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Hepatoprotective activities of polyherbal formulations: A systematic review

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Background: Liver diseases pose a substantial global public health challenge, encompassing conditions such as liver failure, hepatitis, cirrhosis and associated complications Safeguarding the liver becomes important as these conditions impact human health. Hepatoprotective agents play a pivotal role in mitigating liver damage caused by chemicals, drugs and toxins. Polyherbal formulations, combining botanical components from traditional medicine, offer a promising approach to addressing liver disorders. Their popularity arises from a multi-targeted strategy in treating complex diseases, marking a shift in focus toward these formulations.

Aim: The study aimed to conduct a thorough review of the existing literature on the hepatoprotective activity of polyherbal formulations and provide a comprehensive overview of their mechanisms of action. This review provides the overview of the use of polyherbal formulations in the management of liver disease.

Method: A systematic search of electronic databases, including : Scopus, Academia, Elsevier, Science Direct, Wiley, BioMed Central, PubMed, and Google Scholar, was conducted using a combination of keywords such as 'polyherbal formulations', 'hepatoprotective' and 'liver diseases'. Studies published between January 2010 and April 2023 were included in the review.

Results: A total of 61 articles were reviewed, and the studies showed that polyherbal formulations possess significant hepatoprotective activity against various hepatotoxic agents. The mechanisms of action of these formulations include antioxidant, antiinflammatory, antifibrotic and antiapoptotic effects. Additionally, some polyherbal formulations were found to stimulate liver regeneration, enhance bile secretion and promote detoxification processes.

Conclusion: Polyherbal formulations have shown promising hepatoprotective activity, and their multitargeted approach to treating complex diseases makes them a potential alternative to conventional medicines. However, identifying the active compounds responsible for the hepatoprotective effects of these formulations and their pharmacokinetics and pharmacodynamics could provide insights into the development of new and effective drugs for liver disorders.

Contribution: This article contributes to the growing body of literature on the potential of polyherbal formulations as hepatoprotective agents.

Keywords: antioxidant; hepatoprotection; hepatotoxins; liver disease; polyherbal formulation.

Introduction

Hepatoprotective substances or drugs play a critical role in protecting the liver from damage and preventing injury. As a pivotal organ, the liver regulates many important metabolic functions such as detoxification, metabolism and nutrient storage, thereby maintaining homeostasis of the body. Liver impairment can be induced by various factors including pathogens like bacteria, viruses and parasites, autoimmune diseases like autoimmune hepatitis, primary biliary cirrhosis, as well as toxic compounds such as carbon tetrachloride (CCl_4), and excessive consumption of alcohol (Guan & He 2013; Kalra, Yetiskul & Wehrle 2022). In addition, several chemical agents and medications such as antibiotics, antitubercular drugs, paracetamol, aspirin and ibuprofen which are used on a routine basis contribute to cellular and metabolic liver damage, primarily driven by mechanisms such as lipid peroxidation and other oxidative damage (Mistry, Dutt & Jena 2013). According to Manfo, Nantia and Kuete (2014), xenobiotics such as drugs, food additives, alcohol, chlorinated solvents, peroxidized fatty acids, fungal toxins, radioactive isotopes, environmental toxicants and even some medicinal plants are the

leading cause of liver injury or impairment of liver function. The liver disorder encompasses various conditions such as steatosis, fibrosis, hepatitis, cirrhosis and liver cancer which can ultimately result in liver failure and death (Patel, Shah & Tank 2013). In this context, liver disease poses a substantial challenge for both public health and the pharmaceutical industry.

While there are no dedicated allopathic medications that function solely as hepatoprotectants, certain drugs such as colestyramine, cetirizine, naltrexone, spironolactone, furosemide, propranolol, loratadine and vasopressin are employed to manage hepatotoxicity symptoms. Nonetheless, these drugs are not without their limitations, potentially causing adverse effects such as diarrhoea, constipation, flatulence, abdominal discomfort, variable responses and the possibility of exacerbating liver dysfunction (Bhardwaj et al. 2011). In addition, several natural and synthetic compounds like silymarin, curcumin, glycyrrhizin and ursodeoxycholic acid have demonstrated hepatoprotective potential through mechanisms like antioxidation, antiinflammation and antiapoptosis; however, they also have some limitations (Murray 2020; Vargas-Mendoza et al. 2014).

Herbal medicines have been used to cure different ailments since ancient times, and some plant extracts and natural compounds can either protect the liver or induce toxicity (Manfo et al. 2014). Amid this landscape, the efficacy of polyherbal formulations (PHFs) in hepatoprotection assumes increasing significance. Polyherbal medicine is the combination of several herbs and plants to treat various health conditions or to promote overall well-being. This type of traditional medicine has been practised for centuries in many cultures around the world and is still widely used today. The use of multiple herbs in a formula allows for a synergistic effect, where the different constituents work together to enhance the therapeutic effects and minimise potential side effects. Polyherbal medicines can be found in various forms, including teas, tinctures, capsules and topical preparations, and are often customised based on individual needs and symptoms. These formulations have been traditionally used in various cultures for the management of liver diseases, and recent studies have shown promising results in their hepatoprotective effects, with negligible side effects (Iroanya, Adebesin & Okpuzor 2014; Padmanabhan & Jangle 2014; Shetty et al. 2018, 2020). They have been found to contain a variety of bioactive compounds such as flavonoids, alkaloids and terpenoids, which exhibit various pharmacological activities such as antioxidant, antiinflammatory and hepatoprotective effects (Ghayas, Hannan & Rizwani 2022).

The rationale for the review and problem statement

Liver diseases are a significant public health concern globally, and their prevalence is increasing. Conventional drugs used to manage liver diseases can be expensive and with potential side effects, leading to an increased interest in herbal remedies. Herbal medicines, including PHFs, have been used for centuries to treat various ailments, including liver diseases. Polyherbal formulations are gaining popularity because of their potential synergistic effects, improved efficacy and safety compared to single herb formulations. Despite the increasing popularity of PHF, there is a need for a comprehensive review of their hepatoprotective potential against different hepatic dysfunctions. This review aims to discuss the hepatoprotective activities of PHFs based on the results obtained from several studies, assess its effectiveness against hepatic dysfunctions and their mechanisms of action, and provide insight into the potential use of PHF as a safe and effective alternative to conventional drugs for the management of liver diseases.

Methods

A thorough and careful systematic review was conducted using a variety of online databases to gain a complete understanding of the potential of PHFs to protect the liver. This methodical approach ensures that the findings are trustworthy and comprehensive.

The following databases were strategically chosen to ensure that they cover the entire body of literature: Scopus, Academia, Elsevier, ScienceDirect, Wiley, BioMed Central, PubMed and Google Scholar. These databases collectively cover a wide range of scientific disciplines, providing a comprehensive understanding of the hepatoprotective properties of PHFs.

The selection of specific search terms was methodically designed to maximise the retrieval of relevant studies that align with the primary research objective. Search terms used included, but were not limited to, 'polyherbal formulations', 'liver diseases', 'hepatoprotective', 'herbal medicines' and 'liver damage'. These carefully chosen terms ensure the inclusivity of studies investigating various aspects of PHFs' hepatoprotective properties.

To ensure a robust and current perspective, the review was limited to studies published on the hepatoprotective activities of polyherbal medicines between 2010 and 2023. This timeframe allows for the incorporation of the most recent advancements and insights while maintaining a contemporary context.

The final selection of studies was made using stringent criteria. Studies were carefully selected based on their relevance to the central research question, scientific rigour and methodological quality. This strict inclusion criterion ensures that the studies included contribute significantly to the advancement of knowledge in the field. A total of 61 studies were carefully selected for inclusion in this comprehensive review as a result of this meticulous selection process.

The studies chosen collectively investigate the hepatoprotective potential of PHFs, encompassing their effects against a variety of hepatotropic infections and hepatotoxic agents. By

meticulously synthesising the findings of these studies, this review provides a cohesive understanding of the multifaceted hepatoprotective potentials of PHFs and paves the way for deeper insights into their therapeutic mechanisms.

Ethical considerations

Ethical clearance is not applicable to this article, as no survey, human or animal experiment was carried out. The authors make use of available materials from the Internet. All the unique materials used are readily available from the author.

Review findings and discussion

Various research studies have discovered that mixtures of various herbs are surprisingly effective at protecting the liver from harm. Scientists have been studying how these herbal mixtures can help keep the liver healthy, and as a result, numerous studies have been conducted that, when taken together, they provide a comprehensive understanding of how these plant-based interventions work. Experts created these mixtures by combining various natural remedies that act as protectors, shielding the liver from various harmful substances. As we began to look into these published research articles, we discovered a complex system of how these mixtures protect the liver. Researchers in the studies reviewed dedicated significant effort to exploring different combinations of herbs, aiming to find ways to support liver health and maintain its proper function. They have conducted a range of studies with the common goal of reducing liver damage using a mixture of compounds derived from plants. Table 1 displays the hepatoprotective efficacy of PHFs as demonstrated in articles published between 2010 and 2023. Figure 1 and Figure 2 illustrate the hepatotoxins utilised in the experiments to induce liver dysfunction in animal models, as well as the frequency with which each hepatotoxin was used. They include CCl_4 (Ahmad et al. 2020; Arsul, Wagh & Mayee 2011; Balkrishna, Lochab & Varshney 2022; Bera et al. 2012; Gurusamy et al. 2010; Nipanikar, Chitlange & Nagore 2017; Said et al. 2022; Sarhadynejad et al. 2016; Yogi & Mishra 2017), thioacetamide (Balkrishna et al. 2022), hydrogen peroxide (H_2O_2) (Ndefo et al. 2021), gentamicin (Aziz et al. 2017), methotrexate (MTX) (Anila et al. 2015), cadmium chloride ($CdCl_2$) (Singh et al. 2023), D-galactosamine (Khan et al. 2015; Sachdeva, Bajpai & Razdan 2013; Shetty et al. 2020), alcohol (Dey et al. 2020; Kanchana & Jayapriya 2013; Nipanikar et al. 2017; Rafi Reshi et al. 2022; Shetty et al. 2018), cisplatin (Abuzinadah & Ahmad 2020), isoniazid (INH) (Sankar, Rajkumar & Sridhar 2015), acetaminophen (Ali et al. 2014; Fiaz et al. 2017; Gupta et al. 2013; Mayuren et al. 2010; Nipanikar et al. 2017; Patel et al. 2013; Ray, Taraphdar & Gupta 2022; Saroj, Mani & Mishra 2012; Sen et al. 2015; Shakya 2011; Shrivastava & Garg 2015; Singh et al. 2015; Sivakumar et al. 2014; Srivastava, Kaushik & Lal 2018), aceclofenac (Darbar et al. 2010) and ascorbic acid (Fiaz et al. 2017).

Briefly, CCl_4 is one of the most extensively used hepatotoxicants in animal studies; in fact, it was used in 36% of the studies reviewed (Figure 2). It undergoes metabolic activation by cytochrome P450 enzymes to produce highly reactive free radicals, leading to lipid peroxidation, oxidative stress and ultimately hepatocyte damage. This results in the development of liver fibrosis, cirrhosis, necrosis and even hepatocellular carcinoma (Kenjale, Shaikh & Sathaye 2011; Rasheed et al. 2014). Paracetamol ($C_8H_9NO_2$), also known as acetaminophen, is a widely used analgesic and antipyretic medication that is commonly metabolised by the two pathways, glucuronidation and sulfation, which yield non-toxic metabolites that are easily eliminated from the body. However, excessive and chronic consumption of acetaminophen results in the glucuronidation and sulfation pathways being overwhelmed, and acetaminophen being metabolised through a third pathway called cytochrome P450-mediated oxidation. This third pathway results in the production of the toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI), which is quickly neutralised by the antioxidant glutathione (GSH). Excessive consumption of acetaminophen, however, results in the depletion of GSH and the intrahepatic accumulation of free NAPQI which can further bind to the hepatocellular proteins, causing oxidative stress, mitochondrial dysfunction and hepatic damage (Patel et al. 2013; Ray et al. 2022; Srivastava et al. 2018). Thioacetamide is another hepatotoxin widely used to induce liver damage in animal models. Thioacetamide is metabolised by cytochrome P450 enzymes to form toxic intermediates that bind to cellular proteins, induce oxidative stress and cause cell death. The resulting liver injury is characterised by centrilobular necrosis, inflammation and fibrosis. Studies have shown that thioacetamide-induced liver injury in rats is associated with increased expression of proinflammatory cytokines, such as TNF-α and IL-1β, and decreased expression of antiinflammatory cytokines, such as IL-10 (Kumar et al. 2013). Hydrogen peroxide (H_2O_2) is a powerful oxidant that can cause hepatotoxicity through oxidative stress. When H_2O_2 enters the hepatocytes, it can produce reactive oxygen species (ROS), which are highly reactive oxygen-containing molecules. Reactive oxygen species can harm hepatocellular components such as proteins, lipids and deoxyribonucleic acid (DNA). This oxidative stress can impair normal hepatocellular functions, resulting in inflammation, hepatocellular death and, eventually, hepatic damage. The liver's ability to detoxify harmful substances may be jeopardised as a result of the oxidative stress caused by H_2O_2. Reactive oxygen species can also activate signalling pathways that promote inflammation and apoptosis (programmed cell death), exacerbating liver damage (Ndefo et al. 2021).

Furthermore, gentamicin is an aminoglycoside antibiotic that can cause nephrotoxicity and hepatotoxicity. The hepatotoxicity is thought to be caused by the accumulation of the drug in the liver, leading to oxidative stress and cell death. It has been shown to cause liver injury by increasing the levels of liver enzymes, such as alanine transaminase (ALT) and aspartate transaminase (AST), and causing histopathological changes in the liver. Gentamicin-induced liver injury is characterised by increased lipid peroxidation, decreased antioxidant levels and impaired mitochondrial function. This results in liver damage and dysfunction (Aziz

TABLE 1: Hepatoprotective effect of polyherbal formulations.

Commercial name	Formulation with scientific names and plant part	Dosage and duration	Bioassay models	Results	References
RVSPHF567	Ajowan, cardamom, clove, mace and nutmeg	1 mL/kg orally three times daily for the duration of 3 days	In vivo assay using adult Wistar strain albino rats	The findings showed that CCl_4 caused alteration in all the biochemical parameters and centrilobular necrosis, while RVSPHF567 and Liv-52 (control) showed a significant reduction in the serum levels of SGOT, SGPT, ALP, TB and an increase in the level of total proteins and albumin. In the histopathological examination of liver sections, the restoration of normal structural and architectural intactness was revealed, and no evidence of necrosis was detected.	(Kandasamy et al. 2010)
Livina (antituberculosis remedies)	It comprises 50 mg each of *Picrorhiza kurroa, Phyllanthus niruri, Andrographis paniculata, Cichorium intybus, Tephrosia purpurea, Solanum dulcamara, Crinum asiaticum, Alstonia scholaris,* 25 mg each of *Holarrhena antidysenterica, Tinospora cordifolia, Terminalia chebula* and *Asteracantha longifolia*	1000 mg was administered twice orally for a period of 8 weeks	In vivo experiment using human	The result demonstrated that upon administration of Livina, no elevation of SGOT, SGPT and ALP was observed in the patients. Hence, Livina prevented antitubercular therapy (ATT)-induced elevations of the biochemical markers of liver function tested and maintained them within normal range. As a result, the remedy can be used in conjunction with anti-TB chemotherapy to improve adherence to ATT and avoid MDR-TB.	(Gulati et al. 2010)
Polyherbal formulation	*Asteracantha longifolia* (whole plant), *Cyprus rotundus* (bulb), *Bryophyllum pinnatum* (leaf)	250 mk/kg/day orally for 30 days	In vivo assay in adult male Wistar albino rats	The study depicted that the PHF exhibited a significant protective effect against liver damage induced by CCl_4 on the liver, lowering serum and liver activities of AST, ALT, ALP, LDH, ACP, LDH, serum bilirubin, serum cholesterol and serum total protein when compared with the standard drug silymarin. The hepatoprotective activity of the extracts may be attributed to the increased regeneration of hepatocytes and inhibitory effects on microsomal enzymes.	(Gurusamy et al. 2010)
Livina	*Solanum nigrum, Holarrhena antidysenterica, Tephrosia purpurea, Andrographis paniculate, Phyllanthus niruri, Tinospora cordifolia, Terminalia chebula. Asteracantha longifolia, Alstonia scholaris, Berberis aristate, Cichorium intybus, Picrorhiza kurroa*	0.25 mL/day, 0.5 mL/day and 1 mL/day orally for 60 days	In vivo assay using Sprague-Dawley rats	Livina at the doses of 0.5 mL/day and 1 mL/day was found to significantly reduce the damaging effects of aceclofenac on liver functions compared to the control group. This was shown by measuring levels of serum markers such as ALT, AST, γ-glutamyl transpeptidase, ALP, lipid peroxidase (MDA), δ-aminolevulinate dehydratase activity (δ-ALA-D), serum total protein and bilirubin (total and direct) levels in rats serum. The study also showed that Livina had a moderate effect on histopathological changes induced by aceclofenac such as congestion of the central vein, centrilobular necrosis and sinusoidal congestion. The effectiveness of Livina was found to be almost parallel with silymarin, indicating the herbal formulation to be almost as effective as the standard drug.	(Darbar et al. 2010)
Hepjaun syrup (HA-I [aqueous extract], HA-II [alcoholic extract] and HA-III [alcoholic extract in double concentration])	*Lawsonia alba, Eclipta alba, Berberis aristata, Aloe vera, Andrographis paniculata, Boerhavia biffusa, Melia azadirachta, Phyllanthus niruri, Croton oblongifolius, Tephrosia purpurea, Plumbago zeylanica,* and *Picrorrhiza kurroa*	100 mg/kg, 300 mg/kg and 500 mg/kg orally for 14 days	In vivo assay using male Wistar rat	The study demonstrated that pretreatment with HA-I, HA-II and HA-III at a dose of 500 mg/kg significantly reduced the CCl_4-induced elevated levels of SGOT, SGPT, ALP and serum bilirubin in rats with induced hepatotoxicity. Among the test formulations, HA-II exhibited the highest hepatoprotective activity followed by Liv-52, HA-I and HA-III. The results also showed that HA-II had high hepatoprotective activity as confirmed by serum bilirubin levels. Additionally, rats treated with HA-II exhibited the lowest liver weight among the other formulations, indicating the high hepatoprotective activity of HA-II in preventing liver necrosis. The study concluded that the polyherbal formulations HA-II and HA-III can be proposed to be beneficial in jaundice and hepatitis conditions, especially formulation HA-II.	(Patel et al. 2010)
Livactine	*Boerrhavia diffusa, Tinospora cordifolia, Andrographis paniculata* and *Emblica officianalis*	1 mL/kg, 2 mL/kg orally for 10 days	In vivo using Wistar albino rats	Livactine at the dose of 2 mL/kg showed a significant hepatoprotective effect against CCl_4 and paracetamol-induced liver damage in rats, as evidenced by a reduction in elevated serum enzyme levels, including SGOT, SGPT, LDH, ALP, ACP, TB and total protein. The results were comparable to that of Liv-52, a marketed hepatoprotective drug. The hepatoprotective activity of Livactine is believed to be due to the free radical scavenging property of its constituent plant extracts.	(Mayuren et al. 2010)
Hepax	*Plumbago zeylanica, Picrorrhiza kurroa, Sodii carbonas impure, Phyllanthus emblica, Terminalia chebula, Calcii oxidum* and *Potassii carbonas impura*	100 mg/kg and 200 mg/kg orally for 7 days	In vivo assay using male Wistar albino rats	The study showed that pretreating rats with silymarin (100 mg/kg) and Hepax at both concentrations provided significant protection against liver damage induced by CCl_4, paracetamol and thioacetamide. Both silymarin and Hepax were able to maintain liver weight and liver-to-body ratio, normalise SGPT, SGOT, ALP and total bilirubin, and inhibit histopathological abnormalities. Hepax showed dose-dependent protection against all three types of liver damage, and at a dose of 200 mg/kg, its protective effect was comparable to that of silymarin at a dose of 100 mg/kg.	(Devaraj et al. 2011)
Livergen	Andrographis paniculata, Apium graveolens, Berberis lycium, Carum copticum, Cichorium intybus, Cyperus rotundus, Eclipta alba, Ipomoea turpethum, Oldenlandia corymbosa, Picrrorhiza kurroa, Plumbago zeylanica, Solanum nigrum, Tephrosia purpurea, Terminalia arjuna, Terminalia chebula, Trigonella foenumgraecum	2.6 mL/kg orally for 5 days	In vivo study in albino rats	The polyherbal formulation, Livergen, at the dose of 2.6 mL/kg had shown a significant decrease in enzyme levels of SGOT, SGPT, ALP, cholesterol, bilirubin, and a significant increase in enzyme level of total protein.	(Arsul et al. 2011)

Table 1 continues on next page →

TABLE 1 (Continues...): Hepatoprotective effect of polyherbal formulations.

Commercial name	Formulation with scientific names and plant part	Dosage and duration	Bioassay models	Results	References
Livshis	*Aloe barbadensis* (leaf), *Andrographis paniculata* (leaf), *Asteracantha longifolia* (leaf), *Berberis chitria* (bark, stem), *Fumaria parviflora* (leaf), *Phyllanthus fraternus* (leaf) *and Picrorhiza kurroa* (rhizome).	50 mg/5 mL b.w. orally for 27 days	In vivo assay in male albino rats	The results showed that Livshis pretreatment provided significant protection against hepatic damage induced by CCl_4. The Livshis treatment exhibited less dramatic changes in response to CCl_4 compared to the distilled water pretreatment.	(Bera et al. 2011)
Majoon-e-Dabeed-ul-ward (MD)	Crocus sativa, Gentian olivieri, Cusseta reflexa, Rosa damascene, Cichorium intybus, Asarum europaeum, Commiphora opobalsamum, Aquilaria agallocha, Pistacia lentiscus, Nardostachys jatamansi, Cinnamomum zeylanicum, Nardostachys, Bambusa bambos, Cymbopogon jwarancusa, Saussurea hypoleuca, Cuscuta reflexa, Rubia cordifolia, Coccus lacca, Apium graveolens, Aristolochia donga, Commiphora opobalsamum, Syzygium aromaticum, Elettaria cardamomum	250 mg/kg, 500 mg/kg and 1000 mg/kg once only	In vivo using female albino Sprague-Dawley rats	The results showed that treatment with MD had a hepatoprotective effect against acetaminophen-induced liver damage in female albino Sprague-Dawley rats. Treatment with different concentrations of MD reversed the altered levels of AST, ALT, SALP, LDH, bilirubin, albumin, urea and creatinine in a dose-dependent manner, which were elevated due to the administration of acetaminophen. The study also found that MD restored the levels of LPO, GSH content, ATPase and G-6-Pase. The efficacy of MD was found to be comparable to silymarin, which is a known hepatoprotective agent. Therefore, the Unani polyherbal formulation, MD, can be considered a potential hepatoprotective agent.	(Shakya 2011)
Punarnavashtak kwath (PNK)	*Boerhavia diffusa* (root), *Picrorhiza kurroa* (root), *Tinospora cordifolia* (stem), *Zingiber officinalis* (rhizome), *Berberis aristate* (stem), *Terminalia chebula* (fruit), *Azadirachta indica* (bark) and *Tricosanthes dioica* (leaf)	100 mg/kg and 150 mg/kg orally three times at 12 h interval	In vivo (Wistar rats) and in vitro (HepG2 cell line)	The results showed that PNK administration at doses of 100 mg/kg and 150 mg/kg produced significant hepatoprotective effects in rats. It decreased the levels of AST, SALT, SALP and serum bilirubin and increased protein levels. Thiopentone-induced sleeping time was decreased in the PNK-treated animals compared to the CCl_4-treated group. The investigation carried out on the HepG2 cell line depicted a significant increase in the viability of cells exposed to PNK as compared with CCl_4-treated cells. The CCl_4-exposed HepG2 cells showed 25.37% viability while those exposed to PNK ranged between 30% and 88% at 1 µg/mL – 15 µg/mL concentration. The increase in the percentage of cell viability of HepG2 cells treated with PNK at 15 µg/mL concentration was the same as that produced by standard silymarin at 50 µg/mL.	(Shah et al. 2011)
Livomyn	*Andrographis paniculata, Phyllanthus niruri, Cichorium intybus, Boerhavia diffusa, Tinospora cordifolia* and *Picrorrhiza kurroa*	Two doses of 1 & 2 theraupeutic doses, oral administration for 7 days	In vivo (Wistar rats)	Livomyn exhibited significant hepatoprotective effects against ethanol, CCl_4 and D-galactosamine-induced hepatotoxicity in Wistar rats. Livomyn treatment resulted in decreased levels of albumin, bilirubin, SGOT, SGPT, LPO, alkaline phosphate and cholesterol, while total protein and reduced glutathione levels increased in Livomyn-treated groups.	(Kenjale et al. 2011)
Hepatoprotective polyherbal formulation (PHF)	*Coccinia indica* (leaves), *Sida cordata* (leaves) and *Scoparia dulcis* (whole plant)	100 mg/kg/day and 200 mg/kg/day orally for 7 days	In vivo assay using Wistar rat	The study evaluated the protective and curative effects of PHF against CCl_4 and paracetamol-induced hepatotoxicity in rats. The pretreatment with silymarin (100 mg/kg) and PHF (100 mg/kg and 200 mg/kg) showed significant protection against CCl_4 and PCM-induced hepatic damage by maintaining the morphological parameters with the normal range and normalising the elevated levels of biochemical parameters (SGPT, SGOT, ALP and TB) and thus inhibited the histopathological abnormalities caused by the toxins.	(Mistry et al. 2012)
Livshis	*Berberis aristata* (stem bark), *Phylanthus niruri* (leaf), *Andrographis paniculata* (leaf), *Aloe indica* (leaf), *Picrorhiza kurroa* (rhizome), *Asteracantha longifolia* (leaf) and *Fumaria parviflora* (leaf)	5 mg/0.5 mL/100 g through gavage for 14 days	In vivo study on male albino rats	The results of the study showed that the administration of Livshis significantly protected the liver against CCl_4-induced toxicity in male albino rats. The rats treated with CCl_4 showed a significant increase in liver necrosis, lipid peroxidation levels and serum marker enzymes, i.e. SGOT, SGPT and ALP, as well as a decrease in the levels of hepatic antioxidant key enzymes, glycogen content, vitamin C and serum total protein level. The histology of the liver and hematological parameters was also significantly affected in CCl_4-treated animals. However, the administration of 'Livshis' resulted in a significant recovery of these parameters toward the control level, indicating the hepatoprotective effects of the polyherbal formulation.	(Bera et al. 2012)
Polyherbal formulation (PHF) PHF = 1 (300 mg/kg), PHF = 2 (400 mg/kg) and PHF = 3 (500 mg/kg)	*Emblica officinalis* (fruits), *Terminalia chebula* (fruits), *Terminalia bellirica* (fruits), *Picrorhiza kurroa* (rhizomes), *Tinospora cordifolia* (stem), *Swertia chirata* (entire herb) *Azadirachta indica* (bark) and *Adhatoda vasica* (stem bark)	300 mg/kg, 400 mg/kg, 500 mg/kg orally for 7 days	In vivo assay using Female mice	The results showed that the pretreatment with the PHF had good hepatoprotective activity at the PHF-1 dose. The serum levels of liver enzymes were significantly increased in the PCM-treated group and vehicle control group. However, the serum levels of SGOT, SGPT, alkaline phosphatase, serum bilirubin, serum urea, serum creatinine, serum triglycerides and cholesterol were significantly decreased in the groups treated with the polyherbal formulations. The bilirubin total test showed that the level of bilirubin was significantly decreased in dosing groups PHF-2 and PHF-3. Histopathological evaluation of the livers also showed that the PHF-treated mice exhibited significant protection against PCM intoxication, as evidenced by the presence of normal hepatic cords and the absence of necrosis with minimal inflammatory conditions around the central vein.	(Saroj et al. 2012)

Table 1 continues on next page →

TABLE 1 (Continues...): Hepatoprotective effect of polyherbal formulations.

Commercial name	Formulation with scientific names and plant part	Dosage and duration	Bioassay models	Results	References
Polyherbal hepatoprotective formulation	*Andrographis paniculata, Phyllanthus niruri,* and *Phyllanthus emblica*	100 mg/kg, 200 mg/kg and 400 mg/kg orally for 5 days	In vivo assay using Wistar albino rats	The paracetamol-induced elevation level of SGPT, SGOT, ALP, direct bilirubin and LDH was significantly inhibited at 100 mg/kg and 200 mg/kg, while the CCl_4 and ethanol-induced levels of the parameters were significantly inhibited at 200 mg/kg and 400 mg/kg, indicating that the PHF was effective in protecting the liver. The histological studies also supported the biochemical parameters as the liver exhibited almost normal architecture as compared to the toxicant group. Silymarin was used as a standard drug, and PHF showed a significant hepatoprotective effect compared to the control and silymarin (50 mg/kg).	(Tatiya et al. 2012)
Polyherbal tablet formulations (PTF-1 and PTF-2)	*Butea monosperma* (bark), *Bauhinia variegata* (bark) and *Ocimum gratissimum* (fresh leaves)	50 mg/kg and 100 mg/kg, orally once a day for 7 days	In vivo assay using male Wistar rats	The results of the study showed that the PTFs had significant hepatoprotective activity in the rat model of paracetamol-induced liver damage. The formulations were able to reduce the levels of SGPT, SGOT, ALP and TB when compared to the paracetamol-treated group. In particular, the PTF-2 formulation was found to be more effective in reducing the elevated levels of SGPT, SGOT, ALP and bilirubin than the PTF-1 formulation.	(Gupta et al. 2013)
Polyherbal syrup	*Allium sativum, Curcuma longa, Ocimum sanctum* and *Aloe barbadensis*	100 mg/kg, 300 mg/kg and 500 mg/kg orally for 14 days	In vivo assay in adult male Wistar rats	The results showed that paracetamol caused marked elevation in AST, ALT, ALP, lactate dehydrogenase (LDH) and TB, indicating hepatotoxicity. However, co-administration of the polyherbal syrup with paracetamol showed a decrease in these parameters, indicating a hepatoprotective effect.	(Patel et al. 2013)
Herbal formulation	*Curcuma longa* (dried rhizomes), *Occimum sanctum* (leaf), *Murraya koenigii* (leaf) and *Nyctanthes arbrotristis* (leaf)	50 mg/kg, 100 mg/kg and 250 mg/kg p.o.	In vivo using albino rats	The polyherbal preparation at 250 mg/kg exhibited hepatoprotective effects against D-galactosamine-induced liver toxicity in rats. The preparation significantly reduced the levels of serum marker enzymes (ALT, AST and ALP), total and direct bilirubin, and restored the levels of GSH and MDA in liver homogenate to normal levels. Histopathological studies further confirmed the hepatoprotective activity of the preparation compared to D-galactosamine-treated groups. The results obtained were comparable to silymarin, the standard drug used in the study.	(Sachdeva et al. 2013)
Hepatoprotective polyherbal formulation	*Coccinia indica* (leaves), *Sida cordata* (leaves) and *Scoparia dulcis* (whole plant)	300 mg/kg and 500 mg/kg orally for 5 days	In vivo assay using male Wistar rat	The results showed that the administration of CCl_4 caused acute hepatic damage in the positive control group as evidenced by the significant increase in the levels of SGOT, SGPT, SALP and serum bilirubin. However, pretreatment with the PHF at two doses as well as silymarin (100 mg/kg) significantly reduced the elevated levels of SGOT, SGPT, ALP and serum bilirubin induced by CCl_4. In addition, the results showed that PHF was more effective than silymarin in reducing the elevated levels of SGOT, SGPT, ALP and serum bilirubin induced by CCl_4.	(Mistry et al. 2013)
Livomyn	Andrographis paniculata, Phyllanthus niruri, Triphala, Boerhavia diffusa, Amoora rohituka, Chicorium intybus, Adhatoda vasica, Eclipta alba, Zingiber officinale, Berberis aristata, Fumaria officinalis, Embellia ribes, Tephrosia purpurea, Tinospora cordifolia, Coriandrum sativum, Aloe barbadensis and Picrorrhiza kurroa	120 mg/kg/day, 240 mg/kg/day, 480 mg/kg/day orally for 7 days	In vivo (Sprague-Dawley rats)	Livomyn showed significant hepatoprotective activity as indicated by a decrease in serum marker enzymes (SGOT, SGPT and ALP) and an increase in total bilirubin protein (TBP) in a dose-dependent manner. The toxic effects of CCl_4 in the Livomyn-treated group were controlled significantly by the restoration of the levels of serum bilirubin protein and enzymes compared to the CCl_4 treated and silymarin-treated groups. Histopathological studies further confirmed the hepatoprotective activity of Livomyn. The liver sections of animals treated with Livomyn showed moderate to mild multifocal centrilobular necrosis and minimal diffuse granular degeneration, which was almost comparable to the silymarin-treated group.	(Harshitha et al. 2013)
Polyherbal capsule	*Andrographis paniculata* (whole plant), *Phyllanthus amarus* (whole plant), *Asparagus racemosus* (root), *Tinospora cordifolia* (stem), *Boerhavia diffusa* (root) and *Eclipta alba* (whole plant)	100 mg/kg and 200 mg/kg/day orally for 9 days	In vivo method using adult male albino Wistar rats	The polyherbal capsule showed significant hepatoprotective activity in rats with CCl_4-induced hepatotoxicity, as demonstrated by the significant reduction of SGOT, SGPT, ALP, and total bilirubin levels in the serum. The hepatoprotective activity was comparable with the standard drug silymarin. Histopathological studies showed that the polyherbal capsule inhibited the degeneration of hepatocytes and fatty changes in a dose-dependent manner. The study demonstrated the potential of the developed polyherbal capsule as a safe and effective hepatoprotective agent.	(Vadivu et al. 2013)
Polyherbal formulation	*Begonia laciniate* (root), *Cuscuta epithymum* (whole plant), *Dendrobium ovatum* (whole plant)	200 mg/kg and 400 mg/kg orally for 5 days	In vivo assay using albino rats	The research findings indicated that the tested concentrations had a significant protective effect on the liver of rats that were intoxicated with CCl_4. This was observed by the reduction in the elevated serum level of SGOT, SGPT, ALP and TB. In addition, the liver sections of the treated groups showed recovery from CCl_4-induced liver damage as evidenced by the presence of normal hepatocytes. The higher dose of 400 mg/kg demonstrated a marked protective activity, similar to that seen in silymarin-treated rats. Moreover, there was significant attenuation of inflammatory and necrotic changes, and the cellular architecture of the liver was preserved.	(Ganapaty et al. 2013)

Table 1 continues on next page →

TABLE 1 (Continues...): Hepatoprotective effect of polyherbal formulations.

Commercial name	Formulation with scientific names and plant part	Dosage and duration	Bioassay models	Results	References
Clearliv	*Phyllanthus niruri, Eclipta alba, Boerhavia diffusa, Tinospora cordifolia, Tribulus terrestris, Tephrosia purpurea, Indigofera tinctoria, Aconitum heterophyllum, Andrographis paniculata, Rubia cordifolia, Terminalia chebula, Curcuma longa* and *Ricinus cummunis*	800 mg/kg/day and 1000 mg/kg/day orally for 3 days	In vivo (Wistar rats)	Clearliv demonstrated significant hepatoprotective effects against thioacetamide- and DL-galactosamine (GalN)-induced liver necrosis and injury, respectively, at the doses used. The results showed a significant reduction in elevated plasma AST, ALT and ALP levels, and liver lipid peroxidation levels compared to the toxin-administered groups. However, in CCl_4-induced hepatitis, Clearliv had a favourable hepatoprotective effect but the results were not significant. Clearliv 1000 mg/kg showed a significant decrease in ALT levels, but it did not reverse the CCl_4-induced increase in AST levels. Overall, Clearliv showed promising hepatoprotective effects against liver necrosis and injury models in rats.	(Kumar et al. 2013)
F-I, F-II and F-III	*Tinospora cordifolia, Boerhavia diffusa, Phyllanthus amaraus, Euphorbia hirta* and *Wedelia chinensis*	200 mg/kg/day orally for 8 days	In vivo study on healthy adult male Wistar albino rats	The results indicated that the polyherbal formulations at the dose of 200 mg/kg showed a significant hepatoprotective effect against PCM-induced liver damage in rats compared to the control group. The morphological parameters like liver colour and weight showed normal signs in the treated rats, and the histopathological parameters showed less inflammatory cell infiltration, kupffer cell hyperplasia and fatty changes in the liver architecture. The functional parameters of pentobarbitone sleeping time were also improved in the treated rats. The biochemical parameters of SGOT, SGPT, SALP, bilirubin and plasma protein levels were significantly lower in the treated rats, indicating the hepatoprotective effect of the polyherbal formulations.	(Sivakumar et al. 2014)
Herbal syrup	Aegle marmelos, Eclipta alba, Phyllanthus amarus Vanilla, methylparaben, red colour and simple syrup base	500 mg/kg/day orally for 5 days	In vivo assay using male Wistar rats	The study showed that the herbal syrup can be used to treat CCl_4-induced hepatotoxicity in rats as it significantly reduced the levels of ALT and AST in plasma and also reduced the incidence of liver lesions induced by CCl_4. Histopathological examination showed that the formulation reduced the fatty degeneration and vacuole formation induced by CCl_4. It also significantly reduced the levels of SGOT, SGPT, ALP and total bilirubin in a dose-dependent manner compared to the CCl_4-only treated animals. The hepatoprotective effects of the formulation were almost close to that of silymarin at the dose of 200 mg/kg, which is a standard drug used to treat liver disorders. The formulated syrup also restored the hepatic enzyme levels almost to normal after 3 days.	(Rasheed et al. 2014)
GOV	*Gongronema latifolia* (leaf), *Ocimum gratissimum* (leaf) *and Vernonia amygdalina* (leaf)	2 g/kg/day, 4 g/kg/day and 8 g/kg/day orally for 14 days	In vivo (Wistar albino rats)	The results showed that at the doses used, GOV significantly reduced the serum levels of liver marker enzymes, including ALP, ALT, AST, GGT and LDH, which were elevated in the toxin control group, indicating the induction of severe liver damage. The levels of serum cholesterol, creatinine, triglyceride and BUN concentrations were also reduced by GOV. The study revealed that GOV has a hepatoprotective potential against acetaminophen-induced hepatotoxicity in rats.	(Iroanya et al. 2014)
HP4	*Aloe vera* (leaf), *Bacopa monnieri* (leaf), *Moringa oleifera* (leaf) and *Zingiber officinale* 6 (rhizome)	250 g/kg/day and 500 mg/kg/day orally for 7 days	In vivo (mice)	The study found that the administration HP-4 exhibited hepatoprotective effects on mice treated with CCl_4 compared to the control group. The levels of hepatic marker enzymes (AST, ALT, ALP, γ-GT and LDH) were remarkably elevated in the group treated with CCl_4, indicating liver damage. However, the administration of HP-4 prevented the elevation of these enzymes. This suggests that HP-4 has a synergistic action of phytochemicals that exhibit hepatoprotective effects.	(Padmanabhan & Jangle 2014)
Habb-e-Asgand	*Ptychotis ajowan* (fruit), *Withania somnifera* (root), *Gmelina asiatica* (stem), *Curculigo orchioides* (root), *Piper longum* (fruit and root), *Asparagus racemosus* (root), *Zingiber officinale* (rhizome), *Saccharum officinarum* (stem)	250 mg/kg/day orally for 14 days	In vivo (Swiss albino male mice)	The study showed that Habb-e-Asgand had a significant hepatoprotective effect against paracetamol-induced liver injury in mice. PCM alone induced liver function enzymes, cytochrome P450 (CYP), and LPO and inhibited the activity of antioxidant enzymes, while Habb-e-Asgand decreased liver function levels, CYP activity, and LPO levels, and induced antioxidant enzyme activity.	(Ali et al. 2014)
Virgoliv Syrup (VLS)	*Eclipta alba* (whole plant), *Plumbago zeylanica* (root), *Andrographis paniculata* (whole plant), *Boerhavia diffusa* (root), *Solanum nigrum* (whole plant), *Tecomella undulata* (stem bark), *Picrorhiza kurroa* (rhizome), *Cissampelos pareira* (root), *Operculina turpethum* (root), *Embelia ribes* (fruit), *Cichorium intybus* (seed), *Phyllanthus niruri* (whole plant), *Tinospora cordifolia* (stem), *Tephrosia purpurea* (whole plant), *Piper longum* (fruit), *Berberis aristata* (stem), *Cassia occidentalis* (seed)	1 mL/kg/day orally for 7 days	In vivo assay using Sprague-Dawley rats	The findings depicted that the rats administered with VLS showed a significant maximum reduction in serum levels of ALT, AST, ALP and TB levels compared to the CCl_4-treated group. The hepatoprotective effect of silymarin (100 mg/kg) was comparable to that of VLS. Histopathological examination of liver tissues indicates that VLS showed significant hepatoprotective activity against CCl_4-induced hepatic damage, which might be due to the scavenging of free radicals as evident by recovery of antioxidant enzymes such as CAT, GSH and SOD towards normalisation and decreased lipid peroxidation.	(Ingawale et al. 2015)

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TABLE 1 (Continues...): Hepatoprotective effect of polyherbal formulations.

Commercial name	Formulation with scientific names and plant part	Dosage and duration	Bioassay models	Results	References
Amlycure DS	*Andrographis paniculata, Tinospora cordifolia, Phyllanthus niruri, Boerhavia diffusa, Eclipta alba, Ocimum sanctum, Cichorium intybus, Solanum nigrum, Berberis lycium, Plumbago zeylanica, Glycyrrhiza glabra, Foeniculum vulgare, Rheum emodi* and *Picrorhiza kurroa*	Solid form (95 g/kg/day and 285 mg/kg/day for 40 days) and liquid form (1402 g/kg/day and 5608 mg/kg/day for 40 days)	In vivo study on albino rats	The study found that the administration of Amlycure DS at different doses had a significant hepatoprotective effect on the liver, as evidenced by the improvement in biochemical parameters and histological hepatic damage induced by the hepatotoxic antitubercular drug isoniazid in experimental albino rats. The hepatoprotective activity of Amlycure DS was comparable to silymarin, a standard hepatoprotective drug. The study suggested that the hepatoprotective activity of Amlycure DS is due to the presence of phytochemicals, such as andrographolide, neoandrographolide, picroside, kutkoside, phyllanthin and glycyrrhizin, which are known to have potent hepatoprotective properties. The herbal formulation was also found to contain significant proportions of alkaloids, carbohydrates, tannins and flavonoids, which contribute to its hepatoprotective activity.	(Sharma et al. 2015)
Livplus-A	*Eclipta alba* (whole plant), *Phyllanthus niruri* (whole plant), *Cichorium intybus* (whole plant), *Picrorhiza kurroa* (root), *Boerhavia diffusa* (whole plant), *Berberis aristata* (whole plant) and *Andrographis paniculata* (whole plant)	100 g/kg, 200 g/kg and 400 mg/kg orally for 14 days	In vivo albino Wistar rats	The results showed that Livplus-A and silymarin (100 mg/kg) significantly reduced the elevated levels of AST, ALT, ALP, bilirubin (direct and total), GGT, total cholesterol (TC) and triglycerides (TG) and increased levels of total protein (TP) compared to CCl_4 control rats.	(Maheshwari et al. 2015)
Polyherbal preparation	*Andrographic paniculata, Night Jaismine* and *Annona squamosal*	50 g/kg and 100 mg/kg/day for 5 days	In vivo (Wistar rats)	The study found that the polyherbal preparation significantly reduced liver enzyme levels in experimental animals, indicating hepatoprotective activity. The efficacy of the polyherbal preparation was found to be dose-dependent, and the histopathology study of the liver also supports the presence of hepatoprotective activity by showing improved cytoarchitecture of liver cells in the treated groups. The observed efficacy of the polyherbal preparation was comparable to that of the standard drug silymarin. The histopathological examination revealed that the hepatic cells, central vein and portal triad were almost normal in the polyherbal preparation and other groups, indicating potential pharmacological activity against PCM-induced hepatotoxicity due to the synergism of plant extracts.	(Shrivastava & Garg 2015)
Ambrex	*Withania somnifera, amber*, *Pistacia lentiscus*, *Orchis mascula* and *Cycas circinalis*	250 g/kg/day and 500 mg/kg/day orally for 7 days	In vitro assay using Chang liver cells; in vivo assay using Swiss albino mice	Ambrex was found to have hepatoprotective effects against methotrexate-induced hepatotoxicity. Ambrex was able to restore the levels of antioxidants such as superoxide dismutase, catalase, and glutathione to near normal and reduce the elevated plasma levels of aspartate transaminase, alanine transaminase (ALT), alkaline phosphatase, γ–glutamyl transferase (γGT), and total bilirubin. Ambrex also inhibited the formation of hepatic malondialdehyde induced by MTX. In vitro studies showed that Ambrex protected against methotrexate (MTX)-induced hepatotoxicity at the dose of 50 ng/mL and 500 ng/mL. The study further revealed that Ambrex inhibited the overexpression of BAX and suppressed BCL2 and DHRF expressions. The results of the study suggest that Ambrex has potent hepatoprotective effects, which were evident from both in vivo and in vitro results. When compared to the control and silymarin, Ambrex was found to be effective in reducing the levels of SGOT, SGPT, ALP, γGT and total bilirubin. It also had a significant impact on the restoration of antioxidant levels and the inhibition of hepatic malondialdehyde formation.	(Anila et al. 2015)
Polyherbal extract	*Andrographis paniculata*, *Tinospora cordifolia* and *Solanum nigrum*	300 mg/kg/day and 500 mg/kg/day for 7 days	In vivo in Swiss albino mice	The study found that pretreatment with polyherbal extract at a dose of 500 mg/kg exhibited a significant hepatoprotective activity as compared to the PCM group. This was evidenced by a significant ($p < 0.05$) decrease in serum levels of ALT, aspartate aminotransferase, bilirubin and alkaline phosphatase, which are indices of liver injury. Therefore, the polyherbal extract showed significant hepatoprotective effects against PCM-induced hepatotoxicity.	(Singh et al. 2015)
DRDC/AY/8060	*Phyllanthus niruri* (aerial part), *Tinospora cordifolia*, *Azadirachta indica* (bark), *Andrographis paniculata* (whole plant), *Terminalia chebula*, *Emblica officinalis*, *Terminalia belerica* and *Picrorhiza kurroa* (root)	120 mg/kg/day and 240 mg/kg/day for 10 days	In vivo using Wistar rats	Treatment with DRDC/AY/8060 significantly reduced the levels of SGOT, SGPT, serum bilirubin and ALP, as well as decreased lipid peroxidation. In addition, treatment with the remedy significantly elevated serum albumin and glutathione levels compared to toxicant groups. These results suggest that DRDC/AY/8060 has hepatoprotective effects against paracetamol and D-galactosamine-induced hepatic toxicities in Wistar rats. The hepatoprotective effects of the remedy were comparable to those of the standard drugs Liv52 and Livfit.	(Khan et al. 2015)
Polyherbal formulation (PHF)	*Cajanus cajan, Lawsonia inermis Mimosa pudica, Uraria picta* and *Operculina turpethum*	100 mg/kg/day, 200 mg/kg/day and 400 mg/kg/day orally for 7 days	In vivo using albino rats	The results showed that PHF significantly reduced the CCl_4-induced increase in serum levels of SGPT, ALP and total bilirubin, indicating a protective effect on the liver. PHF also prevented the depletion of GSH and the decrease in the activity of SOD, both of which are indicative of liver damage. Additionally, PHF showed a significant decrease in LPO levels, which signifies potent antioxidant activity. The findings suggest that PHF protects liver cells from CCl_4-induced liver damage, and the mechanism may be through the antioxidant effect of PHF. When compared to the control group, PHF and silymarin showed significant reductions in the levels of SGPT, SGOT, ALP, and bilirubin, indicating hepatoprotective effects.	(Ghosh et al. 2015)

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TABLE 1 (Continues...): Hepatoprotective effect of polyherbal formulations.

Commercial name	Formulation with scientific names and plant part	Dosage and duration	Bioassay models	Results	References
Karisalai Karpam tablet	Eclipta prostrata, Wedelia calendulaceae, Indigofera tinctoria, Sphaeranthus indicus, Centella asiatica, Acalypha indica, Coldenia procumbens	50 mg/kg/day, 100 mg/kg/day, and 200 mg/kg/day, orally for 3 days	In vivo using Wistar rats	The study showed that the Karisalai Karpam tablet had hepatoprotective effects against acetaminophen-induced oxidative damage in rats. The herbal remedy reduced the levels of SGOT, SGPT, ALP, and total and direct bilirubin in a dose-dependent manner. In higher doses, Karisalai Karpam prevented the depletion of glutathione in liver tissue. The hepatoprotective activity of Karisalai Karpam was comparable to that of the standard drug silymarin. The study also found that Karisalai Karpam increased the antioxidant defence mechanism in rats.	(Sen et al. 2015)
Heptoplus	*Phyllanthus amarus* (whole plant), *Eclipta alba* (leaf), *Tephrosia purpurea* (leaf), *Curcuma longa* (rhizome), *Picrrohiza kurooa* (root), *Withania somnifera* (root), *Pinius succinifera* (amber), *Pistacia lentiscus* (resinous exudates), *Orchis mascula* (seed) and *Cycas circinalis* (flower)	50 mg/kg/day and 100 mg/kg/day orally for 30 days	In vivo assay using Sprague-Dawley rats	The rats treated with isoniazid and rifampicin showed severe oxidative stress, abnormal serum biochemical markers for liver function and increased liver lysosomal enzyme activity. However, the rats treated with 100 mg/kg of heptoplus and Liv 52 showed a significant decrease in serum transaminases, alkaline phosphatase and lactate dehydrogenase levels. Also, the rats supplemented with heptoplus showed a reduction in the levels of total bilirubin and C-reactive protein. Histopathological analysis revealed that the liver architecture of rats supplemented with heptoplus was normal compared to the rats treated with isoniazid and rifampicin only.	(Sankar et al. 2015)
Zereshk-e-Saghir (ZES)	*Berberis vulgaris, Rosa damascene, Cichorium intybus, Cucumis sativus, Portulaca oleracea, Rheum palmatum,* and *Nardostachys jatamansi*	250 mg/kg/day, 500 mg/kg/day, 750 mg/kg/day and 1500 mg/kg/day orally for 15 days	In vivo assay in a rat model	The results showed that ZES significantly reduced the increased serum levels of ALT, AST and ALP induced by CCl_4 at the doses used. The hepatoprotective effects of ZES were found to be comparable to that of silymarin, a known hepatoprotective agent.	(Sarhadynejad et al. 2016)
Polyherbal formulation	*Calotropis procera* (leaf), *Gymnema sylvestre* (leaf), *Lawsonia inermis* (leaf)	200 mg/kg/day orally for 5 days	In vivo using albino Wistar rats	The study demonstrated that the polyherbal formulation had a protective effect against CCl_4-induced acute hepatic damage in rats. The hepatoprotective effect of the polyherbal formulation was evidenced by decreased levels of serum markers of liver damage such as SGPT, SGOT, ALP, TB, and cholesterol, less damaged hepatocyte cells and histopathological changes such as severe macrovesicular, congestion and microvesicular steatosis. The study further compared the hepatoprotective activity of the polyherbal formulation and individual extracts of various plants against chronic liver damage. The results showed that the hepatoprotective activity of the extracts was in the order of the silymarin > polyherbal formulation extracts > *Gymnema sylvestre* extracts > *Calotropis procera* extracts > *Lawsonia inermis* extracts. The study suggested that the hepatoprotective effect of the polyherbal formulation was due to its phytoconstituents and its ability to reduce inflammatory responses and scavenge free radicals.	(Yogi & Mishra 2016, 2017)
Polyherbal formulation (PoHF)	*Zingiber officinale, Peganum harmala, Cassia angustifolia* and *Operculina turpethum*	500 mg/kg/day orally for 9 days	In vivo (female rabbits)	The study evaluated the hepatoprotective effect of a PoHF and ascorbic acid (AsAc) in female rabbits with paracetamol-induced hepatic damage. The elevation of enzyme markers was considered an indicator of hepatocellular injury. The results showed that serum levels of liver enzymes and total bilirubin were significantly elevated in untreated with any medication compared to the control group. However, the pretreatment with PoHF significantly dropped the liver enzymes (ALT, AST, ALP) and total bilirubin levels. However, oral administration of ascorbic acid (AsAc) caused a significant elevation in the levels of serobiochemicals. The damaging effects of ascorbic acid might be attributed to its prooxidant attitude, as reported by many research studies. Co-administration of PoHF and AsAc showed a statistically non-significant relation with hepatic enzymes compared to those that receive a single dose of paracetamol (PCM). This indicated that the combination of PoHF and AsAc failed to yield liver-protecting effects in ParCM-poisoned animals. Thus, the study concluded that herbal formulation remains an effective means to ameliorate PCM-induced elevation of serum biochemical parameters and changes to the liver histology, while ascorbic acid-induced deteriorating effects in a PCM-intoxicated rabbit animal mode.	(Fiaz et al. 2017)
AHPL/AYTAB/0613	*Eclipta alba, Tinospora cordifolia, Berberis aristata, Solanum nigrum, Boerhavia diffusa, Phyllanthus niruri, Picrorhiza kurroa* and *Andrograhis paniculata*	110 mg/kg/day, 220 mg/kg/day and 440 mg/kg/day orally for 14 days	In vivo (Wistar albino rats)	All the test formulations significantly reduced levels of SGOT, SGPT, ALP and total bilirubin, in CCl_4, ethanol and paracetamol-induced hepatotoxicity models. There was a significant increase in total protein level in all the tested formulations. All the test formulations effectively preserved the structural integrity of the hepatocellular membrane and liver cell architecture damaged by CCl_4, ethanol, and paracetamol. When compared between groups, no statistically significant difference was observed. Therefore, it can be concluded that AHPL/AYTAB/0613 possesses hepatoprotective activity in CCl_4, ethanol, and paracetamol-induced hepatotoxicity in rats.	(Nipanikar et al. 2017)

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TABLE 1 (Continues...): Hepatoprotective effect of polyherbal formulations.

Commercial name	Formulation with scientific names and plant part	Dosage and duration	Bioassay models	Results	References
Tritone (Livosone)	Eclipta alba, Tinospora cardifolia, Curcuma longa and Picrorrhiza kurroa	40.1 mg/kg/day, 81 mg/kg/day and 162 mg/kg/day orally for 14 days	In vivo, using albino Wistar rats	Tritone demonstrated significant hepatoprotective effects against hepatotoxic agents including paracetamol, galactosamine and alcohol. Tritone significantly reduced serum SGOT, SGPT, ALP and total bilirubin levels and showed significant elevation in total protein and cholinesterase levels compared to groups treated with hepatotoxic agents. Tritone also provided significant protection against hepatic damage, as observed in histopathological observations of rat liver. Additionally, inhibition of DNA fragmentation by tritone indicated a protective effect of the formulation on the liver at the molecular level. Tritone showed maximum hepatoprotective potential at doses of 81 mg/kg and 162 mg/kg compared to the standard drugs silymarin (100 mg/kg) and Liv52 (270 mg/kg).	(Medhekar et al. 2017)
Qurs-e- afsanteen®	*Artemisia absinthium, Valeriana officinalis, Rheum emodi,* potassium nitrate and ammonium chloride	50 mg/kg and 100 mg/kg/day orally for 14 days	In vivo assay using rats	The result revealed that the combination of Qurs-e-afsanteen® (50 mg/kg or 100 mg/kg) with gentamicin (80 mg/kg) restored the liver function parameters such as ALT, AST, ALP and TB (mg/dl) towards normal in a dose-dependent manner. The study showed the liver tissues from the group that received a high dose of Qurs-e-afsanteen® along with gentamicin (80 mg/kg) showed a significant ameliorative effect on gentamicin-induced necrosis of the hepatocytes, sinusoidal spaces were normal and cytoplasm was also clear.	(Aziz et al. 2017)
Kadukkai maathirai (KM)	*Terminalia chebula, Piper nigrum, Eclipta alba, Citrus limon* and ferrous sulfate	72 mg/kg/day and 400 mg/kg/day orally for 8 weeks	In vivo (adult female Sprague-Dawley rats)	The study evaluated the hepatoprotective effects of KM against ethanol-induced hepatotoxicity in rats. The biochemical and histopathological changes were assessed. Treatment with ethanol caused a rise in hepatic enzymes, such as ALT and AST, indicating hepatocyte membrane disruption and mitochondrial damage. However, KM, in the therapeutic dosage of 72 mg/kg, exerted a significant hepatoprotective effect against ethanol-induced liver damage in rats. There was a significant ($p < 0.05$) decrease in the serum AST and ALT levels in rats treated with KM 72 mg/kg as compared to the toxic control. The liver parenchyma showed near-normal architecture in the KM 72 mg/kg-treated group as compared to the ethanol-treated group which showed extensive ballooning degeneration of hepatocytes and microvesicular steatosis. The higher dose (400 mg/kg) of KM did not have any beneficial effect on ethanol-induced hepatotoxicity.	(Shetty et al. 2018)
Polyherbal formulation (PHF)	*Solanum nigrum, Silybum marianum, Atrmesia absinthium, Achillea millifolium*, and *Cichorium intybus*	100 mg/kg/day, 250 mg/kg/day and 500 mg/kg/day orally for 14 days	In vivo assay using male Swiss albino mice	The study showed that the PHF most especially at 500 mg/kg significantly improved the level of liver enzymes including ALT, AST, ALP and total bilirubin in the rat's plasma. Histological examination of liver sections also showed that treatment with PHF and silymarin significantly improved the liver architecture compared to the control group.	(Khan et al. 2018)
Hydroalcoholic polyherbal formulation (HAF)	*Bergenia ciliate* (root), *Pedalium murex* (fruits), *Tribulus terrestris* (fruit), *Sphaeranthus indicus* (flower), *Tinospora cordifolia* (stem), *Piper longum* (fruit)	200 mg/kg/day and 400 mg/kg/day orally for 7 days.	In vivo using Wister albino rats	The study found that HAF treatment significantly reduced liver damage induced by acetaminophen. The liver weight, liver function tests (ALT, AST, ALP, serum bilirubin, SGOT, SGPT), and histopathological examination of liver tissues showed significant improvement in the HAF treated groups compared to the control group. This indicates that HAF has a hepatoprotective effect against acetaminophen-induced liver damage in rats. The healing effect of HAF at 400 mg/kg body weight produces more significant results when compared to HAF-200 mg/kg.	(Srivastava et al. 2018)
BSVT	Leaves of *Boerhavia diffusa*, *Solidago virgaurea*, *Vitex negundo* and thymoquinone	25 mg/kg/day, 50 mg/kg/day and 100 mg/kg/day orally for 28 days	In vivo assay using healthy male Wistar rats	This result suggests that the administration of BSVT at the different doses showed a significant protective effect against liver damage in a dose-dependent manner. The protective effect was demonstrated by a decrease in the serum levels of several liver enzymes, including ALT, AST, ALP, and cholesterol. The decrease in enzyme levels suggests that BSVT improved the stability of the liver cell membranes and reduced the leakage of enzymes from inside the cells. Overall, these findings indicate that BSVT has a hepatoprotective effect against liver damage.	(Ahmad et al. 2020)
Kadukkai maathirai	*Terminalia chebula*, *Piper nigrum*, *Eclipta alba*, *Citrus limon* and ferrous sulfate	36 mg/kg/day, 72 mg/kg/day and 144 mg/kg/day orally for 8 days	In vivo assay using rat	The hepatoprotective effect of KM was compared with the standard drug silymarin (50 mg/kg). The results showed that KM 144 mg/kg and silymarin showed a significant decrease in AST, ALP and total bilirubin. Both KM and silymarin significantly prevented the decrease in liver weight. In KM-treated groups, the liver did not show necrosis of hepatocytes, and apoptotic bodies with mild to moderate inflammatory infiltrate in the lobules and portal tracts. Hence, the results of this study confirm the hepatoprotective effect of KM in rats. The biochemical estimation in serum showed that prophylaxis with KM at 36, 72, and 144 mg/kg significantly prevented D-galactosamine-induced rise in AST, ALT, ALP and total bilirubin levels versus those who were administered D-galactosamine alone. Serum ALT level was significantly lower in rats treated with silymarin than in the group which received KM-144 mg/kg ($p < 0.05$).	(Shetty et al. 2020)

Table 1 continues on next page →

TABLE 1 (Continues...): Hepatoprotective effect of polyherbal formulations.

Commercial name	Formulation with scientific names and plant part	Dosage and duration	Bioassay models	Results	References
Polyherbal formulation (CFCT)	*Costus speciosus, Fumaria indica* and *Cichorium intybus*	25 mg/kg/day, 50 mg/kg/day and 100 mg/kg/day orally for 28 days	In vivo study using male Wistar rats	The study investigated the hepatoprotective effects of a polyherbal formulation (CFCT) against cisplatin-induced hepatorenal toxicity in male Wistar rats. The results showed that cisplatin significantly elevated hepatic biomarkers (AST, ALT, ALP and cholesterol) compared to the control group rats, indicating hepatotoxicity. However, the administration of the CFCT formulation significantly ameliorated cisplatin-induced hepatorenal injury. This effect was attributed to the contribution of the CFCT formulation to the antioxidant defence system, by scavenging free radicals and reducing oxidative stress and inflammatory responses. The CFCT formulation showed a dose-dependent amelioration of hepatotoxicity and was found to be as effective as the standard drug, Cystone®, in normalising liver function biomarkers.	(Abuzinadah & Ahmad 2020)
PH 1 PH 2	- *Piper longum, Glycyrrhiza glabra, Acacia arabica, Papaver somniferum* and *Viola odorata*	PH 1 at doses of 6 mg/kg/day and 12 mg/Kg/day; PH 2 at doses of 50 mg/kg/day and 100 mg/kg/day via oral gavage for 3 days	In vivo assay using albino healthy rats	The study showed that PH 2 decreased the alkaline phosphatase levels and increased the SOD and GSH levels in lung tissue homogenates, indicating hepatoprotective effects. Moreover, PH 2 caused a decrease in ALT and AST levels, indicating reduced damage to hepatocytes, while PH 1 had no significant changes in ALT and AST levels.	(Saleem et al. 2020)
BV-7310	*Phyllanthus niruri, Tephrosia purpurea, Boerhavia diffusa,* and *Andrographis paniculata*	15 µg/mL, 50 µg/mL and 100 µg/mL doses for 48 h; 250 mg/kg/day and 500 mg/kg/day for 21 days	In vitro model involved human liver HepG2 cells, and in vivo model involved Sprague-Dawley rats.	The results indicated that BV-7310 demonstrated hepatoprotective effects against alcohol-induced liver damage in both in vitro and in vivo models. In HepG2 cells, BV-7310 (50 µg/mL) prevented ethanol-induced cell death in a dose-dependent manner and showed a synergistic activity of the four plants to attenuate the damages caused by alcohol. Furthermore, in vivo studies showed that BV-7310 at 250 mg/kg and 500 mg/kg protected the alcohol-induced body weight loss and significantly improved the elevated levels of liver enzymes compared to the vehicle-treated group. BV-7310 demonstrated significant hepatoprotective effects in comparison to the control and silymarin. Thus, BV-7310 could be beneficial for the treatment of alcoholic liver disease (ALD) or other conditions, which may cause liver toxicity.	(Dey et al. 2020)
DRHM®	*Cymbopogon citratus* (leaf), *Carica papaya* (leaf), *Mangifera indica* (bark), *Moringa oleifera* (leaf), *Citrus limon, Psidium guajava, Zingiber officinale* and *Allium sativum*	1 mL/kg/day, 2 mL/kg/day and 3 mL/kg/day orally for 14 days	In vivo assay using healthy male Wistar albino rats	The study found that the administration of H_2O_2 caused significant hepatic damage, as indicated by increased levels of AST, ALT and total bilirubin in the serum. However, treatment with DRHM® at different led to a dose-dependent decrease in serum AST, ALT, and total bilirubin levels when compared to the control group. Similarly, rats treated with silymarin at a dose of 100 mg/kg b.w. also showed significantly lower serum AST, ALT and total bilirubin levels compared to the control group. Therefore, both DRHM® and silymarin were effective in reducing the liver damage caused by H_2O_2 intoxication.	(Ndefo et al. 2021)
Heptaliv Holyliv Icturn, J-deenar	*Aphanamixis polystachya, Woodfordia floribunda, Piper longum*, *Zingiber officinale*, Trifala and other ingredients *Cichorium intybus* (root), *Cichorium intybus* (seed), *Rose damascene*, *Nymphaea alba*, *Borago officinalis*, *Cuscuta*, *reflexa* (seed), *Rheum emodi*, and other ingredients *Cichorium endivia* (root), *Cichorium endivia* (seed), *Rose damascene*, *Nympaea nouchali*, *Borago officinalis, Cuscuta*, *reflexa* (seed), *Rheum emodi*, and other ingredients Cuscuta leaf, endive seeds, male fern, water lily, *Borago, gawjban*, *Cuscuta* roots, rhaw chine and other ingredients	2.6 mL/kg/day and 5.2 mL/kg/day orally for 7 days	In vivo assay in mice	The study confirmed that Icturn and J-deenar polyherbal formulations significantly prevented CCl_4-induced hepatotoxicity in mice than other polyherbal formulations, demonstrating their protective effect on the liver. The administration of these two formulations at higher doses (5.2 mL/kg) significantly decreased the levels of AST, ALT, ALP and total bilirubin. The histopathological analysis also revealed significant improvement in liver tissues as a result of treatment with Icturn and J-deenar formulations. In contrast, CCl_4 administration caused significant hepatotoxicity as evidenced by marked elevation in AST, ALT, ALP and total bilirubin, as well as infiltration of inflammatory cells and centrizonal necrosis on histological examination of the liver. Phenobarbitone-induced sleeping time was also monitored, and the results indicated significant improvement in liver function as a result of treatment with Icturn and J-deenar formulations.	(Begum et al. 2022)
Amalakyadi Gana	*Phyllanthus emblica* (fruit), *Terminalia chebula* (fruit), *Piper longum* (fruit) and *Plumbago zeylanica* (root)	500 mg/kg/day and 700 mg/kg/day orally for 7 days	In vivo (Swiss albino mice)	Amalakyadi Gana significantly prevented the PCM-dependent rise in total serum bilirubin, AST, ALT and ALP levels when pretreated and compared with the control. The remedy exhibited dose-dependent hepatoprotective activity in the mice. Significant histological alterations were also observed in the liver tissues. The formulation normalises the liver architecture by decreasing necrotic foci along with the normal liver parenchymal structure and also sustained activity that was comparable to silymarin (200 mg/kg) reference medicine.	(Ray et al. 2022)
Aab-e-Murawaqain	*Solanum nigrum* and *Cichorium intybus*	4.5 mL/kg was orally administered twice a week for 28 days	In vivo (Wistar albino rats)	The results showed that animals treated with CCl_4 exhibited significantly enhanced levels of SGOT, SGPT, ALP, bilirubin and TBARS, reflecting hepatic damage. However, treatment with the Aab-e-Murawaqain formulation at the oral dose of 4.5 mL/kg body weight considerably led to a decrease in serum enzyme levels, indicating an improvement in liver cellular injury.	(Amir et al. 2022)

Table 1 continues on next page →

TABLE 1 (Continues...): Hepatoprotective effect of polyherbal formulations.

Commercial name	Formulation with scientific names and plant part	Dosage and duration	Bioassay models	Results	References
Livogrit	Boerhavia diffusa, Phyllanthus niruri and Solanum nigrum	6 µg/kg, 28 µg/kg and 142 µg/kg for 14 days	In vivo assay using zebrafish model	The study found that Livogrit treatment at an effective dose of 142 µg/kg significantly improved the deviated serum biochemistry compared to the control group. The liver function parameters, including albumin, AST, bilirubin, creatinine, platelet clotting factor, international normalised ratio and sodium blood serum, were evaluated, and results showed that Livogrit was more effective against thioacetamide (TAA)-induced hepatotoxicity than prednisone. The herbal formulation in comparison to prednisone successfully restored the liver dysfunction index to low risk. The liver cytology showed a decline in the hepatocyte cell death that further corroborated the promising curative potential of Livogrit. Livogrit dose-dependently minimised the liver dysfunction index to low risk, and Livogrit treatment significantly reduced the levels of bilirubin and creatinine, which were elevated upon TAA induction.	(Balkrishna et al. 2022)
Dawa-ul-Kurkum and its hydro-alcoholic extract	Nordostachys *jatamansi* (Dried Rhizomes), *Commiphora myrrha* (Gum resin), *Cinnamomum cassia* (Bark), *Saussurea lappa* (Dried roots), *Cymbopogon Jwarancusa* (Flower), *Cinnamomum Zeylanicum* (Bark), *Crocus sativus* (Style and Stigma)	250 mg/kg and 500 mg/kg orally for 6 weeks	In vivo (rats)	Treatment with Dawa-ul-Kurkum and its hydroalcoholic extract revealed hepatoprotective effects. The doses significantly attenuated the effects of ethanol and reduced levels of serum SGOT, SGPT, ALP, total bilirubin and direct bilirubin and increased level of serum total protein as compared to that in the experimental control group. Ethanol-induced liver damage was associated with higher levels of malondialdehyde and nitrates and nitrites (NOx) assay, but lower levels of reduced glutathione (GSH) compared to controls. Dawa-ul-Kurkum and hydroalcoholic treatments elicited different degrees of attenuation in various oxidative stress markers. The increase in body weight observed after treatment with Dawa-ul-Kurkum and its hydroalcoholic extract may be due to the improvement in appetite, which may be attributed to the hepatoprotective effect of Dawa-ul-Kurkum. The hepatoprotective benefits of Dawa-ul-Kurkum suggest that it may be useful in situations of liver dysfunction, anorexia, ascites and abdominal pain.	(Rafi Reshi et al. 2022)
Majoon-Najah (MN) and Majoon-Najah hydroalcoholic extract (MNHE)	*Terminalia bellirica* and *Emblica officinalis*	MN and MNHE were given intragastrically for 15 days	In vivo in guinea pig model	The study found that $CdCl_2$ induced hepatotoxicity and altered liver function markers, serum biochemical indicators, lipid peroxidation, glutathione reductase, superoxide dismutase, glutathione peroxidase, proinflammatory cytokines level and liver cytoarchitecture. However, the administration of MN and MNHE protected the liver from $CdCl_2$-induced injury by lowering raised parameters and increasing enzymatic antioxidants. The herbal remedies showed hepatoprotective effects by scavenging free radicals, decreasing malondialdehyde levels, activating antioxidant enzymes and downregulating proinflammatory indicators.	(Singh et al. 2023)

Note: Please see the full reference list of the article, Aladejana, E.B. & Aladejana, A.E., 2023, 'Hepatoprotective activities of polyherbal formulations: A systematic review', *Journal of Medicinal Plants for Economic Development* 7(1), a206. https://doi.org/10.4102/jomped.v7i1.206, for more information.

CCl_4, Carbon tetrachloride; ALP, alkaline phosphatase; TB, total bilirubin; ALT, alanine transaminase; AST, aspartate transaminase; SGOT, serum glutamate oxaloacetate transaminase; SGPT, serum glutamate pyruvate transaminase; LDH, lactate dehydrogenase; $CdCl_2$, cadmium chloride; LPO, lipid peroxidation; GSH, glutathione; GGT, gamma-glutamyl transferase; TBP, total bilirubin protein; PHF, polyherbal formulation; ACP, acid phosphatase; SALP, serum alkaline transaminase; MDA, malondialdehyde; PCM, paracetamol; H_2O_2, hydrogen peroxide; PNK, Punarnavashtak kwath.

et al. 2017). Methotrexate is a chemotherapy agent that can cause liver injury by inducing apoptosis and oxidative stress. Methotrexate-induced liver injury is characterised by inflammation, fibrosis and necrosis. Methotrexate induces hepatotoxicity by inhibiting dihydrofolate reductase, affecting folate metabolism and causing hazardous compounds to accumulate in rapidly developing liver cells. This buildup causes oxidative stress, inflammation and poor cellular function, eventually resulting in liver damage. Methotrexate can also stimulate an immunological response in the liver and disrupt normal metabolic processes, all of which contribute to its hepatotoxic effects (Anila et al. 2015). $CdCl_2$ is a toxic heavy metal that can cause hepatotoxicity. Its hepatotoxic effects are primarily attributed to its ability to cause oxidative stress and inflammation. Cadmium can disrupt the balance of antioxidants and ROS in liver cells, resulting in an excess of ROS. This oxidative stress can harm cellular components such as lipids, proteins and DNA, impairing cell function and promoting inflammation. Cadmium is also known to disrupt various cellular processes and signalling pathways in the liver. It can disrupt calcium homeostasis, mitochondrial function and energy production, all of which contribute to cellular dysfunction and damage. Furthermore, cadmium has been linked to the activation of specific genes and pathways that promote cell proliferation, potentially increasing the risk of liver cancer over time. The liver is essential in detoxifying harmful substances, such as heavy metals like cadmium. Chronic cadmium exposure, on the other hand, overwhelms the liver's detoxification mechanisms, resulting in cumulative damage and hepatotoxicity, and increased levels of liver marker enzymes, such as ALT and AST (Singh et al. 2023). D-galactosamine causes hepatotoxicity primarily by interfering with protein and ribonucleic acid (RNA) synthesis in hepatocytes. It is taken up by hepatocytes and metabolised to UDP-galactosamine, causing uridine triphosphate (UTP) depletion. The lack of UTP impairs RNA and protein biosynthesis, which is essential for cell function and regeneration. Disruption of these critical cellular processes causes hepatocellular damage, inflammation and apoptosis, ultimately resulting in hepatotoxicity (Khan et al. 2015; Shetty et al. 2020). Alcohol abuse is a common cause of liver disease. Chronic alcohol consumption causes hepatotoxicity, which causes liver damage via a variety of mechanisms. Initially, alcohol is metabolised in the liver by alcohol dehydrogenase and cytochrome P450 enzymes, producing acetaldehyde, a toxic compound that can form adducts with proteins and DNA, causing cellular dysfunction and DNA damage. This causes oxidative stress, mitochondrial dysfunction and

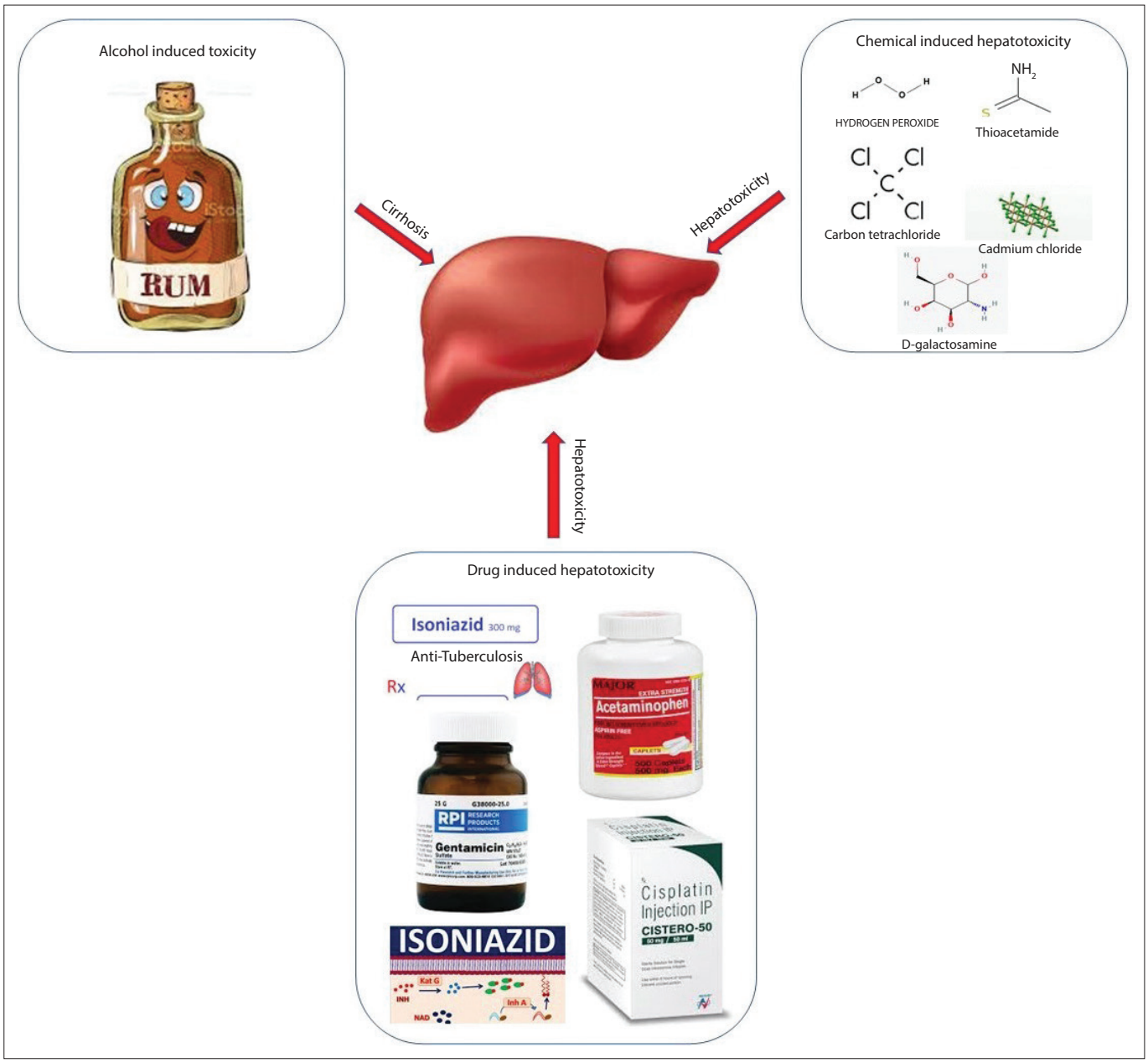

FIGURE 1: List of substances recognised as inducers of hepatic damage in animal models, as discussed in the reviewed research articles. These substances include CCl_4, thioacetamide, H_2O_2, gentamicin, MTX, $CdCl_2$, D-galactosamine, alcohol, cisplatin, INH and acetaminophen.

inflammation, disrupting hepatocyte function and promoting fibrosis. Furthermore, alcohol impairs fat metabolism, resulting in triglyceride accumulation in hepatocytes (fatty liver), exacerbating liver damage. These processes can progress over time to more severe conditions such as alcoholic hepatitis, cirrhosis and an increased risk of hepatocellular carcinoma (Tatiya et al. 2012). Cisplatin is a chemotherapeutic agent used to treat cancer. It can cause hepatotoxicity by inducing oxidative stress and mitochondrial dysfunction. The damage caused by cisplatin can be mitigated by antioxidants, such as N-acetylcysteine and vitamin E (Abuzinadah & Ahmad 2020). Isoniazid, an essential component of tuberculosis treatment, can cause hepatotoxicity via a variety of mechanisms. Hepatic enzymes metabolise the drug, with slow acetylators being more vulnerable due to higher drug levels. Metabolic processing can generate reactive metabolites, resulting in oxidative stress, mitochondrial dysfunction and lipid peroxidation. This disrupts cellular integrity, resulting in inflammation, hepatocyte damage and apoptosis. Furthermore, INH-induced immune responses and immune cell activation in the liver contribute to the overall hepatotoxic effect (Anusha et al. 2018; Sankar et al. 2015; Sharma et al. 2015).

Hepatic enzyme assessments, as demonstrated in the reviewed studies, are critical in evaluating liver injury caused by hepatotoxins (Said et al. 2022). Serum glutamyl pyruvate transaminase (SGPT), serum glutamyl oxaloacetate transaminase (SGOT), alkaline phosphatase (ALP), alanine ALT, AST, gamma-glutamyl transferase (GGT), serum albumin and lactate dehydrogenase (LDH) are the primary

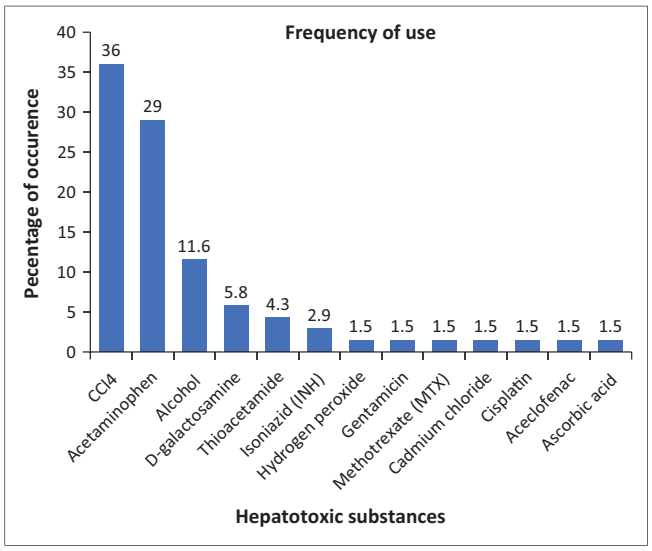

FIGURE 2: Frequency of use of each hepatotoxin in all the reviewed articles.

markers used to diagnose liver damage. These markers are especially sensitive because their serum levels rise after hepatocellular damage (Mistry et al. 2013). The researchers discovered that exposing animals to different hepatotoxins caused significant changes in liver morphology, biochemistry and histology.

Hepatoprotective activity of polyherbal formulations

The hepatoprotective PHF helps the liver clear away the toxins, regenerates the liver cells and prevents liver failure (Vadivu, Vidhya & Jayshree 2013). The review article investigated the hepatoprotective effects of various PHFs against liver damage induced by chemical toxins and drugs in animal models and cell lines. The formulations including DRHM®, hydroalcoholic polyherbal formulation (HAF), Livshis, polyherbal tablet formulations (PTF-1, PTF-2), RVSPHF567, polyherbal syrup, Livomyn, Icturn, J-deenar, Gongronema latifolia, Ocimum gratissimum and Vernonia amygdalina (GOV), Habb-e-Asgand, DRDC/AY/8060, and a polyherbal preparation containing *Phyllanthus amarus*, *Boerhavia diffusa* and *Tephrosia purpurea* were found to exhibit significant hepatoprotective effects against H_2O_2, acetaminophen, CCl_4 and paracetamol-induced liver damage in animal models (Ali et al. 2014; Begum et al. 2022; Harshitha, Rodda & Rao 2013; Khan et al. 2015; Ndefo et al. 2021).

Among these, a formulation known as RVSPHF567 drew attention. It was made from a variety of herbs, including ajowan, cardamom, clove, mace and nutmeg. A dose of 1 mL/kg of the blend, given orally three times a day for 3 days, showed promising results in protecting the liver in a real-life study involving adult Wistar albino rats. It was discovered to affect serum levels of total bilirubin and liver enzymes such as SGOT, SGPT and ALP, all of which are indicators of liver health. Furthermore, RVSPHF567 increased the presence of essential proteins such as total proteins and albumin, indicating improved liver function. Microscopic examination also revealed that the formulation restored the liver's structural integrity and prevented tissue damage (Kandasamy et al. 2010).

In a separate study, Livina, a concoction made up of various plant-based components, was tested for its hepatoprotective potential in people undergoing antituberculosis therapy (ATT). The oral administration of 1000 mg of Livina twice a day for 8 weeks successfully reversed the ATT-induced serum increases in liver function enzymes (AST, ALT and ALP). Furthermore, the treatment not only promotes treatment adherence but also aids in the prevention of the emergence of drug-resistant tuberculosis. This suggests that it has the potential to improve drug efficacy and maintain liver health during tuberculosis treatment (Gulati, Ray & Vijayan 2010). Livina's efficacy was further demonstrated in a study involving Sprague-Dawley rats with aceclofenac-induced hepatic dysfunction. Doses of 0.25 mL, 0.5 mL and 1 mL of Livina, given orally every day for 60 days, demonstrated significant hepatoprotection, such as serum hepatic marker homeostasis, reduction of oxidative damage and positive changes in hepatic histopathology. Surprisingly, Livina's efficacy was comparable to that of the well-known hepatoprotective drug silymarin, highlighting its potential as a valuable hepatoprotective agent (Darbar et al. 2010).

Another formulation made up of *Terminalia chebula*, *Asteracantha longifolia*, *Cyprus rotundus* and *Bryophyllum pinnatum* demonstrated impressive hepatoprotective properties. A dose of 250 mg/kg of the PHF given orally every day for 30 days significantly reduced serum levels of liver function enzymes and bilirubin in adult male albino Wistar rats. The efficacy of this formulation was attributed to its ability to stimulate healthy hepatocellular growth and inhibit specific enzymes, all of which contributed to overall hepatic efficiency (Gurusamy, Kokilavani & Arumuasamy 2010). The Hepjaun syrup formulation, which is available in various alcoholic and water-based extracts, demonstrated significant in vivo hepatoprotective effects against CCl_4-induced hepatic dysfunction in male Wistar rats when given orally every day for 14 days. Among these extracts, one labelled HA-II stood out for its potent hepatoprotective activity, implying potential benefits for jaundice and hepatitis prevention (Patel et al. 2010). Livactine, another formulation containing ingredients such as *B. diffusa*, *Tinospora cordifolia*, *Andrographis paniculata* and *Emblica officinalis* demonstrated in vivo dose-dependent hepatoprotective effects in albino Wistar rats. This was observed in the presence of CCl_4 and paracetamol-induced hepatic damage. Livactine (1 mL/kg and 2 mL/kg given orally for 10 days) effectively reversed elevated serum levels of liver function enzymes, demonstrating efficacy comparable to the well-known hepatoprotective drug Liv-52 (Mayuren et al. 2010).

Hepax, a plant blend made up of *Plumbago zeylanica* and *Picrorrhiza kurroa*, stood out as an exceptional defender against hepatic dysfunction caused by a variety of harmful substances. This formulation (100 mg/kg and 200 mg/kg given orally for 7 days) not only maintained hepatic weight in the male Wistar albino rats but also restored the liver

biochemical parameters to normal levels, and prevented abnormalities in hepatic tissue structure. Its efficacy was comparable to that of the positive control silymarin (100 mg/kg), a well-known hepatoprotector (Devaraj et al. 2011). Also, Livergen, a combination of the herbs *Andrographis paniculata* and *Phyllanthus niruri*, demonstrated significant hepatoprotective effects in Wistar rats against ethanol, CCl_4 and D-galactosamine. A dose of 2.6 mL/kg of this formulation given orally every day for 5 days demonstrated its ability to maintain liver health by modulating SGOT, SGPT and ALP activities, as well as serum levels of cholesterol, bilirubin and total protein, and controlling lipid peroxidation (Kenjale et al. 2011).

In another study, researchers discovered that 250 mg/kg, 500 mg/kg and 1000 mg/kg of the Unani PHF Majoon-e-Dabeed-ul-ward (MD) given once only were effective in protecting female albino Sprague-Dawley rats from acetaminophen-induced hepatic damage. Majoon-e-Dabeed-ul-ward reversed the negative changes in serum liver function enzyme levels, restored oxidative stress parameters to normal and produced results similar to silymarin, highlighting its hepatoprotective potential (Shakya 2011). Punarnavashtak kwath (PNK), another polyherbal blend, demonstrated significant hepatoprotective effects in rats. The PNK doses of 100 mg/kg and 150 mg/kg given orally three times at 12-h intervals were able to lower serum liver function enzyme levels, improve protein levels and even shorten the duration of thiopentone-induced sleep. Punarnavashtak kwath also showed promise in promoting the viability of HepG2 hepatocytes, implying potential hepatoprotective properties (Shah, Shah & Bhatt 2011). The hepatoprotective PHF, which contained *Coccinia indica*, *Sida cordata* and *Scoparia dulcis*, demonstrated its mettle in defending against CCl_4 and paracetamol-induced hepatic damage in Wistar rats. The PHF doses of 100 mg/kg and 200 mg/kg given orally every day for 7 days maintained normal hepatic parameters in terms of structure and biochemistry while also preventing any abnormalities in the liver's tissue structure, highlighting its potential as a hepatoprotective agent (Mistry et al. 2012). Saroj et al. (2012) further confirmed PHF's hepatoprotective abilities in tests on female mice. The PHF doses of 300 mg/kg, 400 mg/kg and 500 mg/kg given orally every day for 7 days demonstrated the blend's potential by providing significant defence against paracetamol-induced hepatic injury. The PHF effectively reduced the paracetamol-induced increases in serum liver function enzymes and bilirubin levels. Histology of the hepatic tissue revealed improved health, highlighting the formulation's all-around liver protection potential.

A powerful defender against CCl_4-induced liver toxicity has also emerged in the form of a polyherbal formulation known as 'Livshis'. This botanical blend at a dose of 5 mg/0.5 mL/100 g given through gavage for 14 days demonstrated its efficacy in male albino rats by reducing oxidative stress, restoring antioxidant enzymes and restoring serum liver marker enzymes (SGOT, SGPT, ALP) to normal levels. It not only repaired the liver on a cellular level but also reversed the negative structural and haematological changes caused by CCl_4 (Bera et al. 2012). A polyherbal blend of *Andrographis paniculata*, *Phyllanthus niruri* and *Phyllanthus emblica* demonstrated resistance to paracetamol, CCl_4 and ethanol-induced hepatic damage. The PHF doses of 100 mg/kg, 200 mg/kg and 400 mg/kg given orally to albino Wistar rats for 5 days demonstrated dose-dependent hepatoprotective effects and the ability to protect the liver against various toxins by significantly lowering serum elevated levels of liver function enzymes (Tatiya et al. 2012). In male Wistar rats, PTF-1 and PTF-2 containing *Butea monosperma*, *Bauhinia variegata* and *Ocimum gratissimum* demonstrated significant hepatoprotective activity. When used to treat paracetamol-induced hepatic damage, 50 mg/kg and 100 mg/kg of each of these formulations given orally once a day for 7 days effectively normalise serum levels of liver enzymes (SGPT, SGOT, ALP) and total bilirubin. PTF-2 was found to be more effective than PTF-1, highlighting the enhanced protection provided by this formulation (Gupta et al. 2013).

A polyherbal syrup containing *Allium sativum*, *Curcuma longa*, *Ocimum sanctum* and *Aloe barbadensis* demonstrated promising hepatoprotective effects. When combined with paracetamol, 100 mg/kg, 300 mg/kg and 500 mg/kg of the syrup given orally every day for 14 days reduced serum levels of liver function enzymes in adult male Wistar rats, indicating its potential as a hepatoprotective agent (Patel et al. 2013). A combination of *Curcuma longa*, *Occimum sanctum*, *Murraya koenigii* and *Nyctanthes arbor-tristis* also demonstrated its ability to protect against D-galactosamine-induced hepatotoxicity in rats. In vivo, 50 mg/kg, 100 mg/kg and 250 mg/kg of this PHF significantly reduced serum levels of liver function enzymes and bilirubin to normal levels, while restoring hepatic antioxidant levels, demonstrating its beneficial effect on hepatic health (Sachdeva et al. 2013). The hepatoprotective power of PHFs was further confirmed by Sivakumar et al. (2014), who focused on paracetamol-induced liver damage in rats. The administered (at 200 mg/kg/day orally for 8 days) polyherbal blends F-I, F-II and F-III which were constituted by the different concentrations of *Tinospora cordifolia*, *Boerhavia diffuse*, *Phyllanthus amaraus*, *Euphorbia hirta* and *Wedelia chinensis* displayed significant hepatoprotective effects, resulting in reduced serum levels of liver function enzymes. Assessments of liver structure and histopathology revealed improvements, suggesting positive effects on hepatic tissue. Enhanced liver functional parameters further underscored the potential of these formulations to restore liver homeostasis.

Rasheed et al. (2014) engaged in an in vivo study involving male Wistar rats to elucidate the effects of an herbal syrup comprising *Aegle marmelos*, *Eclipta alba* and *P. amarus*. Their research included a thorough evaluation of the syrup's therapeutic capabilities against CCl_4-induced hepatotoxicity. Rasheed et al.'s findings were compelling, demonstrating the syrup's significant ability to alleviate CCl_4-induced hepatotoxicity in rats. Notably, plasma concentrations of critical liver marker enzymes such as ALT, AST, SGOT, SGPT,

ALP and total bilirubin were reduced significantly upon oral administration of 500 mg/kg of the syrup every day for 5 days. This decrease highlighted the syrup's potent hepatoprotective properties. Furthermore, histopathological evaluations revealed positive results, indicating that the syrup is effective in reducing fatty degeneration and vacuole formation induced by CCl_4. The similarity of these histopathological improvements to those achieved by the established hepatoprotective agent, silymarin, confirms the efficacy of the herbal formulation.

Iroanya et al. (2014) investigated the hepatoprotective potential of a PHF-labelled GOV in a Wistar albino rat model. Their research focused on the formulation's significant ability to counteract elevated levels of liver function enzymes upon daily oral doses of 2 g/kg, 4 g/kg and 8 g/kg (for 14 days), while simultaneously improving lipid profiles. This dual effect supported its protective role against acetaminophen-induced hepatotoxicity. In a similar vein, Padmanabhan and Jangle (2014) investigated the effect of a natural herbal combination, HP4, on liver protection. The combination when given orally to live mice at 250 mg/kg and 500 mg/kg every day for 7 days showed promise in preventing the escalation of specific liver function enzymes, owing to the synergistic effects of various constituent natural components working together to protect the liver from CCl_4-induced hepatic damage. Similarly, Ali et al. (2014) investigated the hepatoprotective potential of Habb-e-Asgand in male mice. Their research highlighted the significant protective effects of 250 mg/kg of this mixture, given orally every day for 14 days, against paracetamol-induced hepatic injury. This was accomplished by inhibiting the activities of harmful liver enzymes and cytochrome P450 and reducing oxidative damage while enhancing the activities of protective hepatic enzymes.

Ingawale, Shah and Patel (2015) investigated the hepatoprotective effects of Virgoliv Syrup (VLS) in Sprague-Dawley rats. They discovered that 1 mL/kg/day VLS taken orally for 7 days significantly reduced serum levels of liver function enzymes, implying that it can protect the liver similarly to silymarin. The PHF VLS also increases antioxidant enzyme levels, which aids in the reduction of oxidative damage to the liver. Similarly, Sharma et al. (2015) investigated the hepatoprotective effects of Amlycure DS in albino rats. They discovered that Amlycure DS in solid form (95 mg/kg/day and 285 mg/kg/day for 40 days) and liquid form (1402 mg/kg/day and 5608 mg/kg/day for 40 days) protected the liver from damage caused by INH, a hepatotoxic drug. The protective effects of Amlycure DS were attributed to the presence of various natural compounds with hepatoprotective properties.

Maheshwari et al. (2015) investigated the hepatoprotective potential of Livplus-A in a rat-based study in which Wistar albino rats were given 100 mg/kg, 200 mg/kg and 400 mg/kg of the PHF orally for 14 days. Their findings highlighted Livplus-A's remarkable ability to correct serum elevated levels of liver function enzymes while also improving lipid profiles. These findings emphasised its potential as a hepatoprotective agent. Shrivastava and Garg (2015) examined 50 mg/kg/day and 100 mg/kg/day of a PHF blend in Wistar rats for 5 days and found similar results. This formulation provided dose-dependent liver protection similar to silymarin, as well as visible improvements in hepatic tissue health. This convergence of findings suggests that the PHFs may be useful in preventing hepatic damage.

Anila et al. (2015) conducted a thorough investigation of Ambrex's hepatoprotective potential. Using both cell cultures and mice, they discovered that 250 mg/kg and 500 mg/kg of Ambrex given orally every day for 7 days could restore antioxidant equilibrium, reduce elevated serum levels of liver function enzymes and inhibit malondialdehyde – a harmful substance caused by MTX exposure. Singh et al. (2015) investigated the hepatoprotective properties of a PHF composite in a murine model, adding to the growing body of knowledge. Their research discovered that 300 mg/kg and 500 mg/kg of the PHF given daily for 7 days had the potential to significantly reduce deleterious hepatic enzyme levels, indicating its promise in counteracting paracetamol-induced hepatic damage. Khan et al. (2015) broadened the scope of investigation by studying the effects of DRDC/AY/8060 on hepatic health in Wistar rats. The administration of 120 mg/kg and 240 mg/kg of this mixture per day for 10 days demonstrated significant potential in lowering serum levels of liver function enzymes, reducing oxidative damage and increasing antioxidant levels. These findings suggested that it could protect the liver from the ravages of substances such as paracetamol and D-galactosamine.

Ghosh et al. (2015) followed a similar path, focusing on a natural ingredient composite (PHF) and its potential to strengthen liver protection, using albino rats as their experimental model. The formulation at 100 mg/kg, 200 mg/kg and 400 mg/kg doses given orally every day for 7 days demonstrated a significant ability to reduce increases in liver function enzymes, oxidative stress markers and oxidative damage provoked by CCl_4, suggesting its promising role in safeguarding liver integrity.

Sen et al. (2015) conducted a study that revealed the hepatoprotective properties of the Karisalai Karpam tablet. In rats, doses of 50 mg/kg, 100 mg/kg and 200 mg/kg of the tablet taken orally every day for 3 days reduced acetaminophen-induced hepatic oxidative damage. The tablet caused a dose-dependent decrease in hepatic markers, demonstrating its efficacy in reducing hepatic injury. Furthermore, the tablet's ability to maintain GSH levels demonstrated its potential for reducing oxidative stress. Notably, the hepatoprotection conferred by Karisalai Karpam was comparable to that of the established standard drug silymarin, confirming its importance in promoting hepatic health. The formulation's augmentation of antioxidant defences further bolstered its hepatoprotective attributes. Sankar et al. (2015) investigated the hepatoprotective

potential of heptoplus, a blend of *P. amarus, E. alba, T. purpurea, Curcuma longa, Picrrohiza kurooa, Withania somnifera, Pinius succinescens, Pistacia lentiscus, Orchis mascula* and *Cycas circinalis*. Their study focused on its effectiveness in alleviating hepatic damage caused by INH and rifampicin. The study demonstrated the ability of 50 mg/kg and 100 mg/kg of the formulation, given orally every day for 30 days, to significantly decrease harmful hepatic markers, thereby preserving the structural integrity of the liver as evidenced by histopathological analysis in the Sprague-Dawley rats. These findings imply that heptoplus can counteract oxidative stress and restore hepatic function, particularly in cases of drug-induced hepatic dysfunction.

Similarly, Sarhadynejad et al. (2016) investigated the hepatoprotective effects of Zereshk-e-Saghir (ZES) against CCl4-induced hepatic damage in rats. Their investigation revealed that 250 mg/kg, 500 mg/kg, 750 mg/kg and 1500 mg/kg of ZES given orally every day for 15 days effectively reduced elevated levels of hepatic damage markers, highlighting its potential to mitigate hepatic injury. Notably, ZES demonstrated comparable efficacy to the established hepatoprotective agent silymarin, highlighting its significant impact. This study established ZES as a viable contender in strategies for liver protection against chemical hepatotoxins. Yogi and Mishra (2016, 2017) conducted a thorough investigation into a natural ingredient blend containing *Calotropis procera, Gymnema sylvestre* and *Lawsonia inermis*. Their study revealed that 200 mg/kg of the formulation administered orally every day for 5 days protected albino Wistar rats from acute hepatic damage caused by CCl_4. The formulation's hepatoprotection was attributed to the antiinflammatory properties of its natural constituents as well as their ability to scavenge free radicals. The study also highlighted the synergistic potential of the combined formulation, emphasising the value of these plant extracts when used together.

In another study, Fiaz et al. (2017) investigated the hepatoprotective effects of a PHF in female rabbits with paracetamol-induced hepatic dysfunction. The administration of 500 mg/kg of the PHF orally every day for 9 days resulted in significant reductions in elevated serum levels of liver function enzymes and total bilirubin, indicating its potential for mitigating hepatocyte injury. Interestingly, when the PHF was combined with ascorbic acid, its protective effects were negated, highlighting the importance of considering potential interactions between herbal formulations and other medications. Nipanikar et al. (2017) investigated AHPL/AYTAB/0613's hepatoprotective efficacy against CCl4, ethanol and paracetamol-induced hepatic damage. Administering 110 mg/kg, 220 mg/kg and 440 mg/kg formulation orally every day for 14 days resulted in lower serum levels of hepatic enzymes and total bilirubin, ultimately preserving the integrity and architecture of hepatocytes. This comprehensive study confirmed the formulation's ability to protect the liver in a variety of hepatotoxicity models.

Medhekar et al. (2017) conducted a thorough investigation into the hepatoprotective effects of Tritone (Livosone) against various hepatotoxic agents. Dosages of 40.1 mg/kg, 81 mg/kg and 162 mg/kg of the formulation given orally every day for 14 days resulted in significant reductions in serum liver function enzyme levels while improving total protein levels and cholinesterase activities. These changes indicated hepatoprotection at both the microscopic and molecular levels. Surprisingly, Tritone's efficacy at 81 mg/kg and 162 mg/kg was comparable to that of the standard drug silymarin at 100 mg/kg, highlighting its potential as a potent hepatoprotective agent. Aziz et al. (2017) demonstrated the dose-dependent restorative effects of Qurs-e-afsanteen® on hepatic function. Doses of 50 mg/kg and 100 mg/kg of Qurs-e-afsanteen® given orally to rats every day for 14 days in conjunction with 80 mg/kg of gentamicin prevented gentamicin-induced hepatocytic damage, which was confirmed by microscopic examination. This study emphasised the formulation's potential for reducing drug-induced hepatic dysfunction.

Shetty et al. (2018) investigated the potential of kadukkai maathirai (KM) in protecting the liver from ethanol-induced damage. The study found that 72 mg/kg and 400 mg/kg of KM given orally every day for 8 weeks significantly reduced elevated serum levels of liver function enzymes in adult female Sprague-Dawley rats while preserving liver structure at therapeutic doses. Intriguingly, a higher dose of KM did not yield the same benefits, suggesting a potential dose-dependent response. Concurrently, Khan et al. (2018) reported hepatoprotective effects of a PHF like silymarin. The oral administration of 100 mg/kg, 250 mg/kg and 500 mg/kg of the PHF every day for 14 days resulted in improved serum levels of liver function enzymes and improved hepatic histopathological architecture in Swiss albino mice, highlighting its efficacy against hepatic dysfunction. Srivastava et al. (2018) demonstrated the significant efficacy of HAF in preventing acetaminophen-induced hepatic damage in rats. HAF treatment (200 mg/kg/day and 400 mg/kg/day orally for 7 days) was associated with improved liver function tests and reduced histopathological changes, highlighting its potential as a hepatoprotective agent. Ahmad et al. (2020) extensively detailed the dose-dependent protective effects of *Boerhavia diffusa, Solidago virgaurea, Vitex negundo* and thymoquinone (BSVT) formulation against liver damage in rats. BSVT administration (at 25 mg/kg, 50 mg/kg and 100 mg/kg/day orally for 28 days) resulted in lower serum levels of liver enzymes, indicating hepatocellular membrane stabilisation. This study demonstrated BSVT's potential as a potent hepatoprotective agent, significantly improving hepatic health. Shetty et al. (2020) investigated the hepatoprotective potential of KM, a polyherbal preparation containing *T. chebula*, *Piper nigrum*, *Eclipta alba*, *Citrus limon* and ferrous sulfate. Their rat experiment revealed that 144 mg/kg of KM provided significant hepatoprotection. Significant reductions in liver damage markers were observed, as were improvements in histopathological parameters. Furthermore, KM effectively counteracted the increase in serum levels of liver function enzymes caused by D-galactosamine. While silymarin was slightly more effective in lowering serum alanine aminotransferase (ALT), KM's potential in hepatoprotection remains promising.

The CFCT PHF, which contains *Costus speciosus*, *Fumaria indica* and *Cichorium intybus*, has emerged as a potential antidote to cisplatin-induced hepatorenal toxicity. Abuzinadah and Ahmad (2020) investigated the efficacy of 25 mg/kg, 50 mg/kg and 100 mg/kg CFCTs given daily in male Wistar rats, revealing its ability to mitigate cisplatin-induced hepatic biomarker elevation and cholesterol imbalance. The mechanisms of CFCT were linked to its enhancement of antioxidant defences, which reduced oxidative stress and demonstrated hepatoprotective effects comparable to the established standard, Cystone®. According to Saleem et al. (2020), the hepatoprotective effects of two PHFs, PH-1 and PH-2, highlighted the importance of formulation composition and plant interactions in hepatoprotection. It was discovered that 50 mg/kg and 100 mg/kg of PH2 (a blend of *Piper longum*, *Glycyrrhiza glabra*, *Acacia arabica*, *Papaver somniferum* and *Viola odorata*) given orally to albino healthy rats every day for three days significantly reduced ALP levels while increasing superoxide dismutase (SOD) and GSH levels. In contrast, PH-1 did not cause significant changes in ALT and AST levels. These findings highlighted the intricate interplay between botanical components and the importance of composition optimisation in designing effective hepatoprotective formulations.

According to Dey et al. (2020), BV-7310, a combination of *Phyllanthus niruri*, *T. purpurea*, *B. diffusa* and *Andrographis paniculata*, demonstrated promising hepatoprotective properties against alcohol-induced liver damage. The efficacy of 15 µg/mL, 50 µg/mL and 100 µg/mL of BV-7310 given for 48 h in preventing ethanol-induced cell death in HepG2 cells, as well as the efficacy of 250 mg/kg and 500 mg/kg of the blend given every day for 21 days in protecting against alcohol-induced liver damage in Sprague-Dawley rats, was demonstrated. The therapeutic implications went beyond alcoholic liver disease to include a broader range of liver toxicity-related conditions.

Ndefo et al. (2021) demonstrated that DRHM® was an ameliorator in the context of oxidative stress-induced hepatic injury. The study demonstrated the efficacy of 1 mL/kg, 2 mL/kg and 3 mL/kg DRHM® given orally to healthy male Wistar albino rats every day for 14 days in mitigating H_2O_2-induced hepatic damage, as evidenced by decreases in AST, ALT and total bilirubin levels. The similar efficacy of DRHM® to silymarin highlighted its potential in alleviating oxidative stress-mediated liver impairment.

Furthermore, Icturn and J-deenar formulations given orally to mice at 2.6 mL/kg and 5.2 mL/kg daily for 7 days effectively counteracted CCl_4-induced hepatotoxicity in mice (Begum et al. 2022). Elevated serum levels of liver function enzymes were found to improve after treatment with these formulations, which was supported by improved liver histopathology. Similarly, Amalakyadi Gana (500 mg/kg and 700 mg/kg) given orally to Swiss albino mice every day for 7 days demonstrated dose-dependent efficacy against paracetamol-induced hepatotoxicity, comparable to silymarin, highlighting its potential in hepatoprotection (Ray et al. 2022).

Amir et al. (2022) detailed the Aab-e-Murawaqain formulation, offering a robust strategy against CCl_4-induced hepatotoxicity. A significant reduction in serum enzyme levels upon oral treatment of Wistar albino rats with 4.5 mL/kg of the medication twice a week for 28 days signified restored liver health and cellular integrity, affirming the formulation's hepatoprotective potential. Furthermore, Livogrit (6 µg/kg, 28 µg/kg and 142 µg/kg for 14 days) emerged as an effective countermeasure to thioacetamide-induced hepatotoxicity in a zebrafish model (Balkrishna et al. 2022). The restoration of serum biochemical parameters and liver function highlighted Livogrit's potential in reversing liver health aberrations.

In a recent study, Rafi Reshi et al. (2022) investigated the hepatoprotective effects of Dawa-ul-Kurkum and its hydroalcoholic extract using an in vivo rat model. For 6 weeks, rats were given oral doses of 250 mg/kg and 500 mg/kg. Dawa-ul-Kurkum and its extract exhibited significant hepatoprotective properties, effectively mitigating the negative effects of ethanol-induced liver damage. Notably, administration of these substances resulted in a decrease in serum levels of liver injury markers such as SGOT, SGPT, ALP, total bilirubin and direct bilirubin, while simultaneously increasing serum total protein levels. Dawa-ul-Kurkum and its hydroalcoholic extract alleviated ethanol-induced oxidative stress, as evidenced by elevated levels of malondialdehyde, nitrates and nitrites, as well as decreased levels of reduced GSH. Furthermore, the treatment was associated with an increase in body weight, which could be linked to an improved appetite, emphasising Dawa-ul-Kurkum's hepatoprotective potential. These findings highlight the hepatoprotective potential of Dawa-ul-Kurkum and its hydroalcoholic extract against ethanol-induced liver damage. The observed reduction in liver injury markers and oxidative stress indicators, as well as the improvement in appetite and body weight, suggest a multifaceted protective effect. The study suggests that these herbal interventions could be used to treat liver dysfunction, anorexia, ascites and abdominal pain.

Another investigation by Singh et al. (2023) explored the hepatoprotective effects of Majoon-Najah (MN) and Majoon-Najah hydroalcoholic extract (MNHE) using a Guinea pig model. The study involved intragastric administration of MN and MNHE for 15 days. The experiment focused on countering hepatotoxicity induced by $CdCl_2$. The results demonstrated that $CdCl_2$ exposure led to hepatotoxicity characterised by altered liver function markers, serum biochemical indicators, lipid peroxidation, antioxidant enzyme activities, proinflammatory cytokine levels and liver cytoarchitecture. However, treatment with MN and MNHE effectively mitigated these adverse effects by normalising the altered parameters and enhancing enzymatic antioxidants.

The hepatoprotective mechanisms involved the scavenging of free radicals, reduction in malondialdehyde levels, activation of antioxidant enzymes and downregulation of proinflammatory indicators. By enhancing antioxidant defences, reducing lipid peroxidation and suppressing proinflammatory responses, MN and MNHE exhibit a comprehensive defence against hepatotoxic insults.

Mechanism of action of polyherbal formulations

The hepatoprotective effects of PHFs encompass a multifaceted array of interactions that collectively shield hepatocytes from the damaging consequences of diverse hepatotoxins. These formulations demonstrate remarkable efficacy in reducing injuries caused by agents such as CCl_4, alcohol, pharmaceuticals and environmental toxins, allowing for the restoration of normal liver function.

Antioxidant effects

The cornerstone PHFs' efficacy lies in their robust antioxidant properties, attributed to an assortment of phytoconstituents present within these formulations. Flavonoids, alkaloids, terpenoids, phenolic acids and tannins contribute significantly to these antioxidative actions by neutralising free radicals and reducing the burden of oxidative stress on hepatocytes. This role is pivotal, given that oxidative stress is a pivotal driver of hepatic pathogenesis. Through the inhibition of lipid peroxidation and the diminution of ROS, these formulations play a crucial role in protecting hepatocytes from apoptosis and injury (Amir et al. 2022; Ghosh et al. 2011; Singh et al. 2015; Sivakumar et al. 2014; Tatiya et al. 2012). Studies have demonstrated noteworthy antioxidant activities in specific formulations such as PNK, Tritone, ZES and Livactine, underscoring their potential to counteract oxidative stress-induced liver injury (Mayuren et al. 2010; Medhekar et al. 2017; Sarhadynejad et al. 2016; Shah et al. 2011).

Antiinflammatory and antifibrotic effects

Another critical aspect of these formulations is their antiinflammatory and antifibrotic properties. Chronic inflammation and fibrosis are important factors in the progression of hepatic dysfunction (Sharma & Nagalli 2022). These formulations act as potent antiinflammatory agents by modulating proinflammatory cytokines like TNF-α and IL-1β, as well as inhibiting central signalling pathways like NF-κB and MAPK (Padmanabhan & Jangle 2014). Furthermore, they inhibit the accumulation of extracellular matrix proteins such as collagen, reducing fibrosis (Sivakumar et al. 2014). Notable examples of such antiinflammatory prowess can be found in formulations such as KM and Livshis, which have demonstrated the ability to reduce proinflammatory cytokine levels and thus prevent inflammation-induced hepatic damage (Bera et al. 2011; Shetty et al. 2020).

Immunomodulatory effects

Immunomodulatory effects also feature prominently in the mechanisms by which these PHFs exert hepatoprotection (Belapurkar, Goyal & Tiwari-Barua 2014; Hamid et al. 2021). The presence of immunomodulating herbs like *Andrographis paniculata* and *Tinospora cordifolia* within formulations like Livina, PNK, Hepjaun Syrup, Livactine, Livergen, Livshis, DRDC/AY/8060, VLS, Clearliv, BV-7310, Amlycure DS and Livomyn orchestrates regulation of immune cell activity and cytokine production. These effects bolster immune responses against toxin-induced damage, thereby preserving immune homeostasis and mitigating immune-mediated hepatic injury (Rajanna et al. 2021; Saha & Ghosh 2012; Yadav, Yadav & Kharya 2016).

Liver regeneration and cellular function

The facilitation of liver regeneration and cellular function is a significant factor in these formulations' hepatoprotective effects. The stimulation of hepatocyte proliferation and the synthesis of liver-specific proteins ensure not only the restoration of normal hepatic function but also the recovery from damage. Furthermore, the modulation of enzymes governing carbohydrate and lipid metabolism, such as glucose-6-phosphatase and fatty acid synthase, plays a critical role in preventing hepatic steatosis, contributing to the overall rejuvenation of hepatic health (Amir et al. 2022; Tatiya et al. 2012).

Detoxification capacity enhancement

Furthermore, an important aspect of the mechanism of action of PHFs is the enhancement of the liver's detoxification capacity. These formulations improve the liver's ability to neutralise and eliminate toxins by increasing the activity of phase I and phase II detoxification enzymes such as cytochrome P450, GSH S-transferase and uridine diphosphate glucuronosyltransferases. This, in turn, reduces the burden on the liver, lowering the risk of liver damage caused by toxic agents (Ghosh et al. 2011).

To summarise, the hepatoprotective effects of PHFs are due to the complex interplay of antioxidant, antiinflammatory, antifibrotic, immunomodulatory, regenerative and detoxification-enhancing properties. These formulations have a lot of potential as therapeutic interventions for preventing liver damage and maintaining overall hepatic health. However, a thorough understanding of the molecular pathways and interactions mediating these effects necessitates additional research. Such insights are critical in propelling the development of effective hepatoprotective interventions.

Conclusion

In conclusion, the reviewed studies indicated that polyherbal formulations possess significant hepatoprotective activity against various hepatotoxic agents, through multiple mechanisms of action such as antioxidant, antiinflammatory, immunomodulatory activities and hepatocyte regeneration. These formulations contain bioactive compounds such as alkaloids, flavonoids and polyphenols that exhibit diverse biological activities, which help reduce oxidative stress,

inflammation and immune dysregulation that contribute to liver damage. The hepatoprotective effects were evident by the reduction in the levels of serum liver marker enzymes such as ALT, AST, ALP, and GGT, lipid peroxidation as well as restoration of the levels of serum bilirubin protein and enzymes. The herbal remedies also showed a dose-dependent reduction in lipid peroxidation, an increase in GSH and an improvement in liver histopathology. The observed hepatoprotective effects of some of the polyherbal formulations are comparable to those of standard drugs such as silymarin and Liv-52. Overall, these studies provide evidence for the hepatoprotective effects of various polyherbal formulations, which may have the potential for use as alternative treatments for liver diseases. These findings suggest that polyherbal formulations may be a promising alternative to conventional drugs for the prevention and treatment of liver diseases. However, further research is required to identify the bioactive compounds and fully understand the mechanisms of action of these polyherbal formulations. The development of new and effective drugs based on the knowledge gained from these formulations could offer new hope for patients suffering from liver disorders.

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Data availability

Data sharing is not applicable to this article, as no new data were created or analysed in this study.

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