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Hepatoprotective Potential of Medicinal Plants of Kazakhstan: A Review

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ABSTRACT: Liver diseases represent a significant global health challenge, underscoring the need for safe and effective hepatoprotective agents from natural sources. Kazakhstan's rich and diverse flora provides numerous medicinal plants traditionally used for liver ailments. This review evaluates the hepatoprotective potential of seven Kazakhstani spe-cies Glycyrrhiza glabra, Glycyrrhiza uralensis, Silybum marianum, Berberis heteropoda, Artemisia absinthium, Arctium lappa, and Arctium tomentosum focusing on their phyto-chemical composition, pharmacological mechanisms, and experimental evidence. Special attention is given to their efficacy in models of chemically induced hepatotoxicity, particu-larly carbon tetrachloride (CCl_4), as well as their anti-inflammatory and antifibrotic activ-ities, highlighting their promise as sources of novel hepatoprotective agents. The reviewed Kazakhstani plants demonstrate substantial hepatoprotective activity through multiple complementary mechanisms. Glycyrrhiza species, rich in glycyrrhizin and glabridin, exert anti-inflammatory and antioxidant effects, mitigating hepatic steatosis and fibrosis in CCl_4-induced liver injury models. Silybum marianum, a primary source of silymarin, sta-bilizes hepatocyte membranes, promotes liver regeneration, and normalizes serum enzyme levels. Berberis heteropoda, containing berberine, protects against toxin-induced hepatic damage by modulating oxidative stress and apoptosis. Artemisia absinthium and both Arctium species display strong antioxidant potential, reducing malondialdehyde (MDA) levels and restoring endogenous antioxidant enzyme activity. Collectively, these findings indicate that the hepatoprotective properties of these plants are largely mediated through the suppression of oxidative stress and inflammation, key drivers of liver pathology. These results highlight the therapeutic potential of Kazakhstan's medicinal flora as a source of novel hepatoprotective agents and emphasize the need for further phytochemical, phar-macological, and clinical investigations to validate traditional uses.

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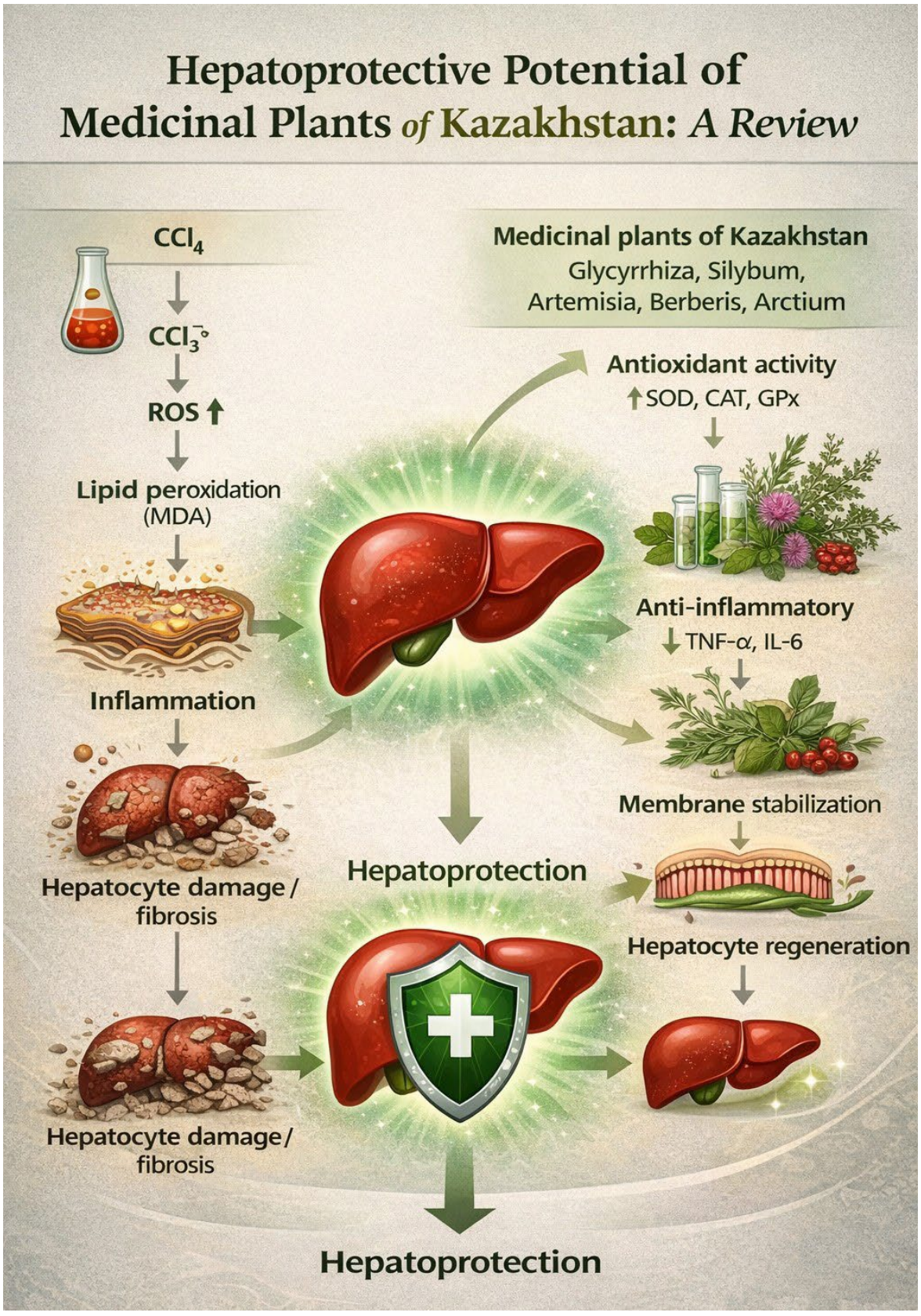
GRAPHICAL ABSTRACT



1. INTRODUCTION

Throughout history, medicinal plants have played a key role in shaping human culture and traditional medicine, occupying a central place in the healing practices of virtually all civilizations. They represent a valuable source of biologically active compounds, many of which form the basis of modern pharmaceuticals (Abbasi et al., 2021). For millennia, plants have been used not only to treat illnesses but also to flavor food, preserve it, and prevent various diseases (Bernal et al., 2020; Aitbekov et al., 2024). The biological activity and medicinal properties of plants are determined by the secondary metabolites they synthesize during their life cycle, which can also influence the growth and development of microorganisms in the environment. This review presents a comparative analysis of the efficacy of several medicinal plants growing in Kazakhstan in models of carbon tetrachloride-induced liver toxicity (Batiha et al., 2020).

Kazakhstan's flora exhibits remarkable diversity in medicinal plants, many of which have long been used in traditional medicine and are of interest as potential sources of novel hepatoprotective compounds (Rasool et al., 2014). Despite this, systematic information regarding the hepatoprotective activity of these plants remains limited. Accordingly, this review aims to consolidate current knowledge on the bioactive constituents of Kazakhstan's medicinal plants, their pharmacological properties, and the mechanisms underlying their hepatoprotective effects, as well as to evaluate their potential for the development of new plant-based therapeutic agents (Ozougwu et al., 2017; Imanaliyeva et al., 2024).

The liver is a central organ in maintaining metabolic homeostasis, performing diverse functions such as carbohydrate, lipid, and protein metabolism, detoxification of xenobiotics, synthesis of plasma proteins, regulation of immune responses, and storage of vitamins and trace elements (Chan et al., 2014; Askerbay et al., 2025). In adults, the liver accounts for approximately 2% of body weight, and its functionality is supported by a unique dual blood supply from the portal vein and hepatic artery.

Owing to its role in the biotransformation of both endogenous and exogenous compounds, the liver is continuously exposed to potentially harmful substances, including medications, environmental toxins, and dietary xenobiotics (Younossi et al., 2014). Metabolism of these compounds may generate reactive metabolites that trigger oxidative stress, inflammatory responses, mitochondrial dysfunction, and disruption of cellular membranes, leading to hepatocyte injury that can range from reversible functional impairment to necrosis and liver failure.

Liver diseases represent a major global health burden (Rui 2014). According to data from the World Health Organization and the Global Burden of Disease study, approximately two million deaths occur annually due to hepatic disorders. The rising prevalence of liver diseases is primarily driven by increasing rates of non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, viral hepatitis, and drug-induced liver injury (DILI) (Stravitz et al., 2019; Ydyrys et al., 2024). Despite advances in medical therapy, effective treatment options remain limited for many forms of liver damage, with liver transplantation often serving as the only definitive intervention in severe cases.

The liver hosts vital biochemical processes, including the detoxification of xenobiotics and endogenous toxins, as well as the synthesis of biologically significant molecules (Nguyen et al., 2008). Therefore, any structural and functional disturbances in the liver can lead to severe systemic consequences. Chronic alcohol intoxication, viral hepatitis, and hereditary metabolic disorders are etiological factors for liver damage (Michalopoulos et al., 2007; Alibek et al., 2024). The pathological process is accompanied by the development of hepatocyte necrosis, the formation of fibrous tissue, increased lipid peroxidation, and the depletion of intracellular glutathione reserves. Most hepatotoxic agents induce damage through the induction of oxidative stress, specifically the activation of lipid peroxidation and other forms of oxidative damage to cellular structures. Natural antioxidants are widely present among secondary plant metabolites. These include polyphenolic compounds (including phenolic acids and flavonoids), as well as terpenoids, such as carotenoids. Regular consumption of foods rich in these biologically active substances is considered a significant factor in the prevention of various pathological conditions, including liver diseases.

In this context, medicinal plants represent a promising source of hepatoprotective agents (Kanawati et al., 2021; Ydyrys et al., 2023). Bioactive plant compounds can modulate critical pathways involved in liver injury, including the attenuation of oxidative stress, suppression of inflammatory responses, stabilization of hepatocyte membranes, promotion of liver cell regeneration, (Losser et al., 1996; Akhmetova et al., 2018) and enhancement of detoxification mechanisms. Secondary metabolites such as flavonoids, phenolic compounds, saponins, alkaloids, and terpenoids play a particularly important role. Well-characterized natural hepatoprotectors, including silymarin from *Silybum marianum*, glycyrrhizin from *Glycyrrhiza glabra*, berberine from Berberis species, and polyphenolic constituents of Artemisia species, have demonstrated significant hepatoprotective effects in experimental models of chemical-induced liver injury.

Thus, medicinal plants are a valuable source of natural compounds with hepatoprotective activity, capable of reducing liver damage caused by toxins such as carbon tetrachloride. The biologically active components of plants flavonoids,

saponins, alkaloids, and phenolic substances provide antioxidant, anti-inflammatory, and restorative effects on hepatocytes, supporting normal liver function and preventing damage progression. The use of plant extracts represents a safe and accessible approach that can be effectively used both in traditional practice and in modern research to develop new natural hepatoprotectors.

2. METHODOLOGY

2.1. PubMed search strategy and PICOT question

To develop the PubMed search strategy, a PICOT research question was used, in which the population was defined as carbon tetrachloride hepatotoxicity (not specified in the search strategy); the intervention was defined by families, species, or active substances of potential medicinal plants with hepatoprotective activity. The comparator was also not specified in the search strategy but was assumed to be conventional therapy or placebo. The outcome was defined based on mortality, acute liver injury, and changes in hepatocyte parameters (hepatocyte degeneration, decreased cell proliferation, half-maximal inhibitory concentration, etc.); finally, the type of study was considered: preclinical, in vitro, in vivo, or in silico. PubMed search strategy performed September 10, 2024, ("Toxic metabolites"[Mesh] OR liver damage*[tiab]) AND ("hepatitis"[Mesh] OR Acute liver failure *[tiab] OR "necrosis of hepatocytes"[Mesh] OR Toxic substances [tiab] OR "cell damage"[Mesh] OR "Carbon tetrachloride"[Mesh] OR Toxicity of carbon tetrachloride [tiab] OR antioxidants [tiab] OR metastasis inhibition[tiab] OR Medicinal plants *[tiab]) AND (preclinic*[tiab] OR "in vitro"[tiab] OR "in vivo"[tiab] OR "ex vivo"[tiab]) NOT (Case Reports[Publication Type]), gave 200 results.

2.2. Inclusion and exclusion criteria

Of the 200 results obtained, we excluded studies that were not conducted between 2005 and 2025, clinical studies, studies of hepatoprotective activity of compounds isolated from medicinal plants, studies in a language other than English or Spanish, studies that did not test the cytotoxicity of metabolites on hepatocytes, and those that used the method as a basis for imparting hepatoprotective properties to compounds. Review included studies conducted on experimental animals (rats and mice) as the study population. The intervention involved administration of medicinal plant extracts, while the control groups received vehicle or standard hepatoprotective drugs such as *silymarin*. The outcomes assessed included biochemical markers of liver damage and histopathological changes.

2.3. Selection process

A total of 200 articles identified in Pubmed were obtained for this review, from which those that were duplicates or not whitten in English or Spanish were removed, leaving 200 articles at the screening stage. The selection consisted of assessing the potential suitability of the study based on the title and abstract, which were distributed so that each article had to be evaluated by at least two researchers, and in case of disagreement or doubt, the entire research team was called upon to evaluate the inclusion or exclusion of the article. After applying the above inclusion and exclusion criteria and evaluating the articles for the search, a total of 80 suitable articles were obtained, which were included in the review.

Quality assessment and risk of bias were additionally considered to improve the methodological rigor of this review. The included studies were evaluated according to the clarity of experimental design, adequacy of control groups, reproducibility of CCl_4-induced hepatotoxicity models, and reliability of biochemical and histopathological outcome measures. Special attention was given to the consistency of reported hepatoprotective effects and the presence of standardized extract characterization.

Potential sources of bias included small sample sizes, insufficient description of randomization procedures, lack of blinding in experimental assessment, variability in plant extract composition, and the predominance of preclinical studies without clinical validation. These limitations were taken into account when interpreting the results and were discussed as factors restricting the direct translation of findings into clinical practice.

3. LIVER INJURY MODELS USED IN HEPATOPROTECTIVE STUDIES

A variety of experimental models are commonly employed to investigate hepatoprotective activity, enabling the replication of liver injury types observed in humans. The selection of a particular model depends on the research objective, such as evaluating antioxidant capacity, anti-inflammatory effects, or antifibrotic potential (Dwivedi et al., 2022).

Chemical models involve the administration of hepatotoxic agents, including carbon tetrachloride (CCl_4), ethanol, paracetamol, or alloxan, which induce acute or chronic liver damage (Loguercio et al., 2011). These models are widely used to examine mechanisms of oxidative stress, hepatocyte

membrane stabilization, and restoration of liver biochemical parameters.

Immunological models are designed to mimic inflammatory liver injury, often through stimulation with lipopolysaccharides (LPS) or autoimmune triggers. They facilitate assessment of the anti-inflammatory effects of test compounds, as well as their influence on cytokine production and activation of immune pathways (Mukhtar et al., 2021).

Fibrosis models typically involve prolonged exposure to toxins or surgical interventions, resulting in excessive activation of hepatic stellate cells and accumulation of extracellular matrix. Such models are applied to study the antifibrotic effects of substances and their ability to prevent or slow the development of scar tissue (Liao et al., 2021).

In vitro models are widely employed in hepatoprotective research due to their rapid, cost-effective, and reproducible nature, as well as their requirement for smaller sample sizes. However, findings from these models generally need to be validated using complementary approaches (Vargas-Mendoza et al., 2014). Ex vivo models serve as an intermediate between in vitro and in vivo systems, though their use is less common. In contrast, in vivo models provide comprehensive information on physiological and pathological responses and are extensively used to evaluate the efficacy of novel compounds. Due to higher costs and the need for multiple experimental animals, in vivo studies are typically conducted after in vitro or ex vivo screening, serving as a critical step prior to clinical trials (Albassam et al., 2021).

Several in vitro systems are available, including hepatocyte cultures and primary liver cells, which are used to study pathophysiological changes induced by various treatments. Well-established models, such as freshly isolated cells in suspension, primary cultures, and clonal cell lines, have significantly contributed to understanding mammalian cell physiology, metabolism, and molecular biology. Hepatocytes isolated via the collagenase method are widely used in biological and biomedical research. Fresh hepatocytes, primary hepatocyte cultures, and immortalized cell lines allow the assessment of hepatoprotective activity and enable elucidation of cellular and molecular mechanisms of action (Vrba et al., 2018). These in vitro approaches represent an optimal platform for screening and selecting potential hepatoprotective compounds while providing detailed insight into their mechanisms at the cellular and molecular levels (Petga et al., 2023).

Precision-cut liver slices (PCLS) represent an ex vivo tissue culture model that preserves the multicellular organization of the liver. In this system, cell–cell interactions and spatial architecture are maintained, allowing detailed morphological studies. PCLS retain functional metabolizing enzymes and bile duct activity, making them a reliable ex vivo platform for investigating liver metabolism and injury. They also serve as an intermediate model between in vitro cell cultures and in vivo experiments, providing a valuable bridge for translational research (Amat et al., 2010).

4. CARBON TETRACHLORIDE (CCL_4)

Carbon tetrachloride is a synthetic chemical compound absent from the natural environment. Figure 1. Physically, it is a colorless, transparent liquid with a characteristic sweet odor, noticeable even at low concentrations (Domitrović et al., 2011). In scientific and technical literature, this substance is also known as carbon chloride, tetrachloromethane, perchloromethane, and benziform. Under environmental conditions, carbon tetrachloride is primarily found in the atmosphere as a colorless vapor. The compound is nonflammable and has low solubility in water (Fareed et al., 2024).

Figure 1 illustrates the chemical structure of carbon tetrachloride (CCl_4) and the main pathways of its hepatotoxic action. Carbon tetrachloride is a well-known hepatotoxic agent widely used in experimental models to induce liver injury. After entering the organism, CCl_4 is metabolized in the liver by cytochrome P450 enzymes, mainly CYP2E1, resulting in the formation of highly reactive trichloromethyl radicals ($\bullet CCl_3$) and trichloromethyl peroxy radicals ($\bullet OOCCl_3$). These reactive oxygen species initiate lipid peroxidation, damage hepatocyte membranes, disrupt mitochondrial function, and trigger inflammatory responses, ultimately leading to necrosis and fibrosis of liver tissue. Thus, Figure 1 demonstrates the molecular basis of CCl_4-induced hepatotoxicity and provides a mechanistic foundation for evaluating the hepatoprotective effects of medicinal plants.

The liver plays a central role in metabolism and is therefore highly susceptible to injury. Carbon tetrachloride (CCl_4)-induced hepatotoxicity is widely used in experimental models because it closely replicates liver damage observed in humans. This toxicity arises through the activation of several cytochrome enzymes, including CYP2E1, CYP2B1, CYP2B2, and possibly CYP3A, leading to the formation of the trichloromethyl radical (CCl_3*). The CCl_3* radical can interact with cellular biomolecules such as lipids, proteins, and nucleic acids, disrupting lipid metabolism and resulting in fatty degeneration. (Scholten et al., 2015).

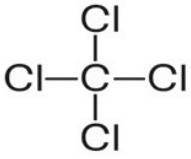


Figure 1. Chemical formula of carbon tetrachloride

Oxidative stress is a key contributor to numerous human diseases; accordingly, animal models typically rodents employing free radical–mediated injury are essential for simulating human liver pathology and evaluating potential therapeutic agents. Among these, CCl_4 remains one of the most commonly used experimental approaches to induce acute or chronic liver injury and investigate hepatoprotective interventions (Kaplowitz et al., 2002).

The trichloromethyl radical (CCl_3*) is generated during the metabolism of carbon tetrachloride (CCl_4) by cytochrome enzymes, including CYP2E1, CYP2B1, CYP2B2, and possibly CYP3A. This reactive radical can bind to critical cellular biomolecules, such as nucleic acids, proteins, and lipids, potentially disrupting physiological processes like lipid metabolism and leading to fatty degeneration (steatosis) (Lee et al., 2007).

Carbon tetrachloride, a simple organic compound with the chemical formula CCl_4, is highly toxic to multiple organs, including the liver, kidneys, testes, brain, heart, and lungs, with the liver being particularly susceptible (Unsal et al., 2021). CCl_4 acts as a potent hepatotoxic, nephrotoxic, and pro-oxidant agent and has been extensively employed in experimental studies to induce hepatotoxicity, as well as to model hepatocellular carcinoma, liver fibrosis and cirrhosis, chemical hepatitis, renal failure, and other forms of organ toxicity.

Although CCl_4 has been widely used to experimentally induce liver necrosis, (Firdous et al., 2021) the precise mechanisms underlying its hepatotoxicity remain incompletely understood. Studies of cellular fractions indicate that CCl_4 primarily targets mitochondria, contributing to oxidative stress and subsequent hepatocyte injury. The formation of free radicals during CCl_4 metabolism underscores the critical role of antioxidants in mitigating its toxic effects (Zhong et al., 2022)

Carbon tetrachloride (CCl_4) is commonly used as a solvent for non-polar substances such as fats and oils, and its acute toxicity has been extensively characterized in numerous animal studies (Lin et al., 2002) It is now widely recognized that the hepatotoxicity of CCl_4 results from its bioactivation by cytochrome P450 enzymes in liver microsomes, producing the highly reactive trichloromethyl radical (CCl_3*). This radical initiates lipid peroxidation of cellular membranes by attacking polyunsaturated fatty acids, generating lipid radicals and reactive aldehydes, and ultimately inducing oxidative stress and liver injury (Wang et al., 2016)

The liver serves as the primary organ for macromolecule metabolism, detoxification of circulating substances, and synthesis of proteins and bile acids. Experimental animal models are essential for elucidating the mechanisms underlying liver disease. Among models of liver fibrosis and cirrhosis, the combination of CCl_4 administration with a high-fat diet (HFD) is widely used, as it closely reproduces the histological and hemodynamic features observed in human liver pathology (Rolle et al., 2021)

The liver is the primary organ responsible for macromolecule metabolism, detoxification of circulating compounds, and the synthesis of proteins and bile acids. Experimental animal models play a crucial role in elucidating the mechanisms underlying liver diseases. Among the various models of cirrhosis and liver fibrosis, the combination of carbon tetrachloride (CCl_4) administration with a high-fat diet (HFD) is commonly used, as it closely replicates the histological and hemodynamic features observed in human liver pathology (Lee et al., 2010).

In the liver, CCl_4 is metabolized by the cytochrome P450 monooxygenase system (CYP family) into the reactive trichloromethyl radical (CCl_3*). This radical interacts with nucleic acids, proteins, and lipids, disrupting essential cellular processes, impairing lipid metabolism (leading to fatty degeneration and steatosis), and reducing protein levels, thereby contributing to hepatocyte injury and functional impairment (Kim et al., 2011).

In addition to its pronounced hepatotoxic effects, carbon tetrachloride (CCl_4) has been shown to cause minor acute systemic toxicity, particularly affecting the peritoneum, mucous membranes, respiratory tract, and central nervous system. As a hepatotoxin, CCl_4 induces varying degrees of hepatocyte degeneration and cell death. Beyond the liver, it exerts adverse effects on the kidneys, blood, and heart by promoting lipid peroxidation and the generation of reactive free radicals (Hamza et al., 2020).

CCl_4 is widely used as a xenobiotic to induce oxidative stress and remains one of the most common agents for experimentally modeling liver fibrosis. Its toxicity depends on both the dose and duration of exposure. At lower doses, it can disrupt calcium homeostasis, trigger lipid peroxidation, stimulate cytokine release, and initiate apoptosis, followed by compensatory cell regeneration (Chang et al., 2014).

The metabolism of CCl_4 occurs primarily via cytochrome P450 monooxygenases, particularly the CYP2E1 isoform located in the endoplasmic reticulum and mitochondria, generating the highly reactive trichloromethyl radical (CCl_3*). This radical targets cellular membranes, promoting lipid peroxidation and hepatocyte lysis, leading to structural liver damage and elevated serum levels of hepatospecific enzymes (Pingili et al., 2020) Due to its well-characterized mechanism of xenobiotic-induced hepatotoxicity, CCl_4 is frequently employed as a model system to evaluate the antihepatotoxic and hepatoprotective potential of drugs and natural compounds (Rahmani et al., 2023).

4. MEDICINAL PLANTS OF KAZAKHSTAN WITH HEPATOPROTECTIVE ACTIVITY

In recent years, there has been growing consumer interest in natural medicines, largely driven by the perception that plant-derived compounds are inherently safe. Concurrently, there is increasing industrial demand for medicinal plants that can be incorporated into food products, nutraceuticals, cosmetics, and pharmaceutical formulations.

Since the beginning of agriculture, plants have served as a major source of medicinal products. The global demand for plant-based medicines, health supplements, pharmaceuticals, and functional foods continues to rise. Medicinal plants are traditionally used to manage a wide variety of health conditions. According to the World Health Organization, approximately 80% of the world's population relies on herbal medicines. Herbal therapies typically utilize fruits, vegetables, dried plant materials, or their extracts to prevent or treat diseases and maintain overall health.

Flavonoids, a common class of plant secondary metabolites, exhibit diverse biological activities, including strong antioxidant effects and the ability to scavenge free radicals. Oxidative stress is frequently implicated in the progression of chronic diseases, often associated with the accumulation of connective tissue (Feduraev et al., 2022).

Figure 2 illustrates the geographic distribution of the studied medicinal plant species across the territory of Kazakhstan. The analysis of distribution patterns indicates that these species exhibit different degrees of occurrence and are associated with specific ecological and climatic zones, including steppe, mountainous, and foothill regions. Figure 2 shows the geographic distribution of the studied medicinal plants across Kazakhstan. The uneven distribution across ecological zones suggests that environmental conditions may influence the phytochemical composition and biological activity of these species.

***Glycyrrhiza glabra* L** - is a perennial herbaceous plant growing to 30–80 (up to 150) cm in height. Stems are erect, strong, simple or branched, usually glabrous or sparsely shortly pubescent, with a few scattered punctate glands or glandular spines. Stipules are small, lanceolate-awl-shaped, and usually fall off by the beginning of flowering. Leaves are odd-pinnate, 5–20 cm long, set on short pubescent petioles 1–2.5 cm long. Leaflets are 3–7 (sometimes up to 10) pairs, oblong-ovate, elliptic or lanceolate, 1.2–5 (6) cm long and 0.9–2.5 cm wide (Wu et al., 2021). The lower surface is densely covered with punctate glands; leaves are often sticky due to an abundant resinous secretion. Inflorescences are relatively loose racemes 5–8 (up to 12) cm long, lengthening during the fruiting period. Peduncles (2.5) 3–5 (7) cm long, shortly pubescent, slightly glandular. Flowers are small, 8–10 mm long. Calyx tubular, 6–8 mm long, shortly pubescent and glandular, with narrowly lanceolate teeth equal in length to the tube or slightly longer than it (Liu et al., 2023). Corolla whitish-violet. Standard oblong-ovate or elliptic, 8–13 mm long and about 5 mm wide, with an acute tip and a

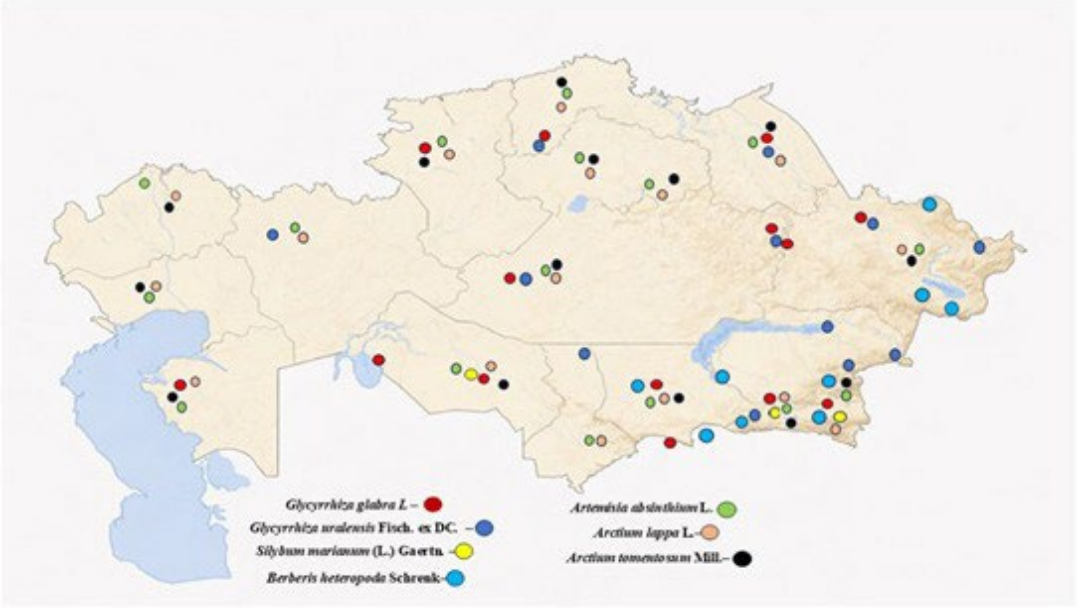


Figure 2. Geographic distribution of the investigated medicinal plant species across Kazakhstan, highlighting their occurrence in different ecological zones (steppe, mountainous, and foothill regions).

short unguis. Wings 8–10 mm long and 2–4 mm wide, their plates oblong, slightly curved, blunt at the apex; unguis about 4 mm long. The keel is 7–10 mm long and 2.5–4 mm wide; the blade is oblong, pointed at the end, and almost straight along the upper edge. The fruit is an oblong pod, straight or slightly curved, 1.5–3 cm long and 4–5 (6) mm wide, glabrous or densely covered with glandular spines, containing 1–6 (7) seeds. The seeds are round-kidney-shaped, smooth, dark brown, 2–3 mm long and 3–4 mm wide (Kim et al., 2006).

Glycyrrhiza glabra is widespread throughout Kazakhstan and is associated primarily with steppe, semi-desert, and floodplain ecosystems. Its range encompasses the northern, central, and southern regions of the country. In northern Kazakhstan, the plant is found in the Tobol-Esyl interfluve and the Irtysh River basin, including the Semei pine forest. In the western regions, populations have been recorded within the Caspian Lowland. In central Kazakhstan, the species is distributed within the Western Uplands (including the Ulytau Massif) and the Eastern Uplands (Karkaraly Region). In the south and southeast, its range encompasses the Aral Sea region, Kyzylorda region, the Chu-Ile Mountains, the Karatau Ridge, and the foothill and mountainous regions of the Western Tien Shan. Thus, the distribution of *Glycyrrhiza glabra* is characterized by a wide ecological amplitude and encompasses a variety of natural and climatic zones of Kazakhstan.

Glycyrrhiza glabra (licorice) is a perennial shrub that can grow up to 2.5 m in height. Its leaves are compound, odd-pinnate, and arranged alternately, with 4–7 pairs of oblong, elliptical, or lanceolate leaflets (Al-Razzuqi et al., 2020). The flowers are narrow, typically papilionaceous, and form axillary spike-like inflorescences, displaying shades from lavender to violet (Sitohy et al., 1991).

Belonging to the legume family (Fabaceae), *Glycyrrhiza glabra* has been valued for its ethnopharmacological properties since ancient times (Sharma 2014). The plant contains a variety of bioactive compounds, including glycyrrhizin, 18β-glycyrrhetinic acid, glabrin A and B, and several isoflavones, which contribute to its diverse pharmacological activities (Pastorino et al., 2018).

Widely employed in Ayurvedic medicine, *Glycyrrhiza glabra* exhibits antibacterial, antioxidant, antimalarial, antispasmodic, anti-inflammatory, and antihyperglycemic properties. Additional studied effects include antiulcer, antiviral, antihepatotoxic, antifungal, and activity against herpes simplex virus, highlighting its broad therapeutic potential (Zhang et al., 2021).

In the absence of highly effective hepatoprotective drugs in modern medicine, various medicinal plants traditionally used for liver disorders, such as *Glycyrrhiza glabra*, have been employed for the prevention and treatment of hepatic diseases, although their mechanisms were historically not well understood (Subramoniam and Pushpangadan, 1999).

The bioactive compounds of *Glycyrrhiza glabra* exhibit therapeutic effects not only in liver diseases but also in conditions such as diabetes mellitus and cardiovascular and cerebrovascular disorders (Alrefaei et al., 2025). Experimental and clinical studies have demonstrated that licorice extracts and isolated constituents possess a broad spectrum of medicinal activities, including anti-inflammatory, antioxidant, antiviral, antimicrobial, hepatoprotective, anticancer, and antidiabetic effects, and may even serve as adjuvants in dental care.

Phytochemically, *Glycyrrhiza glabra* contains triterpene glycosides, polysaccharides, coumarins, alkaloids, aromatic compounds, proteins, and trace elements. Among these, flavonoids and triterpenoid saponins are considered the principal bioactive components. (Liu et al., 2023). Glycyrrhizin, the primary active constituent extracted from licorice roots, is one of the most widely studied herbal agents for liver protection. Experimental investigations have evaluated its hepatoprotective potential in models of carbon tetrachloride (CCl_4)-induced liver injury, demonstrating significant amelioration of hepatic damage (Ikram et al., 2025).

Experimental studies have demonstrated that the aqueous extract of *Glycyrrhiza glabra* significantly improves liver function and promotes the restoration of hepatic tissue in models of acute liver injury when administered at a dose of 2 g/kg body weight once daily. In a study using male albino Sprague Dawley rats with diabetes-induced liver damage, G. glabra exhibited hepatoprotective effects by restoring liver function, reducing oxidative stress, and preserving histological integrity (Yin et al., 2011). Glycyrrhizin was identified as the primary bioactive compound responsible for these therapeutic effects, supporting its potential in managing liver complications associated with diabetes (Yahya et al., 2024).

Furthermore, in models where elevated serum cholesterol adversely affected hepatic and renal function, administration of *Glycyrrhiza glabra* improved both liver and kidney parameters and demonstrated a hypoglycemic effect. In carbon tetrachloride (CCl_4)-induced hepatotoxicity, tissue antioxidant status is disrupted, leading to histopathological abnormalities (Dogra et al., 2021). Treatment with G. glabra reversed these changes, highlighting its potent antioxidant activity. The hepatoprotective mechanism involves suppression of lipid peroxidation and scavenging of free radicals, facilitated by the conjugation of reactive species with glutathione (GSH) and the enzymatic support of glutathione-S-transferase (GST). These findings indicate that *Glycyrrhiza glabra* effectively mitigates CCl_4-induced liver injury through its antioxidant properties in vivo (Bao et al., 2023).

***Glycyrrhiza uralensis* Fisch. ex DC.** is a perennial herbaceous plant 50–70 (up to 110) cm tall with erect, simple

or branched stems, shortly hairy, with small brown glands or glandular spines (Gou et al., 2021). Stipules are small, lanceolate or lanceolate-awl-shaped, falling early. Leaves are odd-pinnate, 10–25 cm long; petioles 2–5 cm, shortly hairy, glandular. Leaflets 4–8 pairs, ovate or oblong-elliptic, 2.5–5 (6) × 1.5–3 cm, shortly hairy below (sometimes above), densely covered with sticky glands, often shiny (Liao et al., 2021). Inflorescences are dense racemes 5–9 cm long on shortly pubescent, glandular peduncles, usually shorter than the leaves. Bracts lanceolate, shorter than calyx, pubescent and glandular (Kim et al., 2006). Flowers 14–23 mm; calyx tubular 8–14 mm, slightly saccularly inflated at base, teeth lanceolate, equal to or slightly longer than tube. Corolla violet with white; standard 15–18 × 5–7 mm, oblong-ovate or elliptic; wings 13–14 mm; keel 10–13 mm. Fruit a linear-oblong pod 3–4.5 × 0.6–0.7 cm, sickle-curved, glabrous or with glandular spines; seeds round-rendiform, 3–5 mm, 3–9 pcs., brown (Yahya et al., 2024).

Glycyrrhiza uralensis has a wide range across Kazakhstan and is found in various natural and geographical zones, from steppe plains to mountain ranges. In the northern regions, the species is distributed within the Tobol–Esyl interfluve, the Irtysh River basin, the Semei pine forest, and the Kokshetau Upland. In the western part of the country, populations have been recorded in the Caspian Lowland and the Mugodzhary Mountains. Central Kazakhstan is represented by localities within the Western Uplands (including the Ulytau Massif) and the Eastern Uplands, including the Karkaraly and Karkara regions. The plant is also found in the Betpak-Dala desert zone and the Balkhash-Alakol Depression. In the eastern and southeastern parts, its range encompasses the Altai mountain range, Zhetysu Alatau, Ile Alatau, and Kungey Alatau. In the south, the species grows within the Karatau Range and in the mountainous regions of the Western Tien Shan. Thus, *Glycyrrhiza uralensis* is characterized by high ecological flexibility and is adapted to the diverse climatic and landscape conditions of Kazakhstan (Komolkriengkrai et al., 2019).

G. uralensis (G. uralensis) is a traditional herbal remedy known for its pronounced hepatoprotective properties, which is confirmed by modern pharmacological research (Ji et al., 2016). The main biologically active components of the plant are flavonoids. Among the total flavonoids of *Glycyrrhiza uralensis* (LTF), the main compounds are a group of flavonoids, the total content of which exceeds 60%. Experimental data indicate that LTF is capable of restoring liver structure and reducing the degree of damage by suppressing inflammatory processes, increasing the activity of antioxidant enzymes, and reducing oxidative stress in liver tissue (Peng et al., 2015). Thus, LTF represents a promising natural source of hepatoprotective substances. A total of 122 compounds, including six previously unknown structures, have been isolated and identified from the roots and rhizomes of G. Uralensis (Wu et al., 2024). These compounds were investigated using 11 cellular and enzymatic bioassays, including Nrf2 activation, NO inhibition, NF-κB suppression, antiviral activity against H1N1, cytotoxicity to HepG2, SW480, A549, and MCF7 cells, and inhibition of PTP1B, tyrosinase, and acetylcholinesterase. Among the identified compounds, isoprenylated phenols were discovered for the first time. (Yu et al., 2015). Echinatin, a potent Nrf2 activator, was selected as an example of a biologically active component. In mouse experiments, it attenuated liver damage induced by carbon tetrachloride (CCl_4) when administered intraperitoneally at doses of 5–10 mg/kg, confirming its contribution to the hepatoprotective activity of licorice. (Liou et al., 2019).

***Silybum marianum* (L.) Gaertn** The baskets are solitary, large, drooping, homogamous; the involucre is broadly spherical, its leaflets are imbricated, the outer and middle ones pass into a leaf-shaped appendage with a spiny-dentate edge, elongated into a long, protruding, (Vargas-Mendoza et al., 2014). lanceolate-awl-shaped straight spine, the inner leaflets of the involucre are entire, with a small appendage or without it; the receptacle is flat, fleshy, membranous-ciliate; all the flowers are identical, fertile, bisexual; the corolla is violet, purple, pink, less often white, with a narrowly cylindrical, elongated tube and a short bell-shaped limb with narrow, linear lobes; the filaments of the stamens are free at the top, stuck together above the base because of mucous hairs, the lower appendages of the anthers are linear-ciliate, the upper ones are arrow-shaped-triangular; The style is thickened at the top, covered with long, branched hairs, with branches that are close together and diverge briefly at the top; the achene is obovate, naked, slightly flattened, with a raised tubercle on the upper surface; the tuft is made up of filmy, toothed bristles along the edge, connected into a ring, inside which is a crown of small hairs (Tolleson et al., 2002).

In Kazakhstan, Silybum marianum is distributed primarily in the southern and southeastern regions, confined to arid and foothill zones. The species' primary locations are within the Kyzylorda region, as well as in the mountainous and foothill regions of the Ile Alatau and Kungei Alatau mountains (Northern Tien Shan). The plant is also found in the Western Tien Shan. Thus, Silybum marianum's range in Kazakhstan is primarily associated with regions with warm climates and relatively mild winters, where the species successfully naturalizes and forms stable populations (Loguercio et al., 2011).

Silybum marianum, commonly known as milk thistle, is a medicinal plant with a therapeutic history spanning over 2,000 years. Traditionally, it has been used as a hepatoprotective agent for the treatment of jaundice, as well as enlargement of the liver and spleen (Jiang et al., 2022). The seeds of

milk thistle are particularly valued, containing approximately 70–80% silymarin flavonolignans and 20–30% polymeric and oxidized polyphenolic compounds, including tannins. (Jin et al., 2017).

The primary bioactive constituent, silymarin, is a standardized extract widely employed for its hepatoprotective properties and is used to manage a range of hepatic and systemic disorders (Polachi et al., 2016). Although silymarin has a long history of use in herbal medicine and has been recently recognized for its liver-protective potential, the precise molecular mechanisms underlying its therapeutic effects are still not fully elucidated (Viktorová al., 2019).

Silymarin administration markedly attenuated the elevation of serum liver enzymes, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), in rats with CCl_4-induced liver injury (Tsai et al., 2008). Additionally, it restored the altered expression of α-smooth muscle actin (α-SMA) in hepatic tissue, indicating its potential to mitigate and contribute to the resolution of liver fibrosis in this experimental model (Selc et al., 2024).

Silybum marianum and *Glycyrrhiza glabra* both demonstrate significant hepatoprotective activity against CCl_4-induced liver injury, with studies indicating that their combined use is more effective than either herb alone (Schümann et al., 2003). Experimental results suggest that higher doses-200 mg/kg of S. marianum and 50 mg/kg of G. Glabra may act synergistically, enhancing liver protection (Yang et al., 2025).

Time-course analyses further reveal that the normalization of serum liver enzymes is treatment-duration dependent, with near-complete restoration of hepatic function observed after six weeks of continuous administration (Morazzoni et al., 1993).

Artemisia absinthium* L. Aster Family-*Asteraceae. *Artemisia absinthium* L., commonly known as wormwood, is widely distributed across Asia, the Middle East, Europe, and North Africa, and is prevalent throughout Kazakhstan. The plant is rich in diverse phytochemicals, including lactones, terpenoids (such as trans-thujone, γ-terpinene, 1,4-terpeneol, myrcene, bornyl acetate, cadinene, camphene, trans-sabinyl acetate, guaiazulene, chamazulene, camphor, and linalool), essential oils, organic acids, resins, tannins, and phenolic compounds.

Artemisia absinthium is a perennial herbaceous plant 60–100 (120) cm tall, completely covered with short appressed hairs, giving it a silvery-gray color (Amat et al., 2010). The root is thick, vertical. The stem is usually single, erect, grooved, densely foliated, branched in the upper part. The leaves are twice or almost thrice pinnately dissected: the lower ones are long-petiolate, the upper ones are short-petiolate or subsessile (Jahromi et al., 2016). The leaf blade is broadly ovate (6–9 × 3–7 cm), green above, grayish below. The terminal lobes are linear-oblong, small (Szopa et al., 2020). The inflorescence is a narrow panicle of small spherical basket-shaped (2.5–3.5 mm), drooping or deflected. Marginal florets are pistillate, few in number; disk florets are tubular, numerous. The fruit is an oblong achene. It is widespread throughout Kazakhstan; it grows as a weed along roadsides, near houses, in fields, meadows, and in the mountains. Thus, *Artemisia absinthium* is found in almost all natural and climatic zones of Kazakhstan, which indicates its high adaptability to a variety of environmental conditions (Kosakowska, et al., 2025).

Additionally, A. absinthium contains flavonoids, including quercetin, and flavonoid glycosides such as isorhamnetin-3-O-rhamnose glycoside, isoquercitrin, quercetin-3-O-D-glucoside, quercetin-3-O-rhamnoglucoside, and isorhamnetin-3-O-glucoside. The plant also possesses a range of phenolic acids, including coumaric, shikimic, salicylic, chlorogenic, and vanillic acids, which contribute to its free radical scavenging and antioxidant activity (Long et al., 2019).

Artemisia absinthium exhibits a range of pharmacological activities, although toxic effects on the nervous system and liver have been reported at high doses. Experimental studies have shown that pretreatment with *A. absinthium* L. significantly ($P < 0.001$) and dose-dependently prevented elevations in serum liver enzymes induced by chemical or immunological insults. (Krebs et al., 2010). Additionally, the plant markedly ($P < 0.05$) reduced lipid peroxidation in hepatic tissues and restored the activities of key antioxidant enzymes, including superoxide dismutase (SOD) and glutathione peroxidase (GPx), to near-normal levels (Wei et al., 2019).

In the BCG/LPS model of inflammation, *A. absinthium* pretreatment significantly suppressed ($P < 0.01$) the levels of proinflammatory cytokines, such as TNF-α and IL-1. Histopathological examination revealed attenuation of hepatocellular necrosis and reduced infiltration of inflammatory cells. Phytochemical analyses indicate that sesquiterpene lactones, flavonoids, phenolic acids, and tannins are major bioactive constituents responsible for its hepatoprotective and anti-inflammatory effects (Zhao et al., 2017).

Recent studies have highlighted the hepatoprotective potential of *Artemisia absinthium*. Experiments investigating the effects of a hydromethanol extract of *A. absinthium* herb on hepatocytes in rats demonstrated significant protective activity (Pazhouh et al., 2020). Further investigations in mice, in which liver injury was induced either by carbon tetrachloride (CCl_4) or by immunological stimulation with lipopolysaccharide (LPS), confirmed these findings. Administration of an aqueous extract of A. absinthium resulted in a marked

reduction in serum liver enzyme levels, inhibition of lipid peroxidation, and restoration of antioxidant enzyme activities, including superoxide dismutase (SOD) and glutathione peroxidase (GPx), under both chemically and immunologically induced hepatic injury (Tarabasz et al., 2020).

Additionally, in the immunological model, pretreatment with *A. absinthium* significantly decreased the levels of proinflammatory cytokines, such as TNF-α and IL-1. Histopathological analyses further demonstrated a reduction in hepatocellular necrosis and inflammatory cell infiltration, supporting the extract's hepatoprotective and anti-inflammatory properties.

***Berberis heteropoda* Schrenk** Schrenk is a shrub native to Central Asia, including the Tian Shan and Zhetysu Alatau ranges, as well as Mongolia and western China. In Kazakhstan, this species grows on southern dry mountain slopes across steppe, forest, and subalpine forest-steppe zones. Among the eight Berberis species found in Kazakhstan, B. heteropoda (also referred to as Berberis sphaerocarpa Kar. & Kir.) is distributed in regions such as Zaisan, Altai, Tarbagatai, Zhetysu Alatau, Ile Alatau, and Kungey Alatau, as well as the Chu-Ile Mountains (Berganayeva et al., 2020).

Berberis heteropoda is a deciduous shrub growing to 2 m tall. Young shoots are brownish-red, turning gray with age (Belwal et al., 2020). Spines are simple or tripartite, 1–3 cm long. Leaves are grayish-green or glaucous, large, up to 7.5 cm long and 4 cm wide, glabrous, and obovate. The margin is entire or finely and indistinctly serrated-spiny; the apex often ends in a small spine. The underside of the leaf blade is characterized by a clearly expressed reticulate venation. The leaves gradually narrow into a petiole up to 3 cm long. The inflorescence is represented by a loose, multi-flowered raceme, including 5–9 yellow flowers (Sun et al., 2022). Peduncles are 6–20 mm long. Sepals are obovate; petals are similar in shape, but approximately twice as long as the sepals. The ovary develops 3–6 ovules on stalks, the length of which is 3–4 times greater than the ovule itself. The fruit is a spherical-oval berry, purple-black in color with a bluish waxy coating, up to 12 mm in diameter. The seeds have a wrinkled surface (Zemtsova et al., 2022).

Traditionally, the roots, bark, stems, and fruits of *B. heteropoda* have been used in herbal medicine, with the fruits historically consumed as tea. In addition to macronutrients such as proteins, fats, and dietary fiber, the plant contains a variety of phenolic compounds, which are considered beneficial for human health (Yang et al., 2013). Recent studies have, for the first time, characterized the composition and content of anthocyanins in the fruits of *B. heteropoda* Schrenk.

Plants of the genus Berberis (family Berberidaceae) are widespread, with nearly 550 species globally (Sun et al., 2014). Extracts and bioactive compounds derived from Berberis species particularly the alkaloid berberine have demonstrated nutritional and pharmacological potential, confirming their value in health-promoting applications (Pérez-Alvarez et al., 2001).

Fruits of *Berberis heteropoda* Schrenk are nutrient-rich and have been shown to contain bioactive compounds with potential health and nutritional benefits. Phytochemical analyses have identified a total of 32 polyphenolic compounds in the fruit extract, highlighting its antioxidant and functional properties (Ivanovska et al., 1996).

***Arctium lappa* L.** Linné, commonly known as burdock or bardana, belongs to the Asteraceae (Compositae) family. Its carrot-like roots are traditionally consumed as a vegetable in parts of Asia, while the plant has long been valued in traditional medicine for its pharmacological properties (Alhusaini et al., 2019). The therapeutic potential of *A. lappa* is attributed to a diverse array of secondary metabolites, including phytosterols, terpenes and terpenoids, hydrocarbons, flavonoids, fatty acids, carboxylic derivatives, lignans, acetylenic compounds, polysaccharides, aldehydes, methoxypyrazines, and monoterpenes and sesquiterpenes (Gao et al., 2018). Historically, the roots have been the primary medicinal part used, with the leaves and seeds also employed occasionally, due to their bioactive constituents. (Branković et al., 2026).

Arctium lappa L., commonly known as burdock, contains two primary bioactive compounds: arctigenin (AR) and its glycoside, arctiin (El-Kott et al., 2015). This medicinal plant and dietary supplement is widely used in Asia, with its roots traditionally valued as a detoxifying agent, particularly for supporting liver function, the body's central organ for blood detoxification.

Arctium lappa L. is a genus of large, non-thorn biennial herbaceous plants with strong stems and large leaves (Mahboubi et al., 2021). Anthodia are homogamous, spherical. The receptacle is flat, weakly fleshy, covered with numerous bristles, initially straight, later spiraling. The wrapper is glabrous or cobwebby; the leaflets of the wrapper are linear or lanceolate, arranged in several rows (Wang et al., 2019). The outer and middle leaflets are narrowed into a deflected point ending in a small hook; the inner ones are more or less membranous, straight. The flowers are bisexual, identical, tubular, with a 5-lobed corolla, all fertile (Zhou et al., 2020). Achenes are oblong, flattened from the sides, ribbed, wrinkled between the ribs (less often almost smooth), truncated at the apex. The crest is short, consisting of uneven, rough bristles that fall off easily. Arctium lappa - Found in all regions of Kazakhstan.

A review of available literature from electronic databases, including Google Scholar, ScienceDirect, Springer, and Magiran, indicates that burdock roots can modulate liver function and protect against hepatotoxicity (Lu et al., 2020).

Although most studies have been conducted in animal models, the findings consistently demonstrate that A. lappa mitigates liver injury induced by ethanol, carbon tetrachloride (CCl_4), acetaminophen, cadmium, and zinc oxide, primarily by restoring and improving liver enzyme activity. These results support the traditional use of burdock as a hepatoprotective and detoxifying agent (Li et al., 2022).

Administration of arctigenin was found to significantly attenuate markers of hepatotoxicity in rats compared to the CCl_4-treated group (El-Kott et al., 2014). Both arctigenin and silymarin markedly reduced serum levels of matrix metalloproteinase-2 (MMP-2), with values of 978 ± 135 and 1177 ± 176, respectively, versus 1734 ± 294 in the CCl_4 group (Mu et al., 2022). CCl_4 injection caused a significant decline in liver antioxidant parameters, including total glutathione, superoxide dismutase (SOD), and glutathione reductase; these reductions were effectively prevented by pretreatment with either arctigenin or silymarin (Sun et al., 2014).

These findings confirm the hepatoprotective potential of *Arctium lappa*, with arctigenin demonstrating a protective effect comparable to silymarin at 200 mg/kg, despite being administered at a lower dose of 15 mg/kg per day (Li et al., 2026). The protective mechanism is likely mediated, at least in part, by the antioxidant activity of arctigenin, which mitigates oxidative stress in hepatocytes, although additional mechanisms may also contribute to its hepatoprotective action (Mssillou et al., 2025).

***Arctium tomentosum* Mill.**, commonly known as downy or spider burdock due to the cobweb-like hairs covering its inflorescences, is a member of the Asteraceae family. Globally, the Asteraceae family comprises 1,150–1,300 genera and approximately 20,000 species, while in Kazakhstan, it includes around 140 genera and over 700 species (Nurmahanova et al., 2024).

Arctium tomentosum is widespread throughout Kazakhstan and is found in most of the country's natural and geographical regions (Aitynova et al., 2022). The species is absent from the southern desert zones, due to its lower tolerance to extremely arid conditions. In mountainous regions, the plant grows to an altitude of approximately 2,000 meters above sea level, above which it is generally not observed. Thus, *Arctium tomentosum* is characterized by a significant range within the temperate continental and foothill ecosystems of Kazakhstan, with a limited distribution in highlands and deserts (Ydyrys et al., 2023).

Arctium tomentosum is a biennial herbaceous plant growing 60–150 cm tall with a fleshy, spindle-shaped root. The stem is erect, robust, branched, longitudinally furrowed, green or brownish. The shoots are cobwebby-pubescent, with papillary hairs and an admixture of glands. The leaves are ovate, with a cordate or broadly cordate base, entire or finely serrated, and obtuse with a short pointed tip at the apex (de Souza et al., 2022). The upper side is green, glabrous or slightly pubescent; the underside is densely whitish or grayish-tomentose (which is an important diagnostic feature of the species) (Rukkumani et al., 2004). The basal leaves are large, up to 50 cm or more long, on long tomentose petioles; the cauline leaves are significantly smaller, on short petioles. The flower heads are spherical, 18–30 mm wide, densely covered with a web-like pubescence, and gathered into a corymbose inflorescence (Pereira et al., 2016). The bracts are dark purple: the outer ones are bent downward and end in a hooked point; the middle and inner ones also have hooked tips. The flowers are purple, tubular, and significantly longer than the inner bracts. The fruit is an inversely conical achene 5–6 mm long, grayish-brown, and wrinkled. The species is widespread in steppe and forest-steppe regions, occurring in meadows, fallow lands, along roadsides, and near human habitation.

Phytochemical analyses have confirmed the presence of arctiin and arctigenin in the fruits of *A. tomentosum*, (Aitynova et al., 2024; Alibek et al., 2021) and studies indicate that nearly all parts of the plant-roots, leaves, seeds, fruits, flowers, and inflorescences-can be used to obtain biologically active extracts. The plant contains a diverse array of bioactive compounds, including hydroxybenzoic and hydroxycinnamic acids and their derivatives, tannins, phenolic compounds and glycosides, flavonoids, coumarins, anthocyanins, amino acids and other nitrogen-containing compounds, polysaccharides, polyacetylene compounds, phytosterols, triterpenoids, and mono- and polyunsaturated fatty acids. This chemical diversity underlies the wide-ranging pharmacological potential of A. tomentosum and related burdock species (Esmat et al., 2022).

Arctium tomentosum Mill. is a relatively underexplored species of the genus Arctium that exhibits notable pharmacological potential. It is recognized in the European Medicines Agency monograph as having pharmacological properties comparable to those of *A. lappa*. This species is considered a promising source of bioactive compounds with a wide spectrum of medicinal activities, including anticancer, antidiabetic, hepatoprotective, hypoglycemic, antioxidant, and antimicrobial effects (Liu et al., 2017).

Phytochemical analyses reveal that arctiin and arctigenin are present in significant amounts throughout all plant organs, while polyphenols are abundant in the roots and aerial parts, and lignans, fatty acids, and anthocyanins are concentrated in the fruits. The hepatoprotective activity of A. tomentosum is largely attributed to its antioxidant properties (Janbaz et al., 2002). In experimental models of CCl_4-induced liver injury, administration of the extract counteracted the suppression of antioxidant enzymes and the rise in malondialdehyde (MDA) levels. Treatment with A. tomentosum extract at doses of 200 mg/kg and 400 mg/kg body weight partially restored the

activity of glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD), while simultaneously reducing lipid peroxidation (Pari et al., 2008).

5. PHYTOCHEMICALS RESPONSIBLE FOR HEPATOPROTECTIVE ACTIVITY

Natural compounds remain a crucial source for the discovery and development of novel therapeutic agents. At present, there is a growing emphasis on creating herbal medicines based on a limited number of components with well-characterized chemical structures and defined biological activity profiles.

Hepatoprotective agents, or hepatoprotectors, are substances that prevent damage to hepatocyte membranes and promote liver cell regeneration. These agents can be classified into different groups depending on their origin.

Today, roughly 40% of all medications in use are derived from plants. Phytotherapy plays a particularly important role in managing hepatobiliary disorders, as herbal remedies can exert multiple complementary effects on key pathogenic mechanisms (Table 1).

6. MECHANISMS OF HEPATOPROTECTION

Medicinal plants with antioxidant and membrane-stabilizing properties can mitigate the damaging effects of CCl_4 and restore liver function.

Carbon tetrachloride (CCl_4) is one of the most common models for experimental study of liver damage. Its hepatotoxic effect is due to metabolic activation involving the cytochrome P450 system, which leads to the formation of free radicals and the development of oxidative stress. As a result, there is an increase in lipid peroxidation, which leads to disruption of cell membrane integrity, the development of mitochondrial dysfunction, and hepatocyte necrosis.

Liver damage caused by Carbon tetrachloride (CCl_4) is associated with its biotransformation in liver cells involving cytochrome P450 enzymes. This process produces highly reactive free radicals, primarily the trichloromethyl radical ($\bullet CCl_3$), which, when reacting with oxygen, transforms into the peroxytrichloromethyl radical ($\bullet OOCCl_3$). These reactive species initiate lipid peroxidation of membrane lipids, causing damage to the cellular structures of hepatocytes. This disrupts membrane integrity, impairs mitochondrial and endoplasmic reticulum function, leading to suppressed protein synthesis and disruption of energy metabolism. The resulting structural changes are accompanied by hepatocyte death, increased inflammatory response, and activation of fibrosis, ultimately leading to disruption of the normal structure and function of the liver. Mechanism diagram: CCl_4 (carbon tetrachloride)

CCl_4 → CYP450 → $\bullet CCl_3$ → $\bullet OOCCl_3$ → Lipid peroxidation → Damage to hepatocyte membranes → Mitochondrial and ER dysfunction → Decreased protein/enzyme synthesis → Necrosis and apoptosis → Inflammation → Liver fibrosis

Mechanism of hepatoprotective action of medicinal plants:

Plant phytochemicals (flavonoids, phenols, saponins, terpenoids) → Antioxidant activity → Neutralization of free radicals → Inhibition of lipid peroxidation → Stabilization of hepatocyte membranes → Reduction of inflammation → Stimulation of hepatocyte regeneration → Normalization of liver enzymes (ALT, AST, ALP) → Restoration of liver structure and function (Figure 3).

Medicinal plants contain biologically active compounds (flavonoids, phenolic compounds, saponins, alkaloids), which have a protective effect on the liver. Medicinal species demonstrating pronounced hepatoprotective potential and actively studied in phytotherapy and experimental pharmacology include *Glycyrrhiza glabra, Glycyrrhiza uralensis*, *Silybum marianum*, *Berberis heteropoda, Artemisia absinthium, Arctium lappa, and Arctium tomentosum.* (Mou et al., 2024).

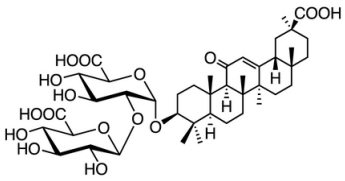
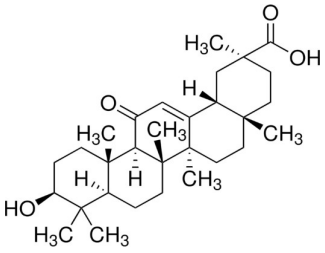
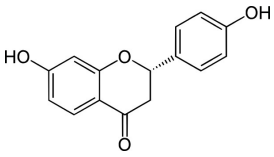
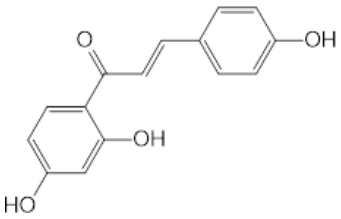
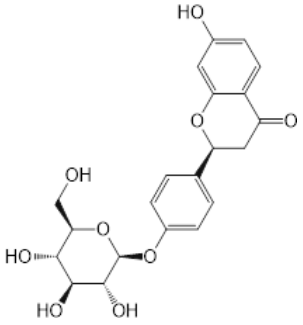
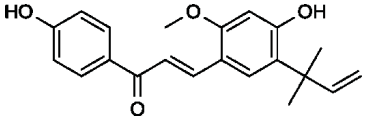
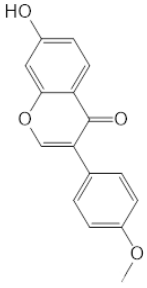
The pharmacological significance of these plants is determined by the presence of a complex of biologically active compounds flavonoids, phenolic components, triterpene structures, alkaloids, and other secondary metabolites. These substances have the ability to reduce the severity of oxidative stress, modulate the inflammatory response, and prevent programmed hepatocyte death. The following section presents data on the phytochemical profile of these species and reveals the molecular mechanisms of their hepatoprotective action. (Wang et al., 2019).

7. RESEARCH GAPS AND FUTURE PERSPECTIVES

Despite the accumulated array of experimental data attesting to the hepatoprotective activity of medicinal plants in Kazakhstan, their translation into clinical practice remains limited due to a number of methodological and applied problems. Studies devoted to species such as *Glycyrrhiza glabra, Glycyrrhiza uralensis, Silybum marianum, Arctium lappa, Arctium tomentosum, Artemisia absinthium*, and *Berberis heteropoda* are mainly based on the use of herbal preparations without proper standardization of their composition.

Significant variability in the phytochemical spectrum, associated with geographical characteristics of growth, ontogenesis phase, raw material harvesting conditions, and extraction methods, negatively affects the reproducibility of results. In addition, the lack of unified approaches to analytical

Table 1
Major phytochemicals and mechanisms of hepatoprotective activity of selected medicinal plants.

Plant	Major phytochemical groups	Biologically active substances	The main mechanism of hepatoprotective action	Source
Glycyrrhiza glabra		Glycyrrhizin	• Antioxidant effect • Inhibition of lipid peroxidation (LPO) • Anti-inflammatory effect (↓ TNF-α, ↓ IL-6) • Stabilization of hepatocyte membranes	Sharma et al. Yin et al. Mou et al. Wang et al.
		18β-glycyrrhetinic acid	• Antioxidant activity • ↓ Lipid peroxidation • ↓ Hepatocyte apoptosis • Modulation of MAPK and PI3K/Akt pathways	Wu et al., 2024 Rajkovic et al.
		Liquiritigenin	• Antioxidant • ↑ Activity of SOD, CAT • Protection against CCl_4-induced liver damage	Kim et al. Zhang et al. Bao et al.
		Isoliquiritigenin	• Antioxidant • Anti-inflammatory • Antifibrotic effect	Liu et al. Yahya et al. Peng et al.
Glycyrrhiza uralensis		Liquiritin	• ↑ SOD, CAT • ↓ ROS • Membrane-stabilizing effect	Gou et al. Kim et al. Yu et al.
		Licochalcone A	• Antioxidant • Reduces inflammatory cytokines • Mitochondrial protection	Ji et al. Liou et al. Wu et al., 2024
		Formononetin	• Pronounced antioxidant effect • ↓ ROS and MDA • ↑ SOD and CAT activity • NF-κB inhibition • ↓ Inflammatory liver infiltration • Protection against CCl_4-induced hepatotoxicity	Liao et al. Tolleson et al. Jin et al.

(*continues*)

Table 1
Continued.

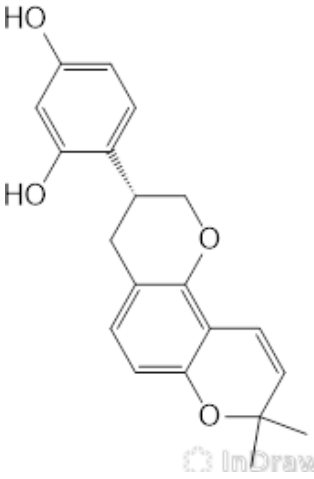
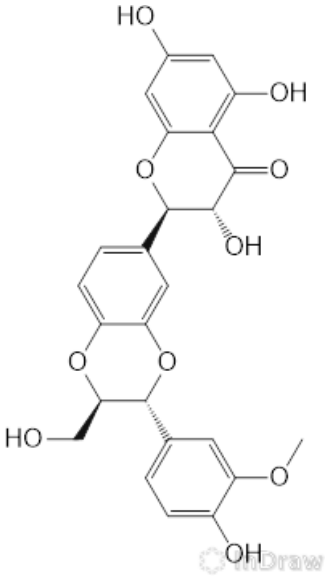
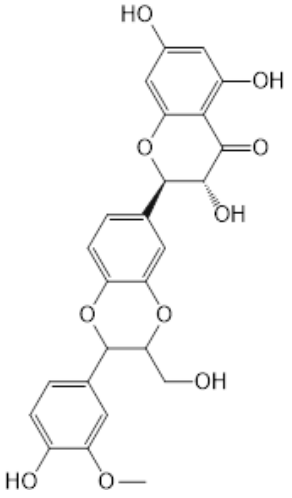
Plant	Major phytochemical groups	Biologically active substances	The main mechanism of hepatoprotective action	Source
		Glabridin	• Pronounced antioxidant activity • ↓ ROS formation • ↓ Lipid peroxidation (MDA) • ↑ Activation of the Nrf2/ARE pathway • Protection of mitochondrial function • ↓ Inflammatory cytokines (TNF-α, IL-1β)	Dogra et al. Komolkriengkrai et al. Yang et al.
Silybum marianum		Silibinin	• ↑ Nrf2 activation → ↑ SOD, CAT, GPx • ↓ Lipid peroxidation (↓ MDA) • ↓ NF-κB → ↓ TNF-α, IL-6 • Membrane-stabilizing effect • ↓ Fibrosis (inhibition of TGF-β) • ↑ Hepatocyte regeneration	Jiang et al. Selc et al. Schümann et al.
		Isosilybin	• Antioxidant • ↓ Inflammation • Antifibrotic effect	Loguercio et al. Albassam et al. Vrba et al.

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Table 1
Continued.

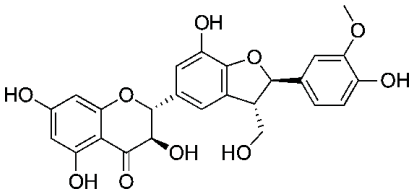
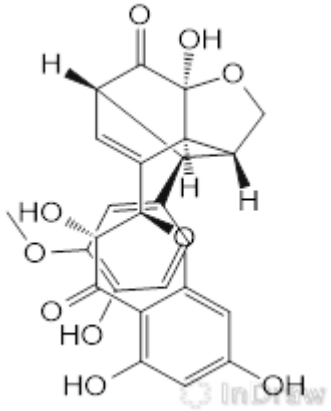
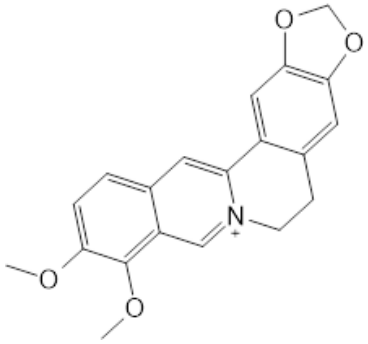
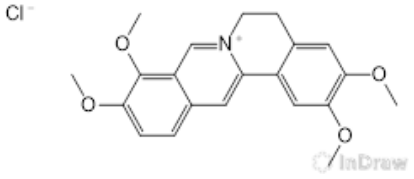
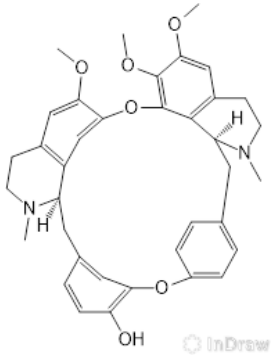
Plant	Major phytochemical groups	Biologically active substances	The main mechanism of hepatoprotective action	Source
		Silychristin	• Membrane protection • ↓ Cytotoxicity • Antioxidant	Viktorová et al. Dwivedi et al. Loguercio et al. Jaffar et al.
		Silydianin	• Stabilization of cell membranes • ↓ Oxidative stress	Morazzoni et al. Mukhtar, et al. Vargas-Mendoza, et al.
Berberis heteropoda		Berberine	• ↓ ALT, AST • ↓ Lipid peroxidation • AMPK activation • ↓ Liver steatosis • ↓ Inflammatory cytokines	Belwal, et al. Li, et al. Domitrović, et al. Prasher et al.
		Palmatine	• Antioxidant • ↓ Oxidative stress • Inflammation • Membrane-stabilizing effect	Long, et al. Tarabasz, et al. Lee, et al.
		Oxyacanthine	• Antioxidant activity • ↓ Lipid peroxidation • ↓ Inflammatory mediators • Membrane-stabilizing effect	Ivanovska, et al. Hamza, et al. Chang, et al.

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Table 1
Continued.

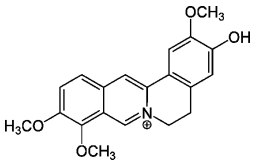
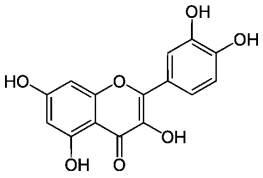
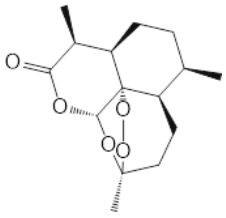
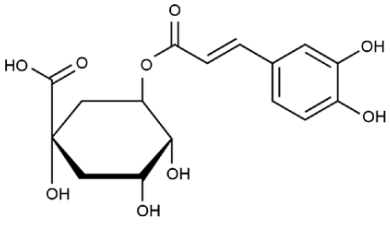
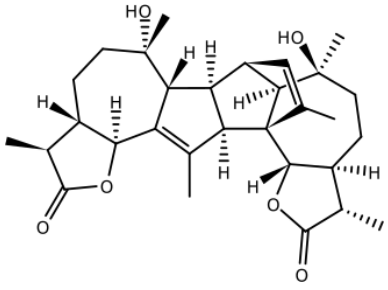
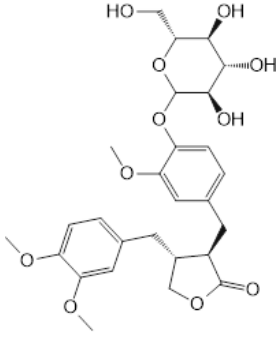
Plant	Major phytochemical groups	Biologically active substances	The main mechanism of hepatoprotective action	Source
		Jatrorrhizine	• ↓ ROS • ↓ Inflammatory processes • Potential for reducing fibrosis	Rolle, et al. Zhong, et al. Wang, et al.
Artemisia absinthium		Quercetin	• Antioxidant and anti-inflammatory effect • Reduction of oxidative stress • Protection of hepatocyte membranes	Wei, et al. Pingili, , et al. Abo-Salem, et al.
		Artemisinin	• Antioxidant activity • ↓ Inflammatory cytokines • Protection of hepatocytes from toxins	Zhao, et al. Petga, et al. Amat, et al.
		Chlorogenic acid	• ↓ ROS • ↓ MDA • ↑ Antioxidant enzymes • Protection against liver steatosis	Ivannikov, et al. Feduraev, et al.
		Absinthin	• Anti-inflammatory action • Antioxidant • Potential membrane protection	Pazhouh, et al. Krebs, et al. Kosakowska, et al.
Arctium lappa		Arctiin	• Antioxidant action • Antifibrotic effect • Modulation of inflammatory cytokines	Zhou, et al. Lu, et al. Li, et al.

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Table 1
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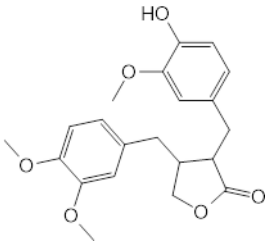
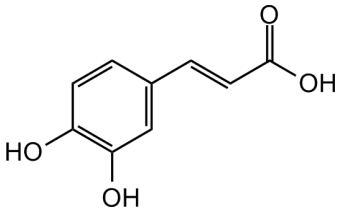
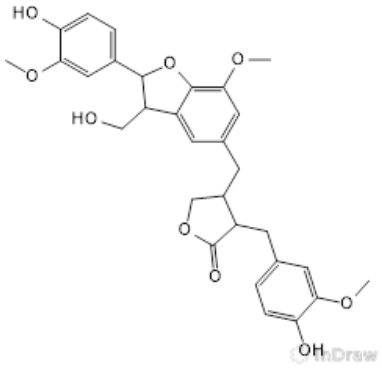
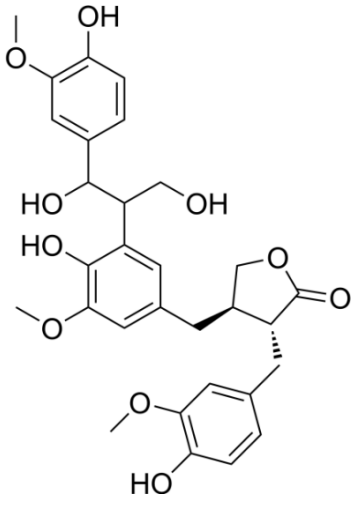
Plant	Major phytochemical groups	Biologically active substances	The main mechanism of hepatoprotective action	Source
		Arctigenin	• Powerful antioxidant • Reduces hepatocyte apoptosis • Nrf2/HO-1 regulation • Reduces liver steatosis	Alhusaini, et al. Li, et al. Zahra et al.
		Caffeic acid	• ↓ Lipid peroxidation • ↑ Antioxidant protection • Membrane-stabilizing effect	Pari et al. Yang, et al. Pérez-Alvarez, et al.
		Lappaol A	• Pronounced antioxidant activity • ↓ ROS and MDA • ↓ Inflammatory cytokines • NF-κB inhibition • Potential antifibrotic effect	Qing, et al. El-Kott, et al. Mu, et al.
Arctium tomentosum		Lappaol C	• Pronounced antioxidant activity • ↓ ROS • ↓ Lipid peroxidation • ↓ NF-κB activation • Antifibrotic effect	Aitynova, et al. de Souza et al.

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Table 1
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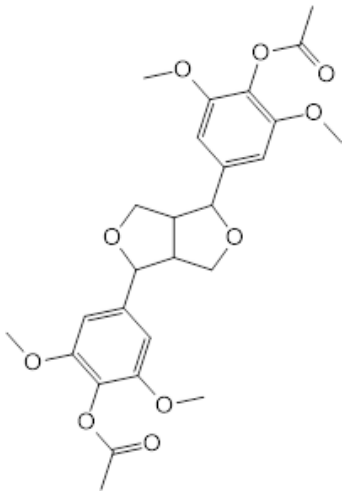
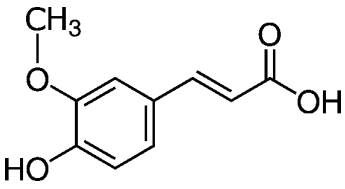
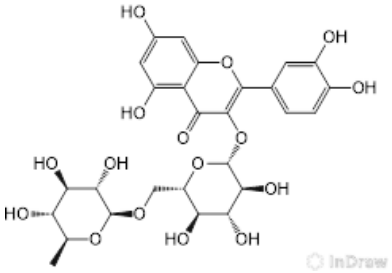
Plant	Major phytochemical groups	Biologically active substances	The main mechanism of hepatoprotective action	Source
		Syringaresinol	• Antioxidant • Membrane-stabilizing effect • ↓ Inflammatory cytokines • Possible involvement in Nrf2 regulation	Mssillou, et al. Pereira, et al.
		Ferulic acid	• ↓ MDA • ↑ SOD and CAT • Anti-inflammatory effect • Mitochondrial protection	Kim et al. Rukkumani, et al. Esmat, et al.
		Rutin	• ↓ NF-κB • ↓ Inflammation • ↓ Fibrosis • Protection of the liver vascular system	Rahmani, et al. Liu, et al. Janbaz, et al.

evaluation including standardized chromatographic profiling (HPLC, LC-MS), quantitative identification of marker components, and systematic quality control limits the comparability of the data obtained. As a result, it is difficult to establish a convincing evidence base and correctly interpret the results of various studies.

Another significant limitation is the limited variety of experimental approaches used. Most studies use models of CCl_4-induced toxic hepatitis and alloxan-induced metabolic liver damage. Although these models allow for effective assessment of the severity of oxidative stress and necrotic changes, they only partially reproduce the complex mechanisms of clinically significant pathologies.

Such experimental systems only partially reproduce the complex pathogenesis of drug-induced liver injury (DILI), non-alcoholic fatty liver disease (NAFLD), as well as autoimmune and viral hepatitis. As a result, the transfer of in vivo data to clinical conditions remains limited, which reduces their prognostic and applied significance and slows down the implementation of results in practical healthcare.

An additional problem is the insufficient depth of study of the mechanisms of action. In many studies, the analysis is limited to the determination of standard biochemical markers (ALT, AST, ALP, bilirubin) and histological evaluation of liver tissue. Meanwhile, key molecular cascades - including Nrf2/Keap1 and NF-κB signaling pathways, apoptosis and autophagy regulation, mitochondrial dysfunction, and proinflammatory cytokine expression - remain poorly understood. The use of modern omics approaches (transcriptomics, proteomics, metabolomics) is sporadic, which does

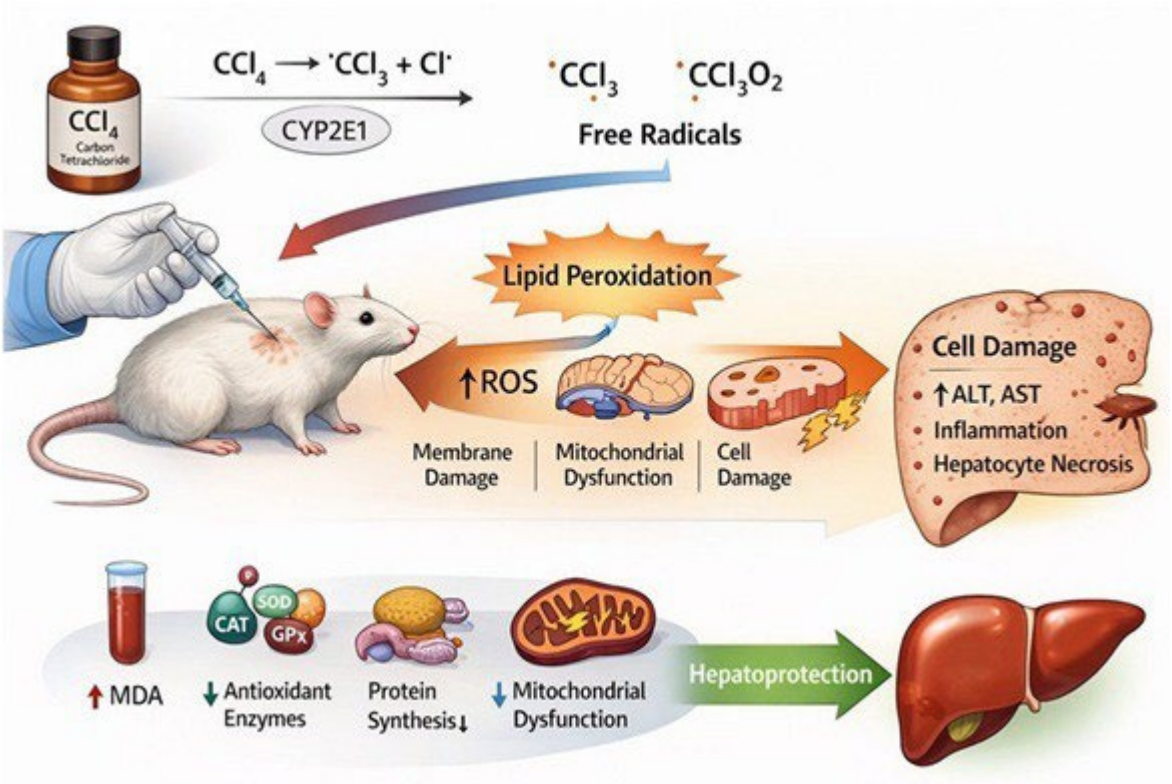


Figure 3. Schematic representation of the mechanism of CCl_4-induced liver damage and the hepatoprotective action of medicinal plants.

not allow for a comprehensive understanding of the pharmacodynamic effects of herbal preparations and their molecular targets.

A significant limitation remains the lack of clinical studies. Although some clinical observations and interventional studies have been published for Silybum marianum, most of them were conducted on limited samples and do not always meet the strict criteria of randomized controlled trials.

For endemic and insufficiently studied species growing in Kazakhstan, the clinical evidence base is virtually non-existent. In addition, there is a lack of data on pharmacokinetic parameters, long-term safety profile, including chronic toxicity, and possible drug interactions. These limitations complicate a comprehensive assessment of the therapeutic efficacy and safety of herbal medicines and hinder their introduction into clinical practice.

Among the priority areas for further research are the standardization of herbal raw materials using modern analytical technologies (LC-MS/MS, GC-MS, NMR), as well as expanding the range of experimental models, including NAFLD/NASH, DILI, three-dimensional hepatocyte cultures, and liver organoids. The use of systems biology and network pharmacology approaches for the analysis of multicomponent phytocompositions and their polygenic effects appears promising.

The transition from early preclinical stages (TRL 2–3) to initial translation stages (TRL 4–6) involves the development of standardized extracts, comprehensive toxicological assessment, and randomized controlled clinical trials. The creation of an interdisciplinary research platform in Kazakhstan could help strengthen the evidence base and increase the international competitiveness of domestic developments in the field of phytoprotective agents.

7. CONCLUSION

The review indicates the high potential of medicinal plants in Kazakhstan as promising sources of biologically active molecules with hepatoprotective effects. Data obtained under experimental conditions demonstrate their ability to exert antioxidant, anti-inflammatory, membrane-stabilizing, and cytoprotective effects in cases of toxic and metabolic liver damage. Of greatest scientific interest are species rich in

flavonoids, triterpene saponins, phenolic components, and alkaloids, which are capable of affecting the key pathogenetic mechanisms of hepatocellular damage.

At the same time, it should be noted that the available evidence base is predominantly preclinical and fragmentary. The insufficient level of standardization of extracts, the limited range of experimental models used, and the incomplete disclosure of molecular mechanisms of action negatively affect the reproducibility of results and complicate their clinical interpretation. For most of the plants studied, there are no large-scale randomized clinical trials, which makes it impossible to give a definitive assessment of their therapeutic efficacy and safety profile.

The promising development of this area involves the implementation of a systematic and interdisciplinary approach combining detailed phytochemical screening, the introduction of modern molecular biology and omics technologies, the expansion of the range of pathogenetically relevant models of liver damage, and the organization of well-planned controlled clinical trials. A key step is the creation of standardized herbal preparations with reproducible qualitative and quantitative composition, proven pharmacological activity, and adequate safety control.

Thus, the medicinal plants of Kazakhstan's flora have significant potential as a platform for the development of new hepatoprotective agents. At the same time, their integration into the practical healthcare system is only possible if the methodological rigor of scientific research is improved, protocols are harmonized, and a convincing evidence base is formed that meets international standards of scientific and clinical verification.

The present review highlights the significant hepatoprotective potential of selected medicinal plants growing in Kazakhstan, including *Glycyrrhiza glabra, Glycyrrhiza uralensis, Silybum marianum, Berberis heteropoda, Artemisia absinthium, Arctium lappa, and Arctium tomentosu*m. The available experimental evidence indicates that these plants exert protective effects against chemically induced liver injury, particularly in carbon tetrachloride (CCl_4) models, through multiple mechanisms such as antioxidant activity, suppression of inflammatory responses, and stabilization of hepatocyte membranes.

Despite the promising pharmacological properties demonstrated in preclinical studies, the current body of evidence remains limited by the lack of standardized experimental designs and insufficient clinical validation. Furthermore, variations in phytochemical composition and dosage regimens complicate direct comparison between studies.

Therefore, future research should focus on well-designed experimental and clinical studies, standardization of plant extracts, and elucidation of molecular mechanisms underlying hepatoprotective effects. Such efforts will be essential for the translation of traditional medicinal knowledge into evidence-based therapeutic applications.

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