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Plant-Derived Phytochemicals as Hepatoprotective Agents: Experimental Evidence from Rat Models

Naina[1*], Phool Chandra[2]
[1]Research Scholar, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad-244001, Uttar Pradesh, India
[2]Professor, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad-244001, Uttar Pradesh, India

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ABSTRACT
Toxin, xenobiotic and metabolic-induced liver diseases are the most common causes of morbidity worldwide. The protective activities of phytochemicals from medicinal plants against hepatic toxins have been reported in experimental rat models. Several natural bioactives, including flavonoids, phenolic acids, alkaloids, terpenoids and saponins, exert hepatoprotection through their antioxidant, anti-inflammatory and anti-apoptotic properties. Research on CCl_4, paracetamol, and thioacetamide-induced models of liver damage underlines that these phytochemicals mediate oxidative stress, maintain cellular membrane integrity and regulate the signalling networks as Nrf2, NF-κB, MAPK and caspase pathways. Furthermore, these agents have been developed into nanosystems, and combinations of new with traditional medicinal plants have helped enhance in vivo pharmacokinetic (PK) profiles and therapeutic efficacy. This review also compiles the experimental data on the hepatoprotective effect of plant-based phytochemicals in rat models, summarising their mechanisms of action, safety considerations and translational importance for hepatic disease management.

INTRODUCTION:

Introduction

Liver disease is a significant global health problem, since it makes many people ill and kills them. The recent epidemiologic evidence indicates that liver diseases, including hepatitis, fatty liver disease, cirrhosis, at hepatocellular carcinoma, are responsible for millions of deaths every year [1]. It's quite easy to damage the liver, whether it's through viral infections, consuming excess alcohol, xenobiotics, or metabolic issues, because of how crucial the liver is for metabolism, detoxification, and homeostasis. Emerging risks from lifestyle and synthetic drugs have led to an increasing incidence of non-alcoholic fatty liver disease (NAFLD) and drug-induced liver injury (DILI) [2]. Despite the reinforced clinical diagnosis and therapy, the prevalence of chronic liver damage increases, especially among the low- and middle-income parts of the world. This demonstrates the necessity of developing more effective and less toxic ways to shield the liver [3]. However, the classical hepatoprotective agents such as corticosteroids, interferons, and other antioxidants are usually less effective with significant systemic reactions. Prolonged treatment might cause drug resistance, toxicity, and side reactions in vivo [4]. Furthermore, the majority of the synthetic drugs relieve symptoms and fail to intervene in liver damage through oxidative stress, mitochondrial malfunction in mitochondria, and inflammatory cascades. Current pharmacological approaches are limited by their expensive load of long-lasting therapy and the lack of any universally effective hepatoprotective drug. So, it is now time to investigate natural compounds that can protect the liver by affecting multiple pathways and with better safety profiles [5].

Plants have long been known to possess medicinal

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properties and are the 'backbone' of medicine, both traditional and modern. Phytochemicals such as flavonoids, alkaloids, terpenoids, phenolic acids, and saponins exert liver protection activities predominantly through their anti-oxidative, anti-inflammatory, and membrane-stabilizing actions [6]. These bioactives may alter how cells communicate (signal transduction), scavenge reactive oxygen species (ROS), and strengthen the body's defenses, including enhanced function of glutathione and catalase. The experimental studies with rats have provided compelling evidence in support of the hepatoprotective effects of plant extracts and phytomolecules against organo toxins like CCl_4, paracetamol and thioacetamide [7]. In a therapeutic context, the inclusion of these plant-based chemicals provides an alternate, environmentally friendly and sustainable strategy for managing liver diseases that can lead to novel drug discovery strategies and clinical utility[8].

Experimental Rat Models of Hepatotoxicity:

Carbon Tetrachloride (CCl_4)-Induced Hepatotoxicity:

The CCl_4 model is ideal for determining the mechanism by which the liver gets damaged and assessing the effects of drugs that may have hepatoprotective properties. Hepatic cytochrome P450 enzymes, particularly CYP2E1, metabolize CCl_4 to form trichloromethyl ($\bullet CCl_3$) and trichloromethyl peroxy ($\bullet OOCCl_3$) radicals [9]. These reactive intermediates induce lipid peroxidation, membrane injury leading to lot of hepatocellular necrosis. Toxicologically, CCl_4 exposure causes biochemical and histopathological changes in livers of rodents characterized by centrilobular degeneration, inflammation, and increased serum levels of liver enzymes including ALT, AST and ALP. This method may be a useful tool for the investigation of phytochemicals that suppress inflammation and free radicals, as they are known to work through this mechanism via other pathways, in order to prevent liver damage by toxins in people [10].

Paracetamol (Acetaminophen)-Induced Hepatic Injury:

Overdose of paracetamol is an established cause of sudden liver failure in man and animals. In rats, hepatotoxicity arises from the metabolic conversion of paracetamol into the reactive intermediate N-acetyl-p-benzoquinone imine (NAPQI) via the CYP2E1 and CYP3A4 enzymes. Excessive NAPQI depletes the liver's glutathione reserves and forms covalent bonds with cellular proteins. This leads to oxidative stress, problems with mitochondria, and death of liver cells. The paracetamol model closely simulates human liver failure, serving as a sound basis for testing the efficacy of hepatoprotective strategies that increase antioxidant status, improve glutathione levels, and modulate apoptotic pathways [11–13].

Thioacetamide and alcohol-induced liver damage

Thioacetamide (TAA) is a strong hepatotoxin commonly employed to establish rat models of chronic liver fibrosis and cirrhosis. Reactive metabolites generated during biotransformation bind to large cellular molecules. This initiates oxidative stress, lipid peroxidation, and inflammation [14]. Long-term administration of TAA promotes histological changes that resemble those observed in human liver fibrosis, including collagen deposition and alterations in the morphology of the liver. Chronic alcohol feeding studies recapitulate the pathophysiological changes observed in ALD, steatosis, inflammation, and fibrosis. These models are of considerable interest for the testing of plant-based agents that prevent oxidative damage, inflammation, and fibrosis [15].

High-fat diet and drug-induced non-alcoholic fatty liver models:

HFD-induced models have been used extensively in an attempt to replicate metabolic and histological phenotypes observed in NAFLD. Prolonged high-fat diet (HFD) has been demonstrated to induce hepatic steatosis, insulin resistance, as well as oxidative stress, reflecting the human setting of metabolic-associated fatty liver disease[16]. Long-term usage of medications such as valproic acid or methotrexate may also induce steatohepatitis by harming mitochondria and generating lipid peroxidation. These models help study how phytochemicals that modify how lipids are broken down, make insulin perform better, and reduce liver inflammation may stop and treat diseases [17].

Relevance and translational value of rat hepatotoxicity models

Rat models of hepatotoxicity provide a crucial connection between basic research and real-world use. Their physiological, metabolic, and genetic similarities to humans make them suitable for evaluating the pharmacodynamics and safety of potential hepatoprotective drugs [18,19]. Additionally, these models enable the regulated reproduction of specific damage mechanisms oxidative stress, inflammation, or fibrosis, thereby allowing mechanistic studies of phytochemical activity. Even though various animals break down food in different ways, research on rats has shown that they may be used to anticipate how humans would react to medicines that preserve the liver. Consequently, experimental rat models are crucial tools in the preclinical evaluation of plant-derived therapies for hepatic diseases [20,21].

Classes of Plant-Derived Phytochemicals with

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Hepatoprotective Potential

The hepatoprotective effectiveness of plant-derived phytochemicals is attributed to their considerable structural diversity and diverse biological actions. Diverse kinds of chemicals, such as flavonoids, phenolic acids, alkaloids, terpenoids, saponins, lignans, and tannins, protect the liver against injury in diverse ways, as shown in **Table 1**. Quercetin and silymarin are two flavonoids that are very good at getting rid of free radicals and changing critical signaling pathways that govern oxidative stress and inflammation [22,23]. Gallic and ferulic acids are examples of phenolic acids that are very good at decreasing things. This keeps cell membranes stable and prevents hepatocyte necrosis.

Alkaloids like berberine and piperine increase the activity of antioxidant enzymes in the body while controlling lipid metabolism and blocking pathways that lead to fibrosis [24]. Terpenoids and saponins, such as ursolic acid, ginsenosides, and glycyrrhizin, have antioxidant, anti-apoptotic, and anti-fibrotic effects that work together to help the liver heal over time. Lignans and tannins, particularly curcumin, ellagic acid, and catechins, safeguard cells by maintaining redox equilibrium and regulating transcription factors such as Nrf2 and NF-κB [25]. All of these types of phytochemicals influence a number of pathways that may harm the liver, including oxidative damage, mitochondrial malfunction, inflammation, and fibrosis. They are attractive candidates for making novel hepatoprotective medicines and nutraceuticals since they have a broad spectrum of actions, are not very toxic, and are found naturally in large amounts [26].

Table 1 Classification of major plant-derived phytochemicals with experimental evidence of hepatoprotective potential in rat models. These bioactive compounds protect hepatic tissue through antioxidant, anti-inflammatory, and anti-fibrotic mechanisms

Class of Phytochemicals	Representative Compounds	Natural Sources	Experimental Evidence/Mechanisms of Hepatoprotection	Ref.
Flavonoids	Quercetin, Silymarin, Kaempferol, Rutin	Onions, apples, milk thistle, citrus fruits	Exhibit potent antioxidant and anti-inflammatory effects; inhibit lipid peroxidation; modulate NF-κB and MAPK signaling; stabilize hepatocyte membranes and enhance enzymatic antioxidants (SOD, CAT, GSH).	[27,28]
Phenolic Acids	Gallic acid, Ferulic acid, Chlorogenic acid	Tea, grapes, coffee, cereals	Protect hepatocytes against oxidative damage; regulate lipid and glucose metabolism; inhibit pro-inflammatory cytokines (TNF-α, IL-6); restore mitochondrial and enzymatic function.	[29,30]
Alkaloids	Berberine, Piperine, Solanine	*Berberis* spp., *Piper nigrum*, *Solanum* spp.	Improve lipid metabolism and antioxidant defenses; suppress TGF-β-mediated fibrosis; enhance bioavailability of other phytochemicals; reduce inflammatory and apoptotic markers.	[31,32]
Terpenoids & Saponins	Ursolic acid, Ginsenosides, Glycyrrhizin	Apples, *Panax ginseng*, *Glycyrrhiza glabra*	Exhibit hepatoprotective, anti-fibrotic, and anti-apoptotic actions; modulate oxidative stress and lipid metabolism; stabilize hepatic membranes and suppress inflammatory mediators.	[33]
Lignans & Tannins	Curcumin, Ellagic acid, Catechins	*Curcuma longa*, pomegranate, green tea	Enhance antioxidant capacity and glutathione levels; inhibit NF-κB and Nrf2 pathways; prevent lipid peroxidation and apoptosis; attenuate hepatocellular necrosis and inflammation.	[34–36]

Mechanistic Insights into Hepatoprotective Activity

Antioxidant and Free Radical Scavenging Effects

Oxidative stress is a major cause of liver damage and its development. A number of phytochemicals that originate from plants protect the liver by being powerful antioxidants and getting rid of reactive oxygen species (ROS). Some substances that halt lipid peroxidation and free radicals include quercetin, silymarin, and gallic acid. This prevents damage to large molecules in cells, including proteins, lipids, and DNA. These phytochemicals also help natural antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) accomplish their jobs better [37]. Phytochemicals stop oxidative stress from killing liver cells and causing apoptosis in liver tissues that have been exposed to toxins by maintaining redox equilibrium and protecting mitochondrial function [38].

Anti-Inflammatory and Cytokine Suppression Mechanisms

Most liver illnesses generate inflammation, which happens when Kupffer cells are activated and pro-inflammatory cytokines are released. Phytochemicals such as curcumin, berberine and chlorogenic acid possess potent anti-inflammatory activity by preventing the generation of key mediators like TNF-α, IL-1β and IL-6 [39]. These substances are COX-2, and iNOS inhibitors, which leads to a reduction in NO and prostaglandins production. Preventing inflammatory cells from entering tissues and producing cytokines promotes healing of damage, accelerating the liver's recovery. So, phytochemicals' anti-inflammatory and antioxidant benefits combine to stop liver damage from worsening [40].

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Modulation of Apoptotic and Necrotic Pathways: Hepatocellular apoptosis and necrosis are the key factors in toxin-mediated liver injury. Phytochemicals also modulate levels of the signaling molecules which enhance and suppress apoptosis. Supplementation with kaempferol, glycyrrhizin, and ginsenosides has been shown to elevate the expression of the anti-apoptotic protein Bcl-2, while suppressing pro-apoptotic proteins such as Bax, caspase-3 and caspase-9[41]. This equilibrium between life and death signals helps the liver keep its structure, preventing hepatocytes from being lost. Phytochemicals can as well inhibit the release of mitochondrial cytochrome c and keep the membrane potential in a steady state. This precludes the induction of caspase-dependent apoptosis. The types of modulatory actions are very important to protect liver cells against injury in acute and chronic liver damage [42].

Stabilization of Hepatocellular Membranes and Mitochondrial Integrity

To maintain liver function when it is under oxidative or toxic stress, the integrity of hepatic membrane is fundamental. Plant compounds like silymarin, rutin, and ursolic acid support the stability of the cell membranes by preventing the lipid peroxidation as well as the release of intracellular enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in to the blood. They also maintain the electron transport chain and ATP production, which continues, keeping the mitochondria safe and preventing energy loss. Restoring mitochondrial activity not only keeps cells' metabolism functioning, but it also avoids oxidative damage and cell death from spreading. A large part of how plant-based chemicals protect the liver is by doing things that preserve membranes [43].

Regulation of Key Molecular Signaling Pathways (Nrf2/ARE, NF-κB, MAPK, Caspases)

Phytochemicals safeguard the liver by altering many molecular signaling pathways that regulate oxidative stress, inflammation, and cellular viability. When the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway is switched on, it increases the transcription of antioxidant response element (ARE)-dependent genes such as heme oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase 1 (NQO1). This makes the antioxidant defense system stronger. Blocking the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway also reduces the levels of inflammatory genes [44]. Controlling mitogen-activated protein kinases (MAPKs) and caspase cascades also stops apoptosis and inflammation. The simultaneous control of Nrf2/ARE, NF-κB, MAPK, and caspase signaling establishes a coordinated defensive mechanism elucidating the protective effects of phytochemicals on the liver [45].

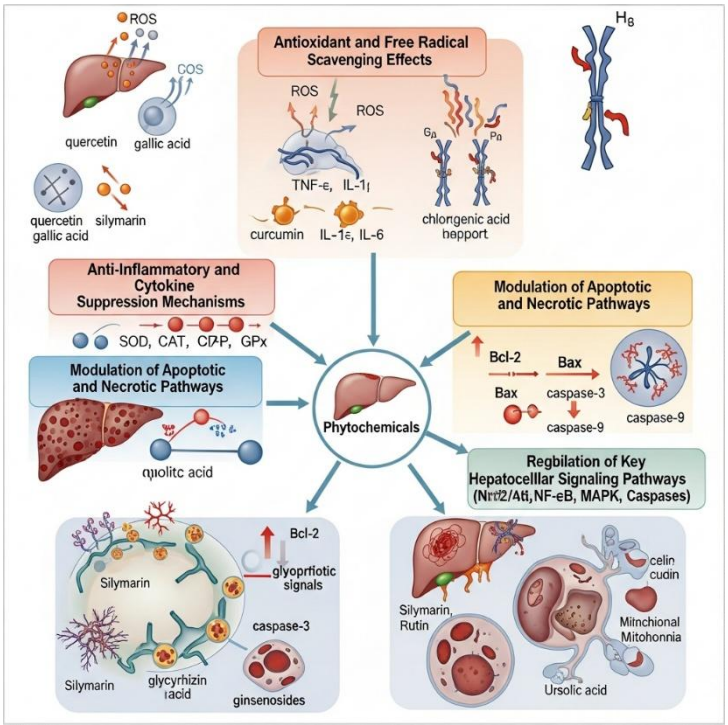

Figure 1 Mechanistic representation of phytochemical-mediated hepatoprotective pathways

The **Figure 1** illustrates the several cellular and molecular mechanisms by which phytochemicals from plants safeguard the liver. Quercetin, silymarin, gallic acid, curcumin, chlorogenic acid,

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glycyrrhizin, ginsenosides, rutin, and ursolic acid all work together to keep liver cells healthy. These phytochemicals lower oxidative stress by getting rid of reactive oxygen species (ROS) and making the body's natural antioxidant defenses (SOD, CAT, GPx) stronger. They halt pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, by blocking the COX-2 and iNOS pathways. They also modify the signals that lead to cell death by raising Bcl-2 levels and lowering Bax, caspase-3, and caspase-9 levels. Keeping the membranes of liver cells stable and the mitochondria intact also helps liver cells remain alive [46]. Phytochemicals defend the liver by activating Nrf2/ARE and stopping the NF-κB, MAPK, and caspase cascades. This creates a coordinated defensive network.

Experimental Evidence from Rat Studies
Phytochemicals in CCl_4-Induced Liver Injury
In CCl_4-induced hepatotoxicity models, compounds including silymarin, quercetin, and gallic acid dramatically decrease lipid peroxidation and serum transaminase levels. These phytochemicals make antioxidant enzymes work better and restore normal liver histoarchitecture, which suggests that they are highly effective at guarding against oxidative and necrotic damage [47–49].

Phytochemicals in Paracetamol-Induced Hepatotoxicity
Flavonoids like kaempferol and rutin, as well as alkaloids like berberine, protect the liver from damage induced by paracetamol by replenishing glutathione, decreasing oxidative stress, and increasing mitochondrial function. The rats that were treated had improved liver enzyme levels and fewer cells that died [50].

Phytochemicals in Alcohol- and Thioacetamide-Induced Hepatic Fibrosis
Curcumin, glycyrrhizin, and ursolic acid are phytochemicals that stop collagen from building up and fibrotic progression in rats that have been given alcohol and thioacetamide. They block the TGF-β and NF-κB signaling pathways, which help fight inflammation and fibrosis [51].

Comparative Evaluation and Histopathological Findings
Comparative studies show that most chemicals from plants restore the structure of liver cells, reduce necrosis, and bring biochemical indicators (ALT, AST, ALP) back to normal [52]. Histological sections of the treated groups typically exhibit reduced inflammation, preserved liver architecture, and the lack of fatty degeneration, consequently confirming their notable hepatoprotective effects [53].

Pharmacokinetic Limitations and Nanoformulation Strategies
Poor Solubility and Bioavailability of Natural Phytochemicals
A lot of phytochemicals are good for the liver, but they don't dissolve well in water, the intestines don't absorb them effectively, and they break down fast in the body. Curcumin, quercetin, and silymarin are examples of chemicals that are not particularly accessible when taken by mouth because they don't pass through the stomach readily and go through a lot of first-pass metabolism[54]. These pharmacokinetic limitations diminish their therapeutic activity and limit the possibility of a practical clinical use, and the implementation of improved delivery strategies to enhance their stability and in vivo availability is clearly required [55].

Nanoparticle and Liposomal Formulations for Enhanced Delivery
Embedded (Nanotechnology based) drug delivery strategies are considered to be better solutions to the problems associated with phytochemicals in nature. Examples of formulations that facilitate molecules dissolution or reduce mortality of active compounds, favoring liver targeting are the polymeric nanoparticle, the solid lipid nanoparticles, and liposomes and nanoemulsions [56]. In experimental models of rats, liposomal silymarin or curcumin nanoparticles showed higher bioavailability, prolonged circulation time and enhanced hepatocellular protective effects. These advances also make it easier to control how drugs are released into the body, and allow for more drug to get inside cells and work at lower doses [57].

Combination and Synergistic Therapeutic Approaches
Combining different phytochemicals or combining them with synthetic medications may protect the liver in a manner that works jointly. For instance, taking piperine and curcumin together makes them more accessible since they don't break down in the liver [58]. Flavonoids and phenolic acids also work together to fight inflammation and protect against free radicals. These kinds of combination techniques, coupled with co-delivery using nanocarriers, are a potential approach to make phytopharmaceuticals work better and be less harmful. This might lead to the next generation of phytopharmaceutical formulations [59].

Safety and Toxicological Considerations
Dose-response relationships and sub-chronic toxicity evaluation
People normally think that phytochemicals from

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plants are harmless, but how much of them there is, how long someone is exposed to them, and how they are ingested all effect how harmful they are. Dose response studies in rat models suggest that many phytochemicals may exhibit biphasic behavior, therapeutic at low doses and possibly harmful at higher concentrations. Sub-chronic toxicity evaluations, including repeated-dose and 28-day studies, are essential for determining the no-observed-adverse-effect level (NOAEL) and guaranteeing long-term liver safety. To reduce the danger of cumulative or idiosyncratic toxicity, consistent dosage regimens and pharmacokinetic profiles are essential [60].

Biochemical and Histological Markers of Hepatic Safety

Both biochemical and histological studies are done to make sure the liver is safe. To evaluate how effectively the liver cells are operating, doctors often analyze serum indicators, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin[61]. In sub-chronic experiments, normal levels of these enzymes, combined with maintained histoarchitecture and the lack of necrosis or fatty degeneration, confirm the non-toxic properties of phytochemical formulations. On the other hand, alterations in these indicators might signal that the liver is under stress or the metabolism is overloaded, which would entail altering the dosage or making the formulation better [62].

Future perspectives in toxicity prediction and standardization

New tools to anticipate toxicity, such as computer modeling, in silico docking, and organ-on-chip technologies, are promising ways to find out whether something is hazardous to the liver before trying it on living things [63]. Using omics-based biomarkers (genomic, proteomic, and metabolomic) together makes it even easier to predict toxicity. In order to give a guarantee that herbal extracts are reusable and have regulatory acceptance, the standardization, identification of active compounds, and implementation of safety regulations at a worldwide level are very important. Combining better systemic toxicity screening protocols and accurate phytochemical characterisation will hopefully lead to more efficacious and safer hepatoprotective drugs in the future [64].

Translational Relevance and Clinical Prospects

Bridging Experimental Outcomes to Human Liver Disorders

Data from rat models of liver injury further elucidate the molecular basis of the hepatoprotective effects of phytochemicals, but careful consideration should be given to interspecies metabolic and pharmacokinetic diversity when extrapolating these findings to human liver diseases. Numerous phytochemicals, including silymarin, curcumin and glycyrrhizin have also been reported to exert favourable effects in clinical or preclinical studies by ameliorating liver enzyme profile, oxidative stress and inflammatory pathways. Nonetheless, the clinical validation needs a standardized preparation, well-monitored studies and longer evaluations for safety to ascertain its efficacy in other groups of patients with hepatic diseases (e.g., NAFLD, hepatitis) including cirrhotic subjects [65].

Potential for Phytochemical-Based Hepatoprotective Drug Discovery

Phytochemicals offer a large and largely untapped resource of potential novel hepatoprotective drugs. They work on a whole bunch of different things: antioxidant, anti-inflammatory and anti-fibrotic, which works quite well with the way that liver diseases work [66]. in addition, we can know about the molecular targets and as well as significant bioactive compounds more easily on account of modern technologies for discovering novel drugs (such as sar analysis, freunds adjuvant, network pharmacology). The combination of nanocarrier systems and chemical changes can also prevent these herbal substances from solubility, stability, low bioavailability turning as therapeutically useful hepatoprotective medicines [67].

Integration into Personalized and Preventive Hepatology

Customized and preventive precision medicine strategies, incorporating variability in the genotype-metabolic phenotype, as well environmental exposures may be the roadmap of hepatoprotection. Phytochemicals exert high efficacy and low toxicity, they can be used as adjuvants or nutraceuticals in personalized hepatology to prevent the occurrence and recurrence of diseases [68]. The development of pharmacogenomics and metabolomics will allow personalized phytochemical treatment based on the unique hepatic metabolic profile of each individual. The inclusion of proof-of-principle phytotherapies into prophylactic hepatology would thereby dramatically lower the burden of liver diseases and the long-term outcome, globally [69].

CONCLUSION

Liver diseases remain a major global health problem, which is caused by many causes, including pollutants, drugs and alcohol. Approved hepatoprotective drugs often show poor compliance with the treatment and may cause side effects; hence, a safe, effective therapy is required urgently to

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protect the liver from damage. Both experimental and preclinical data strongly support the therapeutic role of plant-based phytochemicals, viz flavonoids, phenolic acids, alkaloids terpenoids and lignans associated with mechanisms like antioxidant, anti-inflammatory, anti-apoptotic as well as antifibrotic pathways. Rat models of hepatotoxicity (CCl_4, paracetamol, thioacetamide) studies from others consistently indicate that phytochemicals sustain hepatic enzyme equilibrium and histoarchitecture and reduce oxidative/inflammatory damage. The clinical application of these drugs is restricted due to their low water solubility, bioavailability and rapid metabolism. Novel nanotechnology approaches, such as liposo-mal and nanoparticle delivery vehicles, have demonstrated improved pharmacokinetic profile and hepatic targeting potential of these natural molecules. Pre-clinical data are encouraging and sufficient; however, complete toxicologic investigations, uniform formulations, and controlled trials in man are necessary to prove safety and repeatability. Inclusion of the phytochemicals in mainstream hepatology, with backup from pharmacogenomic data, computer modeling and personalized strategies is a thought forward move for liver disease prevention and treatment. In conclusion, the plant-derived phytochemicals are an important class of bioactive molecules with strong hepatoprotective potential. Further interdisciplinary research into pharmacology, nanoscience and clinical medicine is necessary to convert these natural products from experimental potential to efficacious hepatoprotective drugs with evidence based.

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