PHARMACEUTICAL SCIENCES

THE USE OF PLANT-DERIVED HEPATOPROTECTIVE AGENTS IN THE TREATMENT OF LIVER DISEASES

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Abstract

Hepatoprotectors are medicinal agents that enhance the liver's resistance to pathological factors and restore its functions in various types of damage. Plant-derived hepatoprotectors exhibit membrane-stabilizing, antioxidant, regenerative, detoxifying, choleretic, and anti-inflammatory effects to protect hepatocytes from injury. The most commonly used plant-based hepatoprotectors include preparations of milk thistle (silymarin), extracts of globe artichoke (Cynara scolymus), and combined formulations such as Hepabene (manufactured by Merckle GmbH/Ratiopharm International GmbH, Germany), Levasil (manufactured by Mepha Ltd, Switzerland), and Holiver (manufactured by Hau Giang Pharmaceutical Joint-Stock Company MG Pharm, Vietnam), among others.

Keywords: *hepatoprotective agents, liver diseases, plant-derived drugs, natural medicines.*

Introduction. According to the World Health Organization, more than 2 billion people worldwide are affected by liver diseases, a figure that exceeds the prevalence of HIV infection by a factor of 100 [7]. Pathogenetic pharmacotherapy and the prevention of hepatic injury should be grounded in the administration of agents whose mechanisms of action target one or several key links in the pathogenesis of liver damage. For more effective protection of the liver against toxicants of diverse origins, it is essential to employ hepatotropic agents capable of acting through multiple pathogenetic pathways while providing the most comprehensive correction of hepatic injury [10, 16, 26].

At present, a wide range of pharmacological agents has been developed for the treatment of drug-induced liver injury. Experimental studies have demonstrated that diverse pharmacotherapeutic regimens are capable of achieving clinical efficacy [26]. Drug-induced liver injury accounts for approximately 10 % of all cases of acute hepatitis, 5 % of hospital admissions, and 50 % of cases of acute liver failure [2, 4-5].

Modern therapeutic approaches to liver diseases include pharmacotherapy, which has demonstrated limited clinical benefit due to its adverse effects on the body [2-4]. In recent years, the use of naturally derived phytochemicals for the treatment and mitigation of liver diseases has gained considerable popularity [10, 18]. It has been reported that 80 % of the global population prefers medications containing plant-derived compounds [12]. Herbal preparations exhibiting antioxidant and anti-inflammatory properties are considered safe and effective agents for alleviating chronic disorders of the body [12, 20].

The aim of the study was to examine and describe plant-derived hepatoprotective agents used in the treatment of liver diseases of various origins.

Materials and methods. To achieve the stated objective, scientific publications containing data on the experimental use of plant-derived hepatotropic agents for the treatment of hepatitis of various origins in the period 2014–2024 were analyzed. The search was conducted using the Google Scholar, Web of Science, and PubMed databases.

Statement of the topic. Hepatoprotectors are medicinal agents that enhance the liver's resistance to pathological factors and restore its functions in various types of damage [4,10]. They exhibit membrane-stabilizing, antioxidant, regenerative, detoxifying, choleretic, and anti-inflammatory effects, thereby protecting hepatocytes from injury [17]. The hepatoprotective effect can be demonstrated by various drugs capable of improving metabolic processes in the body, inhibiting lipid peroxidation, exhibiting antihypoxic activity, stabilizing and restoring the structure of cellular and subcellular membranes, and protecting mitochondrial and microsomal enzymes from damage [4, 10].

The hepatoprotective effect of plant-based preparations is attributed to the presence of various chemical components. According to recent studies, flavonoids, polysaccharides, lignans, alkaloids, terpenes, and other compounds exhibit hepatoprotective activity and exert a positive effect on liver metabolic processes [10]. Their mechanisms of action primarily involve the inhibition of lipid peroxidation, promotion of hepatocyte membrane restoration, scavenging of reactive oxygen species, suppression of mitochondrial dysfunction, and downregulation of inflammatory factor secretion.

A classification of plant-derived hepatoprotectors has been developed by researchers (Table 1) [7, 10, 12, 18-22].

Table 1 – Classification of plant-derived hepatoprotective agents

Bioflavonoid-based preparations		
Preparations based on *Silybum marianum*	Multicomponent preparations	Combined
	Heparsil, Darsil, Legalon, Levasil, Karsil, Silybor, Simepar, Silimarol, *Silybum marianum* fruits, etc.	Hepabene (extracts of milk thistle and fumitory), hepatofalk planta (extracts of *Silybum marianum*, celandine, and turmeric (saffron)), *Silybum marianum* extracts with propolis, etc.
Artichoke-based preparations	Artichoke, Artichol, Hofitol, Holiver, Rafaholin, Cinarix	
Other combination/complex therapeutic agents	Liv-52, Liva, Livomin, the herbal mixture “Detoxifit”, “Svitanok” drops	
Essential phospholipid preparations		
Plant-derived preparations	Essentiale N, Essentiale Forte N, Esel Forte, Livolin Forte, Brenciale	

Currently, the most commonly used plant-derived hepatoprotectors include preparations of *Silybum marianum* (silymarin), extracts of globe artichoke (*Cynara scolymus*), and combination formulations such as Hepabene (manufactured by Merckle GmbH/Ratiopharm International GmbH, Germany), Levasil (manufactured by Mepha Ltd, Switzerland), Holiver (manufactured by Hau Giang Pharmaceutical Joint-Stock Company MG Pharm, Vietnam), and others [1, 10, 12, 15, 20].

The study of the chemical composition of *Silybum marianum* revealed a significant amount of bioflavonoids, which has led to the widespread use of preparations from this plant in hepatology [20]. Notable examples include Silybor, Legalon, Karsil, and others. Silymarin is an extract of *Silybum marianum* and consists of seven flavonolignans (silibinin, isosilibinin, silicristin, isosilichristin, and silydianin) and flavonoids (taxifolin) [20, 26].

Silibinin is the main component not only in terms of content but also in clinical activity. Its anti-inflammatory effect is mediated by the tumor necrosis factor α (TNF-α)-dependent inhibition of nuclear factor NFκB activation, which modulates the synthesis of numerous pro-inflammatory mediators and caspases. In addition, silibinin inhibits phosphodiesterase, thereby slowing the degradation of cAMP and, consequently, promoting a decrease in intracellular calcium concentration in hepatocytes.

Scientists investigated the efficacy and therapeutic properties of silymarin in combination with antiviral agents (lamivudine and interferon) in the treatment of chronic hepatitis [19]. They found comparable effectiveness of silymarin and antiviral drugs in normalizing aminotransferase activity. An experimental study was conducted on mice administered silymarin at a dose of 200 mg/kg [19]. According to the study results, silymarin prevents ALT elevation, normalizes lipid peroxidation processes, reduces serum levels of reduced glutathione, neutralizes free radicals, and decreases oxidative stress in the experimental animals induced by ethanol administration at a dose of 5 g/kg.

Various *in vitro* studies have established the primary mechanisms of silymarin’s protective effects, which involve the inhibition of lipid peroxidation using erythrocytes, isolated and cultured hepatocytes, and human mesangial cells [20]. According to the literature, silymarin exhibits anti-inflammatory, antifibrotic, and antiproliferative activities [20]. It has been found that silymarin has low absorption when administered orally; however, a daily dose of 420 mg demonstrated positive therapeutic potential in patients with acute hepatitis [8].

According to the literature [12], treatment with Legalon has been shown to normalize membrane metabolism, stabilize hepatocyte membrane structures, and reduce lysosomal membrane permeability. It has been established that in patients with acute viral hepatitis, therapy with Legalon leads to an improvement in general condition, including the disappearance of fatigue, abdominal and joint pain, and partial normalization of biochemical parameters [7, 12]. Several authors [7] indicate the appropriateness of using Legalon in the management of liver cirrhosis.

The hepatoprotective effect of Silybor has been demonstrated in studies conducted on various animal models of experimental hepatitis and mechanical jaundice [11]. Treatment with Silybor reduces destructive changes in the liver, decreases serum transaminase activity, and normalizes pigment, protein, and lipid metabolism. In the therapy of chronic hepatitis, Silybor exhibits activity comparable to that of Legalon [8].

In the treatment of liver injuries of various etiologies, complex plant-based preparations are frequently used. One such preparation is 'Afosil,' which contains dry extract of artichoke leaves, a silybin–phosphatidylcholine complex, vitamin E, and black pepper extract [1]. Afosil provides comprehensive hepatoprotection: it prevents hepatocyte membrane damage, inhibits free radical reactions and lipid peroxidation in cellular membrane enzyme systems, and reduces immunopathological and inflammatory processes in the body. The multifunctional activity of the biologically active components in Afosil also allows for the regulation of gastrointestinal tract functions [15].

Essentiale Forte N belongs to plant-derived essential phospholipid preparations. This preparation influences lipid metabolism, exhibits membrane-stabilizing, hepatoprotective, and antioxidant activities, improves metabolic processes in hepatocytes, and promotes the elimination of cholesterol from the body

[9]. According to the literature [9], in chronic liver diseases of alcoholic etiology (cirrhosis, chronic hepatitis, fatty liver disease), the therapeutic effect of Essentiale Forte N occurs after 2–6 months of treatment. Experiments in rats have shown that essential phospholipids are effective in blocking the expression of the profibrogenic gene TGF-β1 and the synthesis of procollagen alpha-1 mRNA, leading to reduced accumulation of type I collagen in hepatocytes and inhibition of liver fibrosis development [24].

According to the literature [14], the preparation "Livina" is effective against liver dysfunction. This was confirmed in a clinical study involving patients receiving antituberculosis drugs. Research by co-authors [19] demonstrated that administration of 'Hepato-Plus' to rats at doses of 50 mg/kg and 100 mg/kg for 30 days provided hepatoprotective effects against oxidative liver damage by enhancing antioxidant defense and restoring liver enzyme activity in serum. However, the researchers noted that the hepatoprotective effect of the preparation is dose-dependent [17,19].

In Asian countries, the preparation "Catergen" is frequently used for the treatment of hepatitis [22]. Chemically, Catergen is a synthetic analogue of a bioflavonoid derived from a species of Indian acacia and is structurally similar to natural tea alkaloids (catechins). This preparation exhibits antioxidant, membrane-stabilizing, and choleretic activities. Experimental studies have shown that Catergen demonstrates both preventive and therapeutic effects in various models of liver injury, including fatty degeneration, alcoholic hepatitis, and partial hepatectomy.

Liv. 52 contains medicinal plants traditionally used in folk medicine (active constituents include the bark of *Capparis herbacea*, seeds of wild chicory, black nightshade, Senna occidentalis, *Tamarix gallica*, seeds of common yarrow, and iron oxide). Evidence suggests that the preparation protects liver parenchyma from toxic agents (through induction of cytochrome P-450 and acetaldehyde dehydrogenase), exhibits some antioxidant activity (by increasing cellular tocopherol levels), normalizes Na^+/K^+-ATPase activity, and reduces the amount of hepatotoxic lysoleucine [18, 22].

Among the plant-derived products investigated for potential hepatoprotective activity is resveratrol (3,5,4'-trihydroxy-trans-stilbene) [5]. This polyphenol was first synthesized from *Veratrum grandiflorum*. K. Du and colleagues [5] demonstrated that resveratrol inhibits further nuclear DNA fragmentation and the release of apoptosis-inducing factor and endonuclease G from mitochondria. Resveratrol prevents liver damage caused by free radicals and inflammatory cytokines, induces antioxidant enzymes, and increases glutathione levels in acetaminophen-induced hepatotoxicity [5, 13].

J. Xu and colleagues [Xu] demonstrated that salidroside (a phenylethanoid glycoside) protects the liver from acetaminophen-induced hepatotoxicity when administered orally to mice at doses of 50 or 100 mg/kg two hours prior to toxicant exposure. Salidroside reduced lipid peroxidation, pro-inflammatory cytokine levels, and restored liver enzymes along with antioxidant defenses [25]. Experimental studies also revealed histopathological preservation and suppression of caspase-3 and hypoxia-inducible factor-1α expression in the liver [23].

One of the modern plant-derived hepatoprotective agents is Rhein. It exhibits antioxidant, anti-inflammatory, antitumor, neuroprotective, and hepatoprotective properties [16]. According to the literature, Rhein restores liver enzymes and reduced glutathione levels, while inhibiting lipid peroxidation and improving the histological integrity of cellular membranes in paracetamol-induced hepatitis and renal toxicity in rats.

The preparation Ropren, derived from pine needles, contains a concentrate of polyprenols [10]. It is suggested that exogenous polyprenols participate in the synthesis of dolichols (involved in glycoprotein formation), cholesterol, and coenzyme Q in the body [19]. Its efficacy as a hepatoprotective agent has been demonstrated during isoniazid administration [7].

El-Sayed and colleagues [6] demonstrated that pterostilbene, administered at a dose of 50 mg/kg for 15 days prior to toxicant exposure, exhibits hepatoprotective effects against acetaminophen-induced hepatotoxicity. This effect is mediated by the restoration of liver enzymes, inhibition of lipid peroxidation and pro-inflammatory cytokines, and enhancement of antioxidant activity, accompanied by a reduction in hepatocyte death. Histopathological studies confirmed the protective effect of pterostilbene against acetaminophen-induced liver tissue damage [6].

Luteolin, a flavone with the chemical name 2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromen-4-one, is found in numerous plants, fruits, and flowers [21]. This compound is known for its multifaceted therapeutic effects, including benefits in liver diseases. Studies have shown that animals receiving luteolin orally at doses of 10–100 mg/kg/day, administered 1 or 3 days prior to acetaminophen exposure, exhibited reduced inflammatory processes in hepatocytes and restoration of the antioxidant defense system [21].

Conclusions. The results of the literature review on the use of plant-derived hepatoprotective agents indicate several advantages of their application: they do not cause serious side effects, reduce the risk of intoxication, do not lead to dependence, have a minimal number of contraindications, and are cost-effective. In the development of pharmaceutical agents, it is relevant to create new drugs with hepatoprotective activity based on natural substances.

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