, 2022). The illness has a tendency to manifest itself clinically as a sudden death, and in most cases, there are minimal premonitory signs; the victims may experience depression, fever and recumbency. The post-mortem findings show a swollen and fragile liver with necrotic areas surrounded by hyperemia (Manjunathareddy *et al.*, 2024). However, the subcutaneous tissues appear dark because of venous congestion (Shinya *et al.*, 2025). Diagnosis is made on characteristic lesions, as well as bacteria isolation or PCR confirmation (Ma *et al.*, 2022).

Fascioliasis is a major economic problem of the liver in the world caused by *Fasciola hepatica* or *Fasciola gigantica* (Ahmad *et al.,* 2021; Zerna *et al.,* 2021; Winaya *et al*., 2023). The infection occurs through the intake of metacercariae contaminated vegetation, especially in soft marshy pastures in which the snail host of the intermediate generation (Lymnaea species) flourishes (Drescher *et al.*, 2023). Once the immature flukes are ingested, they move through the intestinal wall and liver parenchyma, producing a large amount of tissue damage, and eventually settle in the bile ducts as adults (Kahl *et al.*, 2021). Disease occurs in forms of acute, subacute or chronic basing on the intense and stage of the infection. With acute fascioliasis, a drastic outcome of a huge invasion of recently laid flukes, the liver will bleed, anemia will appear, weakness will be observed, and the patient will die suddenly (Lalor *et al.*, 2021). The more widespread in cattle is chronic fascioliasis, which is characterized by loss of weight, decreased milk production, anemia, submandibular edema (bottle jaw) and general un-thriftiness (Admassu *et al.*, 2015). The typical findings in biochemistry are high levels of GGT, AST, and alkaline phosphatase as an indication of damage to the liver and the biliary (McGrowder *et al.*, 2021). Pathologically, the affected livers have fibrosis, thickened bile ducts, and adult flukes (Csivincsik *et al.*, 2023).

Liver diseases in sheep and goats: Copper toxicity is a significant hepatic condition in small ruminants (Borobia *et al.*, 2022). Copper toxicity is more prone to occur in sheep than in other livestock species (Trouillard *et al.*, 2021). The imbalance between the intake and the excretion of excess copper through bile in animals causes disease (Wu *et al.*, 2025). There may be a gradual accumulation of copper in the liver because of factors like high levels of copper in the diet, low levels of molybdenum and sulfur levels in the diet, and long-term feeding of cattle or poultry rations to sheep (Solaiman *et al.*, 2024). The hepatocytes

fill up with copper over time and, in cases of stress or liver damage, the hepatic copper is discharged into the blood abruptly, leading to acute hemolytic crisis (Penning *et al.*, 2023). The chronic stage of copper poisoning is often silent clinically, but when an exacerbating factor occurs, it causes acute hemolysis (Teschke and Eickhoff, 2024). These factors include depression, anorexia, hemoglobinuria, jaundice, tachycardia, and pale or icteric mucous membranes. The urine normally changes from dark red to brown because of hemoglobin leaking out (Umar *et al.*, 2024). Serum levels are found to be high on liver enzymes, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) with an increase in bilirubin and reduction in packed cell volume (PCV) (Bakhasha *et al.*, 2024). In post-mortem, the liver appears heavier, friable yellowish, with kidneys dark and gunmetal in color, which is a characteristic of copper toxicosis (Molín *et al.*, 2021).

Liver diseases in equines: Equine serum hepatitis or Theiler's disease is a deadly, acute, and hepatic disease in horses that is followed by massive hepatocellular necrosis and liver acuteness (Zehetner *et al.*, 2021). It is traditionally linked with the management of biological products of equine origin like tetanus antitoxin or hyperimmune serum. The primary cause of Theiler's disease in equines is parvovirus (Yoon *et al.*, 2021). Theiler's disease is characterized pathologically by extensive hepatic necrosis with loss of functional parenchyma (Tharwat *et al.*, 2025b). Liver is mostly small, flaccid and of a friable nature with discoloration (Tomlinson *et al.*, 2019). Being clinically related, affected horses develop lethargy, anorexia, icterus, photosensitivity, and such neurological symptoms as ataxia, head pressing, or inappropriate behaviour related to hepatic encephalopathy. Lab findings indicate significantly high levels of serum liver enzymes, mainly sorbitol dehydrogenase (SDH), gamma-glutamyl transferase (GGT) and aspartate aminotransferase (AST) and hyperbilirubinemia and unduly protracted coagulation time, which demonstrate grievous dysfunction of the liver (Divers *et al.*, 2022). The illness is very fatal because it has acute hepatic failure and endotoxemia (Prepeliuc *et al.*, 2025). Theiler's disease is considered being one of the most critical hepatopathies in horses that has a high rate of progression and close relation to the administration of biologic products (Pilz *et al.*, 2022).

Hepatic lipidosis is a metabolic disease affecting horses, ponies and donkeys, which is caused by the excessive mobilization of the fat content of the body, and leading to the accumulation of triglycerides in the hepatocytes (Mendoza *et al.*, 2024). It is most commonly present in ponies, miniature horses and donkey species most susceptible to lipid metabolism disorders (Goodrich and Behling-Kelly, 2022). Pregnant and lactating mares, as well as obese animals, are particularly vulnerable because the hormonal and metabolic requirements elevate lipolysis, leeching non-esterified fatty acids (NEFAs) into the bloodstream (Daradics *et al.*, 2021). In the event that the hepatic oxidation or very-low-density lipoprotein (VLDL) export systems are overwhelmed, triglycerides would build up in hepatocytes, causing hepatic malfunction and cellular death. Hepatic lipidosis presents with the clinical symptoms of anorexia, lethargy, icterus, depression, and indicators of metabolic exhaustion (weakness and impaired coordination) (Mistry and Yeoman, 2023). Laboratory findings are usually marked by a high level of serum triglycerides, a rise in the activities of the hepatic enzymes (GGT, AST, SDH) as well as higher levels of bilirubin (Kathak *et al.*, 2022). These parameters indicate the hepatic load and metabolic dysfunction. The liver is enlarged, pale, oily, and greasy in gross appearance because of lipid infiltration (Abdelatty *et al.*, 2025). At the microscopic level, hepatocytes show lipid deposits and vacuolar degeneration (Jin *et al.*, 2025). The situation interferes with gluconeogenesis, energy metabolism, and may end up in hepatic failure in case the imbalance between fat mobilization and utilization continues. Hepatic lipidosis in horses can thus be regarded as one of such metabolic liver diseases, which points to the likeness of the species to energy shortages and lipid imbalances (Slavik *et al.*, 2025).

Liver diseases of canines: Chronic hepatitis (CH) is a disease that is highly common and progressive in dogs (Assawarachan *et al.*, 2021). CH is characterized by presence of persistent inflammation, hepatocellular necrosis, and variable levels of fibrosis that can eventually result in cirrhosis and subsequent hepatic failure (Borgia *et al.*, 2021). CH is usually insidious and has a long subclinical period before it reaches clinical manifestation. Multiple causes have been associated with chronic hepatitis, such as canine adenovirus Type-1, immune mediated, genetic and exposure to hepatotoxins or medications (Puzzo and Kay, 2025). Some breeds, e.g. Doberman Pinschers, Cocker Spaniels and Labrador Retrievers, seem to be prone to idiopathic or immune-mediated types of disease (Dosenberry *et al.*, 2025). CH is diagnosed by inflammatory infiltrates of hepatocellular parenchyma by mononuclear inflammation, continued hepatocellular apoptosis or necrosis and progressive fibrotic alterations (Choi, 2025). Replacement of functional hepatocytes with fibrous tissue fluid occurs slowly during the pathogenesis of the disease, which worsens the bile flow, protein synthesis, and detoxification dynamics. Clinically, the manifestations in infected dogs can be nonspecific (i.e., lethargy, inappetence, weight loss, and vomiting) and advanced (i.e. icterus, ascites, coagulopathies, and liver encephalopathy, i.e., loss of liver functionality). Normally, laboratory results display higher serum liver enzymes, especially of alanine aminotransferase (ALT), and alkaline phosphatase (ALP), and a high bilirubin concentration, hypoalbuminemia, and longer clotting times. This progression of fibrosis in canine populations is a progression caused by the chronic inflammatory process and is outcome enforceable (Antar *et al.*, 2023).

Copper-associated hepatopathy (CAH) is a serious hepatic disease of dogs, which is characterized by a genetic accumulation of excessive copper in the liver, resulting in oxidative trauma, inflammation, and hepatocellular necrosis (Ullal *et al.*, 2022). This disease may be caused by a primary genetic defect of copper metabolism or a secondary condition caused by cholestasis or other hepatic impairments, which prevent the excretion of copper. Primary forms have been linked to mutations of genes controlling copper transport, leading to excessive stores of copper in the liver, secondary accretion may ensue in co-

morbidity with other chronic hepatic conditions (Araf *et al.*, 2022). Some of the particularly susceptible breeds are Bedlington Terriers, Doberman Pinschers, Labrador Retrievers and West Highland White Terriers. Centrilobular degeneration of hepatocellular continues to multifocal necrosis and chronic active hepatitis, finally washing up to fibrosis and cirrhosis when uncontrolled. In a clinical setting, dogs with copper-associated hepatopathy can have an insidious loss of appetite, lethargy, and mild weight loss at the onset, and more severe cases of the disease lead to jaundice, ascites formation and hepatic failure. Biochemically, the characteristic pattern of increased ALT and AST activities, and serum copper and ceruloplasmin is highly observed (Siddiqi *et al.*, 2023). The histology shows granules of copper in the hepatocytes, especially centrilobular areas, and can be accompanied by both inflammation and fibrotic restructuring (Malarkey *et al.*, 2005). Copper-associated hepatopathy can thus be seen as a significant metabolic and degenerative liver disease among dogs, making it clear that homeostasis of trace elements is key in ensuring a healthy liver, as well as in breed-specific susceptibility to disorders in copper metabolism.

Liver diseases of felines: Cholangiohepatitis is a series of inflammatory liver diseases in cats primarily of the bile ducts (cholangitis) and of the periportal hepatic parenchyma (Schreeg and Cullen, 2025). It is one of the most prevalent chronic liver diseases in feline populations. It usually involves inflammation of the pancreas (pancreatitis) and the intestines (inflammatory bowel disease). There is a broader classification of cholangiohepatitis into neutrophilic and lymphocytic categories according to histopathologic characteristics and assumed pathogenesis (Mitsui *et al.*, 2021). The neutrophilic type is mostly related to the ascending bacterial infection through the intestine through the bile ducts, whereas the lymphocytic type is believed to be based on immune-mediated response or persistent antigenic stimulation. Histologically, the disease is typified by inflammatory infiltrates around bile ducts and portal region, proliferation of the bile ducts and intermittent levels of hepatocellular necrosis or fibrosis (Vij *et al.*, 2022). Progressive liver damage often shows fibrosis and structural changes in long-term cases. The clinical signs and symptoms may include lethargy, anorexia, vomiting, icterus, and intermittent fever. Biochemical observations usually include high serum ALT, ALP and gamma-glutamyl transferase (GGT) enzymes, hyperbilirubinemia, and high bile acids, which are observed because of cholestasis and a destroyed liver (Assawarachan *et al.*, 2021). Ultrasonographical examination can reveal biliary dilation and irregular hepatic echotexture as having been observed in inflammation and fibrosis (Tharwat *et al.*, 2025b). Cholangiohepatitis is a complicated inflammatory disease, which highlights the close communication between the hepatobiliary system, gastrointestinal tract and immune responses in cats. This is because the disease is chronic and relapsing, which adds to the morbidity in feline patients and its difficulty in distinguishing it with other overlap clinical and biochemical hepatobiliary disorders.

Fatty liver syndrome, also referred to as hepatic lipidosis, is the most prevalent acquired liver disease in cats (Ji *et al.*, 2023). Fatty liver syndrome is a result of excessive deposition of triglycerides in the hepatocytes, combined with hepatic dysfunction and metabolic imbalance (Rinaldi *et al.*, 2021). Most of the instances of the disease are secondary and linked with long-term anorexia or stress-induced or underlying disease, but idiopathic cases have also been reported. Cats are especially prone to hepatic lipidosis because of their specific lipid metabolism (Verbrugghe *et al.*, 2021). The most at risk are obese middle-aged cats, particularly when their energy balance is negative or that they have other associated diseases like diabetes mellitus, pancreatitis or cholangitis. Liver develops the pathological signs of severe lipid infiltration by being large, pale, and friable (Helmer *et al.*, 2021). Histologically, hepatocytes show diffuse vacuolar degeneration with lipid droplets, which are cytoplasmic, resulting in the displacement of the nucleus representative of macro-vesicular steatosis. Symptoms in ill cats consist of extended anorexia, excessive weight reduction, icterus, and vomiting accompanied by lethargy and in some cases with hypersalivation or variations in neurological functions because of hepatic encephalopathy. The clinical laboratory results are usually characterized by a significant increase in the concentration of alanine aminotransferase (ALT), alkaline phosphatase (ALP), and bilirubin analyses and a metabolic derangement such as a decrease in the level of potassium or an increase in the level of alkalosis (Wang *et al.*, 2025).

Liver diseases of poultry birds: Inclusion body hepatitis (IBH) is an acute viral infection that is mostly seen in young broiler chickens ageing between 3 to 7 weeks (El-Shall *et al.*, 2022). Fowl adenoviruses (FAdVs) are the cause of the disease, especially the serotypes of FAdV-D and FAdV-E (Sadekuzzaman *et al.*, 2024). Fowl adenoviruses are transmitted both vertically by the carrier hens, which are the breeders, and horizontally through the contaminated faeces. Immunosuppressive infections used concomitantly with other immunosuppressive infections, e.g., Infectious Bursal Disease Virus (IBDV) or Chicken Anaemia Virus (CAV) are particularly prone to birds, as they suppress host defense and favor viral replication. IBH is pathologically manifested as enlarged, friable, pale to yellowish, with multiple foci or broad haemorrhages (Tsiouris *et al.*, 2022). Hepatocytes have basophilic or eosinophilic intranuclear inclusion bodies, cellular degeneration and necrosis with mononuclear inflammatory infiltrates around them microscopically. It can also be enlarged and necrotic in the spleen and kidney. Affected flocks have a clinical manifestation characterized by the abruptness of morbidity and mortality rates of between 2-30%, depending on the viral strain virulence, and flock immunity (Farag *et al.*, 2024). Before birds die, they may exhibit depression, ruffled feathers, anorexia and anaemia. Haematological results comprise decreased haematocrit rates and high liver enzyme concentrations. IBH has economic implications through mortality, poor growth performance and predisposition to secondary infections because it is immunosuppressive (Mo, 2021).

Mechanism of Hepatotoxicity in Animals: The liver is a central organ in metabolism, detoxification, and homeostasis, making it particularly vulnerable to toxic

injury (Vicidomini *et al.*, 2024). Hepatotoxicity in animals occurs when the liver's ability to metabolize and eliminate harmful substances is overwhelmed, resulting in biochemical, structural, and functional impairment of hepatocytes. The process involves a complex interplay of metabolic activation, oxidative stress, mitochondrial dysfunction, calcium imbalance, inflammation, cholestasis, and fibrosis, ultimately leading to cellular necrosis or apoptosis (Jurcău *et al.*, 2022).

Absorption and Metabolic Activation: The pathway starts with the intake and metabolic activation of poisonous substances. Majority of the hepatotoxins acquire access to the animal body by ingestion, inhalation or by dermal absorption and are carried to the liver by the portal circulation (Awuchi *et al.*, 2022). In hepatocytes, the compounds can be challenged to Phase I and Phase II biotransformation (Palmisano *et al.*, 2025). Phase I metabolism, which is primarily catalysed by cytochrome P450 enzymes like CYP2E1, CYP3A4 and CYP1A2, transforms lipophilic compounds, rendering them more hydrophilic, by introducing functional groups that are reactive (Mokhosoev *et al.*, 2024). Although such trends normally help in detoxification, on most occasions they produce reactive intermediates that are more toxic than their parent molecules. Acetaminophen gets metabolized by CYP2E1 to N-acetyl-p- benzoquinone imine (NAPQI). Phase II metabolism, conjugation of endogenous molecules (sulfate, glucuronic acid, or glutathione) is usually facilitated to trigger excretion (Järvinen *et al.*, 2022).

Oxidative Stress and Lipid Peroxidation: Oxidative stress plays a central role in hepatotoxicity (Al-Baqami and Hamza, 2021). During xenobiotic metabolism, reactive oxides and reactive nitrogen oxides are generated i.e. superoxide anion, hydrogen peroxide, hydroxyl radicals, and peroxynitrite. When these reactive molecules surpass the potential of the antioxidant defence mechanisms such as glutathione (GSH), superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx), then it leads to the lipid peroxidation of the cell membranes. Oxidative breakdown of membrane lipids generates reactive aldehydes such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), which cause additional photodegradation of proteins and nucleic acids (Liu *et al.*, 2021a). Mitochondrial dysfunction, DNA fragmentation, and activation of apoptotic promoting signalling cascades are also caused by oxidative stress. GSA caused by glutathione depletion especially renders hepatocytes very vulnerable to free radical damage, which worsens the extent of membrane disruption and enzyme leakage.

Mitochondrial Dysfunction: Mitochondrial dysfunctions have significant importance in the development of hepatotoxicity (Mihajlovic and Vinken, 2022). There are various toxins, such as aflatoxins, carbon tetrachloride, and microcystins, which inhibit the mitochondrial oxidative phosphorylation and dysregulate the electron transport chain and lead to reduced ATP generation (Moloi *et al.*, 2024). Swelling and rupture of the mitochondrial matrix and release of pro-apoptotic proteins like cytochrome c (Fiorucci *et al.*, 2022). This follows loss of mitochondrial membrane potential and opening of mitochondrial permeability transition pores (MPTPs). With the depletion of ATP stores, it causes a change in the mode of cell death from apoptosis to necrosis (Hanson *et al.*, 2023). However, compromised β-oxidation of fatty acids through the mitochondrial damage adds to lipid retention and the onset of the hepatic steatosis (Panov *et al.*, 2024). Such energy failure and oxidative imbalance combination creates a vicious cycle of progressive liver damage.

Disruption of Calcium Homeostasis: Calcium homeostasis disruption is also an important factor in hepatocellular injury (Thoudam *et al.*, 2023). When subjected to toxic stress, intracellular calcium augmentation by membrane damage and calcium-isolating organelle injury like the endoplasmic reticulum appears. High levels of cytosolic calcium stimulate the proteins, phospholipases and endonucleases that break down vital structural and regulatory proteins, phospholipids and nucleic acids (Matuz-Mares *et al.*, 2022). Overload of calcium by mitochondria also positively interacts with the opening of the permeability transition pore which enhances oxidative stress and loss of ATP witnessed (Endlicher *et al.*, 2023). These eventually cause cellular injury and cell death irreversibly by necrosis or apoptosis, as per the energy status of the cell.

Inflammatory Response and Immune-Mediated Damage: A key stimulating factor in hepatic toxicity is the inflammatory action (Gong *et al.*, 2023). Necrosis of the hepatocytes results in release of damage-associated molecular patterns (DAMPs) including high-mobility group box 1 (HMGB1) proteins, ATP, and DNA fragments (Liu *et al.*, 2021b). This stimulates the Kupffer cells through the Toll-like receptors. Stimulated Kupffer cells release proinflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin- 6 (IL-6) that attract neutrophils and monocytes to the injured area (Solleiro-Villavicencio *et al.*, 2025). These immune cells produce more ROS and proteolytic enzymes, which further cause tissue injuries. In other cases, the adaptive immunity is also harmful in the condition where hepatotoxicants form a hapten-protein complex, activating cytotoxic T-cells. Prolonged inflammation causes a self-sustaining loop of damage, and necrosis with eventual consequences in permanent liver injury (Mondal *et al.*, 2022).

Cholestasis and Bile Duct Injury: The altered bile formation and secretion mechanisms causing cholestatic injury are caused by certain hepatotoxins (Langedijk *et al.*, 2021). Some mycotoxins and agents like anabolic steroids, chlorpromazine, and others inhibit the bile salt export pump (BSEP) or multidrug resistance associated proteins (Jetter and Kullak-Ublick, 2020). This causes a buildup of hydrophobic bile acids in hepatocytes. These free bile acids serve as detergents, which harm cellular membranes, causing apoptosis of hepatocytes and cholangiocytes. Bile canaliculi and duct structural damage further inhibits bile flow, resulting in intrahepatic cholestasis, jaundice, and secondary oxidative stress (Palmeira and Rolo, 2004). Drawing the long-term effects, the cholestatic damage might result in the inflammation of the bile ducts and portal fibrosis.

Fibrosis and Chronic Liver Injury: Chronic hepatotoxicity is commonly linked to fibrosis, which occurs because of prolonged inflammatory reaction and recurring hepatic cellular damage (Johannessen *et al.*, 2023). Hepatic stellate cells (HSCs), which are located in the space of Disse, are activated and convert into myofibroblast-like cells (Sanz-García *et al.*, 2021). The extracellular matrix proteins that are released by these cells are very high levels of collagen type I and III and they disturb the regular sinusoid structure. This fibrogenic response is mediated by cytokines that include transforming growth factor-beta 1 (TGF-β1), platelet-derived growth factor (PDGF), and interleukin-13 (IL-13) (Kraik *et al.*, 2024). The over-deposition in the extracellular matrix leads to hepatic fibrosis, sinusoidal perfusion, and malfunction in metabolism (Liu *et al.*, 2022).

Hepatoprotective activity of botanical compounds: Botanical compounds are well known of their diverse biological activities (Rashid *et al*., 2024; Abbas *et al.*, 2025). Medicinal plants whose botanical compounds have been found to have hepatoprotective effects have received considerable interest as a means of preventing a broad array of liver diseases in humans and animals (Al-Hoshani *et al*., 2024; Shahzad *et al*., 2024). As the main organ of detoxification, metabolism, and production of the necessary biomolecules, the liver is very vulnerable to damage under the influence of xenobiotics, drugs, toxins, infection, and oxidative stress. Conventional hepatoprotective medications are frequently restricted by toxicity, expense, and lessened activity in chronic illness (Park *et al.*, 2022). Scientists have focused on the development of new alternative drugs based on botanical compounds because of the limitations of conventional drugs. Persuasive and renovative effects on the liver tissues have been reported in plant-based phytochemicals like phenolics, flavonoids, alkaloids, terpenoids, saponins, phenolic acids, lignans, and glycosides because of various cellular and molecular processes involved (Table 1).

Phenolics: The phenolic compounds are a wide range of secondary plant metabolites (Barbol and Alsayeqh, 2024). The hepatoprotective properties of phenolics are attributed to their strong antioxidant, anti-inflammatory, and cytoprotective properties (Xia *et al.*, 2025). Their protective effect on the liver is because of multiple biochemical and molecular pathways aimed at oxidative stress, inflammation, mitochondrial functioning, and detoxification systems. The metabolic and hepatoprotective activity of phenolics is illustrated in Fig. 1. The antioxidant activity of phenolics is one of the

Table 1: Hepatoprotective activities of different botanical compounds

Sr. no.	Botanicals	Family of the plants	Bioactive compounds	Class of the compounds	Botanical parts used	Disease	Investigation medium	Animal specie	Results	Reference
1.	*Vitis vinifera, Camellia sinensis, Salvia rosmarinus*	Vitaceae, Theaceae, Lamiaceae	Total phenolic compounds	Phenolics	Seeds	Liver Abscess	In vitro	Cattle	*Camellia sinensis* showed the most potent activity against liver abscesses in liver	(Salih *et al*., 2024)
2.	*Oenanthe javanica*	Apiaceae	Total phenolic compounds	Phenolics	Whole plant	Hepatitis B	In vivo & In vitro	Duck	Total phenolic extract from *Oenanthe javanica* inhibited the replication of HBV in Hep G2.2.15 cells line	(Han *et al*., 2008)
3.	*Eugenia uniflora L., Harpagophytum procumbens, Psidium guajava L., Stryphnodendron adstringens*	Myrtaceae, Pedaliaceae, Myrtaceae, Fabaceae	Quercetin, gallic acid, tannins	Flavonoids and phenolics	Whole plant	Fasciolosis	In vitro	Cattle	Extract of *E. Uniflora* exhibited 100% effectiveness against *F. hepatica* at the concentration of 0.10%.	(Marques *et al*., 2020)
4.	NA	NA	Silymarin	Flavonoids	Silymarin was purchased commercially	Thioacetamide-induced chronic liver fibrosis	In vivo	Mice	Hepatoprotective activities of silymarin were observed significantly against Thioacetamide-induced liver damage.	(Chen *et al*., 2012)
5.	*Curcuma longa*	Zingiberaceae	Silymarin	Flavanolignin	Rhizome	Thioacetamide-induced liver cirrhosis	In vivo	Mice	The liver biochemistry and immunohistochemistry were seen significantly lower in the mice groups treated with the extract from *C. longa*	(Salama *et al*., 2013)
6.	*Glycyrrhiza glabra*	Fabaceae	Multiple saponin compounds	Saponins	Leaves	High-fat diet-induced hepatotoxicity	In vivo	Rats	G. glabra significantly reduced the hepatic steatosis as compared to the control group of rats	(Goorani *et al*., 2019)
7.	*Glycyrrhiza glabra*	Fabaceae	Glycyrrhizin	saponins	Roots	Metabolic syndrome-induced liver damage	In vivo	Rats	Rats provided with the glycyrrhizin showed reduction in the oxidative stress, apoptotic cell death, and inflammation of liver	(Sil *et al*., 2015)
8.	*Phyllanthus niruri*	Phyllanthaceae	Multiple phenolics compounds	Phenolics	aerial parts of *Phyllanthus niruri* L.	CCl_4 induced toxicity	In vitro	Rats	*P. niruri* isolates exhibited potent hepatoprotective activity against CCl_4-induced hepatotoxicity in clone-9 and Hepg2 cell lines	(Ezzat *et al*., 2020)
9.	*Picrorhiza kurroa*	Plantaginaceae	Picroside I & II	Iridoid glycosides	Leaves	Toxin-induced liver injury	In vivo	Mice	*P. kurroa* reduced the serum ALT/AST and antioxidant enzyme restoration	(Almeleebia *et al*., 2022)

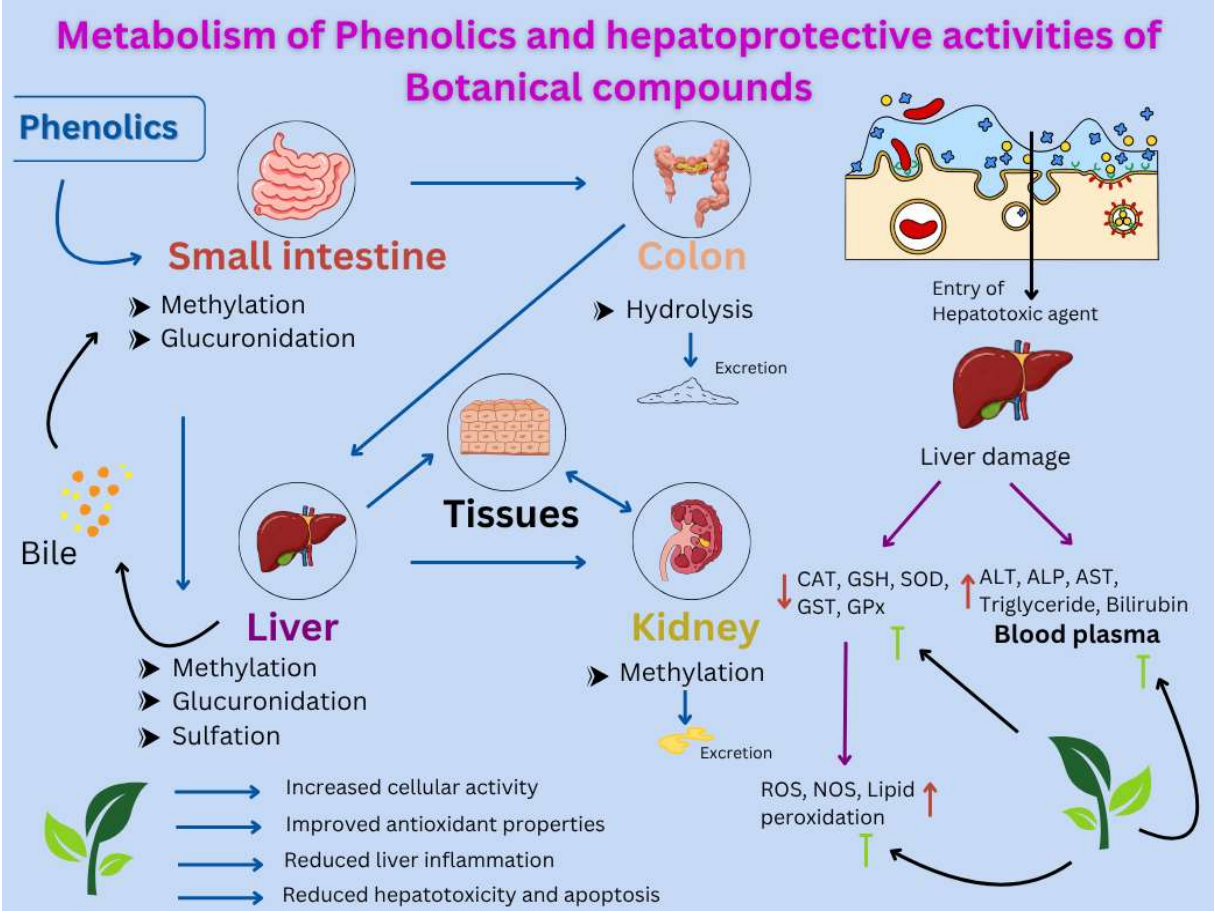

Fig. 1: Metabolism of Phenolics. The blue arrows show the activity of phenolics at different stages. Upward arrows show the upregulation and down arrows downregulation of enzymes.

keyways by which it provides hepatoprotection (Costea *et al.*, 2022). These act as direct scavengers of reactive oxygen and nitrogen species (ROS and RN) including anions of superoxide, hydroxyl radicals and peroxynitrite through the donation of electrons or hydrogen atoms, which stabilize the free radicals. Moreover, most phenolics chelate transition metals such as iron and copper, thus inhibiting the Fenton reactions and consequent generation of highly reactive hydroxyl radicals (Gulcin and Alwasel, 2022). In addition to direct scavenging, phenolic molecules increase the endogenous antioxidant system by stimulating the Nrf2/ARE pathway to activate the above-mentioned key detoxifying and antioxidant enzymes. These enzymes include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), heme oxygenase-1 (HO-1), and glutathione S-transferase (GST) (Tripathi *et al.*, 2025). The collective antioxidant reinforcements are useful in preserving cellular redox balance and inhibiting lipid peroxidation of hepatocyte membranes (Dery *et al.*, 2025). Besides the anti-oxidative properties, phenolics have been shown to have potent anti-inflammatory properties. The inhibition of the NF-KB signalling pathway by them suppresses the expression of pro-inflammatory mediators including TNF- 2, IL-1, IL-6, and COX-2, and at the same time attenuates the expression of inflammatory proteins through the MAPK signalling cascade. Phenolics also inhibit hepatic inflammation by reducing the production of prostaglandins and leukotrienes by inhibiting COX and LOX enzyme activity (Giménez-Bastida *et al.*, 2021). Phenolics also defend hepatocytes by stabilizing mitochondrial integrity. They inhibit mitochondrial permeability transition pore (MPTP) opening, preservation of membrane potential, preservation of ATP generation, and inhibition of cytochrome c release, therefore, preventing apoptosis and necrosis.

Another key mechanism involves modulation of detoxification systems (Kumar *et al.*, 2023). Phenolics control both Phase I and Phase II enzymes of metabolism, decreasing bio-activation of hepatotoxins through cytochrome P450, and increasing conjugation and excretion of toxins through increased enzymes such as UDP-glucuronosyltransferase (UGT) and GST (Kalgutkar *et al.*, 2007). In addition, the phenolics prevent lipid peroxidation, stabilize the hepatocellular membranes, and lower the serum levels of liver enzymes (ALT, AST, ALP), which indicates the maintenance of the integrity of hepatocytes. They also have positive effects by the regulation of the gut-liver axis through the favourable effect of beneficial microbiota such as Lactobacillus and Bifidobacterium, which reduces the lipopolysaccharide (LPS) translocation and decreases the Toll-like receptor 4 (TLR4)-induced hepatic inflammation (Kanmani and Kim, 2018). Moreover, phenolic compounds possess anti-fibrotic effects because they inhibit the activation of hepatic stellate cell (HSC) and collagen deposition activation by blocking the TGF-b1 signalling and

stimulating the regeneration of hepatocytes via hepatocyte growth factor (HGF) and epidermal growth factor (EGF) pathways. The hepatoprotective effect of phenolics is multidimensional, which entails oxidative stress reduction, inflammatory responses, mitochondrial preservation, promotion of detoxication, and prevention of apoptosis and hepatic fibrosis (Machado *et al.*, 2023). All these effects together protect the liver structure and liver functionality and, hence, phenolic compounds would be interesting therapeutic leads in hepatotoxicity prevention of chemical, drug and environmental hepatotoxicity in human and veterinary medicine. Because of the diverse hepatoprotective mechanisms of phenolics, they should be considered as the most suitable candidates for the development of new potent hepatoprotective drugs. However, further research is needed for the evaluation of safety index and toxic effects of phenolics in various animal species.

Alkaloids: Alkaloids are a diverse group of naturally occurring nitrogen-containing compounds widely distributed in plants (Zenk and Juenger, 2007). Alkaloids are well known for their broad pharmacological activities, including significant hepatoprotective effects. Their mechanisms of liver protection are complex and multifactorial, involving antioxidant, anti-inflammatory, anti-apoptotic, and detoxification-enhancing actions (Huang *et al.*, 2025). These compounds help preserve hepatocellular architecture and function against toxic insults caused by drugs, environmental contaminants, and metabolic byproducts. The hepatoprotective activity of alkaloids is largely mediated through their potent antioxidant and free radical scavenging properties (Venmathi Maran *et al.*, 2022). Various alkaloids, such as berberine, matrine, and piperine, effectively neutralize reactive oxygen species (ROS) and reactive nitrogen species (RNS), including superoxide anions, hydroxyl radicals, and peroxynitrite (Gjorgieva Ackova *et al.*, 2023). This prevents oxidative damage to cellular macromolecules like lipids, proteins, and DNA. In addition to directly scavenging radicals, alkaloids enhance the endogenous antioxidant defence system by upregulating key enzymatic antioxidants such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), while also increasing intracellular levels of reduced glutathione (GSH). This activation is often mediated through the Nrf2/ARE signalling pathway, which controls the transcription of cytoprotective and detoxification genes, including heme oxygenase-1 (HO-1) and glutathione S-transferase (GST). By restoring redox homeostasis, alkaloids mitigate lipid peroxidation and protect hepatocyte membranes from structural damage (Wang *et al.*, 2022).

Alongside their antioxidant actions, alkaloids exert strong anti-inflammatory effects by modulating key molecular signalling cascades (Yang *et al.*, 2021). They inhibit the activation of nuclear factor kappa B (NF-κB), a transcription factor that governs the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. However, they also inhibit the enzymes like inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) (Rahmawati *et al.*, 2024). Suppression of NF-κB activation leads to a decrease in cytokine production and infiltration of inflammatory cells into hepatic tissue. Alkaloids also regulate the MAPK pathway, particularly ERK, JNK, and p38 kinases, thereby reducing the expression of inflammatory mediators and preventing hepatocellular inflammation (Kim *et al.*, 2022). Furthermore, certain alkaloids inhibit the synthesis of eicosanoids by blocking COX and lipoxygenase (LOX) pathways, which further dampens hepatic inflammation and tissue injury (Xue *et al.*, 2024). These mechanisms make alkaloids suitable candidates for the development of new plant-based products as hepatoprotectives against multiple liver diseases. However, the adverse effects and safety index of alkaloids need further research for the formation of new effective drugs.

Flavonoids: Flavonoids comprise an extensive and diverse group of polyphenolic compounds commonly present in plants, in fruits, vegetables, and in medicine (Dias *et al.*, 2021). Flavonoids have a high reputation of being strong antioxidants, anti-inflammatory, anti-apoptotic and detoxifying, and these properties make them significant contributors to their hepatoprotective effects (Khan *et al.*, 2021). Their molecular pathways of liver protection are synergistic and consist of multiple pathways that counter oxidative stress, inflammation, mitochondrial dysfunction and toxin-induced injury, thus maintaining hepatocellular stability and functioning. The hepatoprotective effect of flavonoids is through the stabilization of mitochondrial activity. Mitochondria are very important in energy metabolism and apoptosis regulation, and flavonoids prevent oxidative stress-related dysfunction (Kung *et al.*, 2021). They maintain mitochondrial membrane potential, inhibit opening of the mitochondrial permeability transition pore (MPTP) and release of cytochrome c (Sapian *et al.*, 2021). This activity prevents caspase activation and apoptotic cell death. Through effective oxidative phosphorylation and ATP production, flavonoids make sure there is a supply of energy required to sustain hepatocyte survival and regeneration during stress levels (Machado *et al.*, 2023).

Flavonoids also regulate the detoxification processes in hepatocytes (Liao *et al.*, 2024). They inhibit over-expression of cytochrome P450 (CYP) enzymes, which produce toxic intermediates among reactive toxins during the metabolism of xenobiotics (Eaton *et al.*, 2025). Flavonoid supplements accelerate Phase II conjugation pathways, which raise the expression of hepatic conjugation enzymes (Al-Ishaq *et al.*, 2021). These enzymes include UDP-glucuronosyl glycosyltransferase (UGT) and glutathione S-transferase (GST), to metabolize lipophilic toxins into water-soluble compounds and excrete them. Such twofold modulation is used to assist in detoxifying the noxious compounds and avoiding bio-activation of the hepatotoxic agents. Moreover, flavonoids possess anti-apoptotic and cytoprotective effect regulation on the expression of apoptotic proteins (Jazvinšćak Jembrek *et al.*, 2021). They activate anti-apoptotic proteins like Bcl-2 and Bcl-xL and suppress pro-apoptotic proteins like Bax, Bad, caspase-3 and caspase-9 and effectively inhibit apoptosis in the hepatocytes (Rahman *et al.*, 2021). Cell survival signalling pathways are also activated by the flavonoids, and they include PI3K/Akt, which facilitates proliferation and repair of hepatocytes after injury (Shamsan *et al.*, 2024). Flavonoids showed effective

mechanisms against liver damage and have hepatoprotective activities. However, their safety index and toxicity in animals should be evaluated to make new potent formulations.

Conclusions: Liver is responsible for performing multiple vital body functions, including metabolism, bile production, detoxification, and antioxidant defense in animals and humans. Diseases associated with the liver in animals represent major health and economic concerns because of their impact on productivity, survival and metabolism. Liver dysfunction leads to cellular degeneration, inflammation and oxidative stress. Conventional drugs used as hepatoprotectives are effective, but their use is limited by various adverse effects, rising issue of antimicrobial resistance and residue concerns. These limitations of conventional hepatoprotective drugs make the scientists focus on new herbal alternative treatments. Medicinal plants and their bioactive compounds, including phenolics, flavonoids, terpenoids, saponins, and alkaloids, exhibit potent anti-inflammatory, anti-oxidative, and membrane-stabilizing activities that aid in the recovery and preservation of hepatic integrity. The hepatoprotective, immune-stimulating mechanisms of the botanical compounds improved liver profile, including AST, ALT, bilirubin, and copper level in liver. According to this review, botanicals compounds have significant positive effects on carcass quality, immunity and health of gut microbiota. However, further research should be conducted to check the toxicity and safety index of the botanical compounds against liver of different animal species.

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