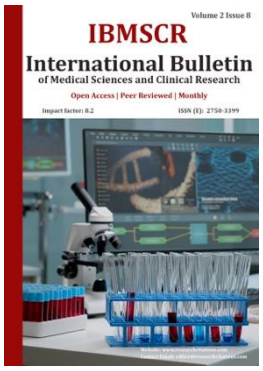

HEPATOPROTECTIVE AGENTS: DEFINITIONS, MECHANISMS, CLINICAL USE, AND PRACTICAL MONITORING

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https://doi.org/10.5281/zenodo.18720623

Abstract. Hepatoprotective agents are medicines and bioactive compounds used to protect liver cells from damaging factors (viral infections, alcohol, medications, toxins, and metabolic stress) and to support recovery processes. In most cases, they do not replace etiological therapy; rather, they are considered an adjunct that acts on specific links of pathogenesis alongside cause-directed management (antiviral treatment, withdrawal of the toxic agent, alcohol abstinence, and metabolic control). From a pathophysiological perspective, hepatoprotectors may reduce oxidative stress, improve membrane stability, attenuate inflammatory mediators, optimize bile flow, and enhance a regenerative microenvironment. The choice of a particular agent depends on the dominant type of liver injury (predominantly cytolytic vs. cholestatic patterns), disease severity, comorbid background, and the risk of polypharmacy. This narrative review summarizes a practical classification of hepatoprotectors, rational selection principles according to clinical syndromes, laboratory and instrumental monitoring, safety considerations, drug–drug interactions, and the boundaries of available evidence. The aim is to present a structured, indication-based approach to hepatoprotective therapy with patient safety as the primary priority.

Keywords: hepatoprotector, hepatocyte, oxidative stress, cholestasis, silymarin, ursodeoxycholic acid (UDCA), N-acetylcysteine (NAC), essential phospholipids, ademetionine, drug-induced liver injury (DILI), monitoring.

Introduction

Introduction. The liver is the central “metabolic platform” of the human body: it regulates carbohydrate, lipid, and protein metabolism, provides biotransformation of medications, detoxifies endogenous and exogenous substances, produces bile, and significantly influences immune and hemostatic balance. When the liver is injured, the problem is not limited to abnormal laboratory values; energy metabolism, inflammatory signaling, the gut–liver axis, and microbiota-related processes are also reconfigured. Therefore, liver diseases present with a broad clinical spectrum, including fatigue, dyspepsia, right upper-quadrant discomfort, pruritus, jaundice, bleeding tendency, edema, and others.

In clinical practice, the most frequent causes of liver injury include viral hepatitis, alcohol-associated liver disease, toxicity related to medications and dietary supplements (DILI), fatty liver disease associated with metabolic syndrome (NAFLD/MAFLD spectrum), as well as cholestatic conditions (intrahepatic cholestasis and biliary tract disorders). Although these

etiologies differ, they share common "core" pathogenic links: oxidative stress, lipid peroxidation of cellular membranes, mitochondrial dysfunction, activation of inflammatory mediators, engagement of apoptotic/necrotic pathways, and disturbed bile flow and bile-acid homeostasis, ultimately promoting progression toward fibrosis.

Methodology. This article was prepared as a scientific and practice-oriented narrative review. The conceptual model is based on a "syndrome-oriented clinical decision" framework. Three directions were prioritized: (1) pathophysiological mechanisms and terminological clarity regarding hepatoprotectors; (2) rational selection principles for common clinical patterns (cytolytic, cholestatic, toxic, and metabolic); and (3) monitoring and safety, including laboratory/instrumental follow-up, polypharmacy, adverse effects, and triage of severe cases. This is not an original clinical or experimental study; it is an educational synthesis and does not provide individualized prescriptions, doses, or treatment orders. Any decision to use medications should be made after medical assessment and in accordance with current clinical guidelines.

Results. The review indicates that selecting hepatoprotectors using a one-size-fits-all approach is less effective than logical matching to the dominant clinical syndrome and pathogenic targets: (a) which laboratory profile predominates—cytolysis or cholestasis; (b) whether an underlying cause has been identified and brought under control; and (c) whether patient-specific factors limit safety (polypharmacy, pregnancy, severe renal failure, allergy, coagulopathy). Figure 1 illustrates the relationship between pathogenesis and therapeutic targets.

1) Mechanistic details. Oxidative stress is a universal mechanism of liver injury: increased free radicals oxidize membrane lipids, disrupt ion channels and transport systems, and reduce mitochondrial energy production. During this process, antioxidant defenses (particularly glutathione) are consumed. This explains the concept of using precursors such as NAC to replenish glutathione stores. The inflammatory cascade is related to cytokine signaling, Kupffer cell activation, and endothelial dysfunction. Flavonoids and certain complex preparations may modulate anti-inflammatory pathways. In cholestasis, bile-acid homeostasis is disturbed, and hydrophobic bile acids become toxic to hepatocytes; UDCA, a hydrophilic bile acid, helps shift this balance.

2) Groups and practical tasks. Figure 2 presents a simplified map of hepatoprotector groups. In practice, it is useful to define the choice through the following "tasks": (i) antioxidant support (if oxidative stress predominates); (ii) mitigation of cholestasis (pruritus, elevated ALP/GGT, and bilirubin); (iii) support of membrane stability (cytolytic pattern and toxic exposures); and (iv) metabolic modulation (insulin resistance and dyslipidemia). These tasks are not mutually exclusive, but the priority differs across patients.

Tables

Table 1. Hepatoprotector groups: mechanisms and use (simplified)

Group	Examples	Primary effect	Typical situation
Plant flavonoids	Silymarin	Antioxidant activity; membrane protection	Cytolytic/metabolic background; adjunct
Bile acids	UDCA	Anti-cholestatic	Cholestatic patterns (etiology-dependent)

Amino-acid precursors	NAC	Support of the glutathione system	Toxic injury (selected cases)
Methyl donor/modulator	Ademetionin	Methylation/transsulfuration support	Cholestasis + cytolytic component; individualized
Membrane components	Essensial fosfolipidlar	Membrane structure support concept	Adjunct; evidence is heterogeneous

Table 2. Minimal monitoring panel and practical interpretation

Marker	Meaning	Practical note
ALT/AST	Cytolytic activity	Before initiation and after 2–4 weeks; guided by dynamics
ALP/GGT	Cholestasis/biliary component	If cholestasis worsens, reassess the bile ducts
Bilirubin	Excretory function and cholestasis	If rapidly increasing, urgent evaluation is needed
INR (zaruratda)	Severity marker	An increase suggests the need for specialized care
Albumin	Long-term synthetic function	Helps prognosis in chronic conditions
UTT	Biliary tract and parenchyma	First-line assessment in cholestasis

Table 3. Common mistakes in practice and the correct approach

Incorrect approach	Correct approach
Prescribing hepatoprotectors without identifying the etiology	First, search for the cause: history + labs + ultrasound; then choose an adjunct strategy
Continuing a suspected drug in possible DILI	Stop the suspected agent and assess severity (bilirubin/INR)
Ignoring possible obstruction in cholestasis	Assess bile ducts; if obstruction is present, etiology-directed intervention is the priority
Expecting improvement without lifestyle change in metabolic disease	Weight management, physical activity, and metabolic control are the foundation
Long-term “prophylaxis” without a monitoring plan	Goal-directed course + reassessment at 2–4 weeks; re-evaluate if no benefit

Discussion

Discussion. Clinical debates about hepatoprotectors often relate to the choice of endpoints. In studies, reductions in ALT/AST are frequently used as primary outcomes because they are convenient to measure. However, clinically meaningful outcomes for patients include symptom relief, risk of decompensation, complications, need for hospitalization, and long-term prognosis. Therefore, hepatoprotectors should not be selected merely to “normalize laboratory tests,” but to achieve a clearly defined clinical objective.

The strength of evidence varies across agents. UDCA is considered a standard approach in certain cholestatic diseases, and NAC has a firmly established role as an antidote in acetaminophen toxicity. For silymarin, laboratory improvements and, in some settings, histologic changes have been reported, yet results are not uniform. This heterogeneity may reflect differences in etiology, treatment duration, and comorbid background (obesity, diabetes, alcohol use), as well as variability in concomitant interventions (diet and physical activity). In practice, this means that an agent that benefits one patient may produce minimal effects in another. From the perspective of rational pharmacotherapy, the principle of minimalism is useful: unnecessary medications reduce adherence, increase costs, and raise the probability of adverse events. Before starting a hepatoprotector, the clinician should define the goal: relief of pruritus, improvement of a specific laboratory profile, support during recovery, or restoration of antioxidant reserves in toxic injury. When the goal is clear, monitoring becomes meaningful.

Safety and polypharmacy. Patients with liver disease often receive several drugs simultaneously (antidiabetics, antihypertensives, antithrombotics, and others), which increases the risk of drug–drug interactions, adverse effects, and adherence problems. “Natural” herbal supplements are not always safe; some may be hepatotoxic. Therefore, clinicians should actively ask about supplements as part of the medical history, document the full medication list, and plan a follow-up schedule. Practical triage—when to refer urgently: rapid progression of jaundice, persistent vomiting and a marked decline in appetite, altered mental status, signs of bleeding, abdominal distension, or rising INR may indicate evolution toward severe liver failure. In such cases, the priority is urgent medical assessment and specialized care rather than adding another hepatoprotector.

Limitations. This article is a review and does not mandate any specific agent, dose, or regimen. Its purpose is to structure clinical reasoning: prioritize etiological therapy, select an adjunct aligned with the dominant syndrome, and carry out systematic monitoring. In the future, local clinical registries, real-world data, and standardized composite endpoints (clinical + laboratory + quality of life) may further clarify the evidence base for hepatoprotectors. Future directions. Strengthening evidence will require biomarkers and standardized outcomes—not only ALT/AST, but also bile-acid profiles, non-invasive fibrosis indices, quality-of-life measures, and real-world registries. A phenotype-based approach (cholestatic, metabolic, toxic phenotypes) may improve clinical logic more than the “one drug–one disease” paradigm. At the health-system level, simplified protocols and better access to monitoring can substantially increase the practical value of hepatoprotective strategies.

Conclusion

Conclusion. Hepatoprotective agents are adjunct strategies that complement etiological and pathogenetic management of liver diseases. Their selection should be syndrome-oriented, account for safety and polypharmacy, and be accompanied by planned monitoring. The key principle is to treat the underlying cause—viral infection, alcohol, toxin/medication exposure, and metabolic factors. Hepatoprotectors may support recovery by reducing oxidative stress, stabilizing membranes, and alleviating cholestasis. If the triad of “goal–monitoring–safety” is maintained through clinician–patient collaboration, hepatoprotective therapy becomes more rational and potentially beneficial in practice.

As a practical recommendation, applying the principle of "a short, goal-directed course + measurable outcomes + safety control" for each patient reduces unnecessary polypharmacy around hepatoprotectors. Patient education—limiting alcohol and unregulated supplements, completing laboratory tests on time, and recognizing warning signs that require urgent care—is an integral component of therapy.

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