Pandey *et al. Egyptian Liver Journal* (2023) 13:14
https://doi.org/10.1186/s43066-023-00248-w

Egyptian Liver Journal

REVIEW

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Promising hepatoprotective agents from the natural sources: a study of scientific evidence

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Abstract

Background Natural bioactive components derived from plant secondary metabolites have been pronounced as valuable alternatives for anticipating and subsiding hepatotoxic effects and its chronic complications based on experimental verification. The focus of this review is to elucidate the commonly used modern medicine for the treatment of liver disease and how major phytoconstituents have been tested for hepatoprotective activity, mechanism of action of some promising agents from natural sources, and clinical trial data for treating in patients with different liver diseases by the aid of natural phytoconstituents.

Main text The review shows fifteen major isolated phytoconstituents, their biological sources, chemical structures, utilized plant parts, type of extracts used, hepatoprotective assay method, and their possible mechanism of action on the hepatoprotection. Nine promising hepatoprotective leads from natural sources with their chemistry and hepatoprotective mechanism are mentioned briefly. The review further includes the recent clinical trial studies of some hepatoprotective leads and their clinical outcome with different liver disease patients. Scientific studies revealed that antioxidant properties are the central mechanism for the phytoconstituents to subside different disease pathways by upsurging antioxidant defense system of cells, scavenging free radicals, down surging lipid peroxidation, improving anti-inflammatory potential, and further protecting the hepatic cell injury. In this review, we summarize recent development of natural product-based hepatoprotective leads and their curative potential for various sort of liver diseases. Furthermore, the usefulness of hit and lead molecules from natural sources for significant clinical benefit to discover new drug molecule and downsizing the problems of medication and chemical-induced hepatotoxic effects is extrapolated.

Conclusion Further research are encouraged to elucidate the pharmacological principle of these natural-based chemical agents which will stimulate future pharmaceutical development of therapeutically beneficial hepatoprotective regimens.

Introduction

The liver, largest organ in human body, contributes 2% of our body weight, weighing almost 1.5 kg in a fully grown adult [57]. The liver is the site for drug metabolism and biotransformation, thereby having defensive role in the body against toxic foreign chemical agents. Due to these, the liver is exposed to drugs, chemicals, and other xenobiotics in different concentrations which finally results in liver injury. There are over hundreds of etiology causing hepatic diseases. The most profound causes

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of hepatic disease consist of microbes (hepatitis virus A, B, C,*Cytomegalovirus*, Epstein-Barr virus, and yellow fever virus); disease related to metabolic syndrome (fatty liver disease caused by obesity, hemochromatosis, and Wilson's disease); xenobiotics (alcohol, drugs, and chemicals); hereditary-related hepatic diseases; autoimmune diseases (biliary cirrhosis, hepatitis, and sclerosing cholangitis); and liver malignancies [75]. End result of hepatic diseases is disturbance and loss of workdays, compensation in quality of personal life, squeezing in expected life span, and financial burden to the individual as well as to the society, subsequently resulting in mortality and morbidity.

Around the globe, near to 2 million people are fading away each year because of hepatic complexities among which 1 million are due to complication of cirrhosis and another half are cognated to liver carcinoma and viral hepatitis [60, 107]. At present, the most prevalent cause of death is cirrhosis ranking 11 (1.16 million deaths) and liver cancer which ranks 16 (788,000 deaths) for death complication, and in combination, they account for 3.5% of all deaths worldwide [54, 107]. High intake of alcoholic product is the major factor for liver disease in global context [142]. A report published by the World Health Organization showed that among the total alcohol consumer worldwide which is predicted to be around 2 billion, slightly less than half, i.e., 75 million, are diagnosed with disorders related to the alcohol use specifically to several alcohol-associated liver disease [11, 181]. In 2015, more people died with viral hepatitis-related disease (1.34 million deaths) than by human immunodeficiency virus (HIV) (1.06 million deaths) or malaria (0.44 million deaths) and similar to the number caused by tuberculosis (1.37 million) [154, 178]. Among the morbidity cause by viral hepatitis, total of 96% is accounted for hepatitis B virus (66%) and hepatitis C virus (30%) which is mainly due to the cirrhosis complication and profusion of liver cancer [154].

Drug-induced liver injury (DILI) is one of the major problems associated with the treatment for several acute and chronic disease conditions. Research studies revealed that antitubercular drug (isoniazid), antipsychotic (chlorpromazine), penicillin antibiotic (amoxicillin), and histamine antagonist (cimetidine), analgesic and antipyretic (acetaminophen), and HMG-CoA reductase inhibitors (statins) are major drugs causing DILI [15, 143]. In West region of the globe, amoxicillin/clavulanic acid-induced liver injury occurs in 1 in 2350 [17], whereas combined antitubercular drug-induced liver injury is more profound in the east region [22, 198]. Among them, India and Nigeria have highest burden of DILI followed by China and South Korea having herbal and alternative medicine-induced liver injury [34, 156], WHO [179]. Globally, antimicrobial agents are considered as the major cause of idiosyncratic DILI [33, 170, 201]. The above latest figures depict that the worldwide liver disease burden has increased with growing time showing massive influence on the public life around the globe WHO [

Traditional medicine is prevalent all over the world which plays important role for preventive and curative purpose for people in developing countries [31]. According to the definition given by the WHO, "Traditional medicine is regarded as diverse health practices, approaches, knowledge and beliefs incorporating plant, animal, and/or mineral based medicine, spiritual therapies, manual techniques and exercises applied singularly or in combination to maintain well-being, as well as to treat, diagnose or prevent illness" [196].

Hepatic problems are one of the highly pronounced reason for mortality and morbidity in human [109, 114]. Liver damage is usually related to cell necrosis, diminution, and increase of liver biomarkers such as aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), total bilirubin (TB), total protein (TP), an increase in tissue lipid per oxidation, and oxidative damage [36, 100]. Traditional medicine from the natural sources has significant effect in the management of the hepatic diseases. Many natural phytoconstituents have been demonstrated to be effective hepatoprotective agents, while many more are claimed to have hepatoprotective and hepatocurative activity. Natural product-based phytoconstituents are regarded as the best and most validated source for developing novel therapeutic agents, but poor absorption, distribution, metabolism, and elimination followed by few toxicological properties still restrain the wide utilization of them for therapeutic purpose. In the last couple of decades, researcher and scientist are more encouraged for finding out more promising hepatoprotective agents from plant source to develop novel modern medicine for different liver aliments [61, 161].

In view of these facts, this review is effort to evaluate the available proven scientific data on the following:

(i) Recently developed modern medicines for liver disorder
(ii) Major phytoconstituents from the natural sources with their hepatoprotective activity
(iii) Promising hepatoprotective agents from the natural sources with its mechanism of action
(iv) Clinical trial data of some promising hepatoprotective leads in patients with different liver diseases
(v) Common mechanism of action of natural product-based leads for the protection against different liver diseases

Review method

The information about liver disease, clinical trial of recent hepatoprotective leads, promising hepatoprotective agents, and specific phytoconstituents was gathered by systematic literature survey with reference to the publications published mostly from 2000 to 2022. A comprehensive systematic literature survey was carried out in different scientific search engines such as Google Scholar, Wiley, PubMed, Taylor & Francis, ScienceDirect, and Springer to find required information. Major keywords used to search and to retrieve the related articles are "Liver disease," "Hepatoprotective," "Hepatoprotective AND Plant," "Hepatoprotective AND Herbal," "Hepatoprotective AND Natural Product," "Hepatotoxicity," "Hepatotoxicity AND Ethnopharmacology," and so forth.

Results

Some clinical significance of allopathic drugs for liver disorder

Due to the recent advancement, medication evaluation based on evidence, standard pharmacopeia, and randomized placebo control clinical trial to outline the clinical efficacy of modern medicine is more frequent. Therapies developed with synthetic hit and lead compounds relying in the principle of allopathic medicine have significant risk–benefit ratio, often expensive and less effective [117, 163]. Some liver-protective medicines and their adverse effects are depicted in Table 1 below.

Major bioactive phytochemicals with hepatoprotective activity

Active hepatoprotective phytoconstituents discovered in experimental laboratory mouse model during the experiment in mouse with different liver diseases are mentioned in Tables 1 and 2. Their chemical structures are illustrated in Fig. 1.

Some promising hepatoprotective agents from natural sources

Silymarin (family: Asteraceae)

Silymarin, an active compound of *Silybum marianum* (L.) Gaertn., commonly known as "milk thistle," is one of the oldest plant which has been commonly utilized for the treatment of liver diseases [90, 102].

Dried seeds are major sources of active phytoconstituents, which contain four flavonolignans isomer, i.e., silybin, isosilybin, silydianin, and silychristin. The complex mixture of these four flavonolignans isomer is known as silymarin [47, 73].

Silymarin shows hepatoprotection via various underlying mechanisms of which most common are modulation of enzymatic and nonenzymatic liver biochemical markers [170, 173] and induction of nuclear factor-erythroid 2-related factor 2 (Nrf2) expression [70]. In addition, anti-inflammatory properties of silymarin have been proved in several models of liver damage. In rats, with alcoholic fatty liver model, silymarin acted by downregulating the expression of nuclear factor kappa B (NF-κB), interleukin-6 (IL-6), mission mode project-2 (MMP-2), mission mode project-13 (MMP-13), transforming growth factor beta-1 (TGF-β1), tumor-suppressor Krueppel-like factor, collagen α1 expression, and platelet-derived growth factor (PDGF) signaling when tested in hepatotoxic damage animal models [30, 194]. Likewise, silymarin could inhibit cells infected by HCV via TNF-α-induced activation of NF-κB and its nuclear translocation [104, 131]. Silymarin is well tolerated by patients with good safety profile [132]. Poor water solubility of silymarin is being overcame by silymarin-loaded solid nanoparticles which enhance its antioxidant and hepatoprotective activity in comparison with crude silymarin [20].

Glycyrrhizin (family: Leguminacae)

Glycyrrhizin, a triterpenoid glycoside isolated from the root of *Glycyrrhiza glabra* L. commonly known as liquorice root, has been used in traditional medicine system of Nepal, India, China, and other countries for the treatment of jaundice [121, 186]. It is a mixture of potassium and calcium salt of glycyrrhizinic acid, and other phytoconstituents involved are glycyrrhetinic acid, beta-sitosterol, hydroxycoumarins, and flavonoids [50, 147].

Glycyrrhizin shows hepatoprotective effect via various mechanisms such as increasing antioxidant defense in hepatic cell and as anti-inflammatory agent [121, 147]. High-mobility group protein box (HMGB1) are either diminished or interrupted for binding to glutathione S-transferase omega-1 (GSTO1) promoter region by glycyrrhizin to show anti-inflammatory effect [74, 93]. Not only glycyrrhizin, its metabolite, and glycyrrhetinic acid inhibited collagen αI(I) gene expression in liver fibrosis caused by CCl_4 [110]. Glycyrrhetinic acid also helps in liver cell growth through the mechanism of epithelial growth factor receptor (EGFR) binding, stimulating DNA synthesis in liver cells by extracellular signal-regulated kinases (ERK2)-mediated pathway [25, 71], which helps in liver regeneration. During interferon alpha (IFN-α)-based therapy failure, glycyrrhizin administered through intravenous route dramatically lowered the serum alanine transaminase level after 12 weeks of therapy and improved liver fibrosis and necrosis caused by inflammation after 52-week treatment in patients with hepatic disease [97]. Moreover, it is also effective in prevention of HCV-related liver cirrhosis in older patients [62, 106]. In a study using in vitro cell model and in vivo animal models with hepatic injury, it was revealed that

Table 1 Commonly used allopathic medicine for liver protection with clinical application

S.no	Modern medicine	Disease condition	Mechanism of action	Clinical outcomes	Reference
1	Corticosteroids	Reduce cytokine production Antifibrotic	Switch off multiple activated inflammatory genes through inhibition of histone acetyltransferase (HAT) and recruitment of histone deacetylase 2 (HDAC2) activity to the inflammatory gene transcription complex	Studies revealed that it has less significant effect nowadays, and implication in future as liver-protective agent is also less recognized	[68, 165]
2	Interferons	Antiviral, antifibrotic	Inhibits hepatitis B and C virus replication by decreasing RNA transcription, occurring from covalently closed circular DNA	Hepatitis B and C could be treated. Antifibrotic activity is still not tested and proved in human. Side effects at therapeutic dose include depression, anxiety, agitation, suicidal ideation, and even suicide	[112, 133]
3	Lamivudine	Hepatitis B and cirrhosis	Converted intracellularly to its triphosphate form which then competes with cytosine triphosphate for incorporation into the developing viral DNA strand	Continuous usage might result in the development of resistant with hepatitis B virus	[85, 188]
4	Propylthiouracil	Alcohol hepatic diseases	Reacts with some of the oxidizing species derived from the respiratory burst in neutrophils and act as antioxidant resulting in the suppression of alcohol-induced hepatic necrosis	Render metabolically compromised patients hypothyroid	[8, 69]
5	Colchicine	Against gout, antifibrotic	Disrupts tubulin leading to subsequent down-regulation of multiple inflammatory pathways and modulation of innate immunity	Beneficial properties were not demonstrated recently. Very toxic at high doses	[112, 160]
6	Pentoxifylline	Severe alcoholic hepatitis	Inhibits TNF-alpha synthesis and inflammation	Have appropriate therapeutic implication for hepatorenal syndrome due to its excellent safety profile. Patients with xanthine hypersensitivity should avoid use of pentoxifylline	[111]
7	Ursodeoxycholic acid	Non-alcoholic fatty hepatic disease	Inhibits DNA repair, coenzyme A, cyclic AMP, p53, and phagocytosis and inhibits induction of nitric oxide synthetase	Useful in the treatment of hepatobiliary diseases by ameliorating hepatic histology, enzymes, and different oxidative stress Long use of ursodeoxycholic acid in human might result in taurine depletion	[44, 148]
8	Rosiglitazone	Non-alcoholic fatty hepatic disease	Activates intracellular receptor class of peroxisome proliferator-activated receptors (PPARs), specifically PPARγ	Increase risk of heart attack	[27, 82]

Table 2 Some major phytoconstituents with hepatoprotective activity

S. no	Name of bioactive phytoconstituent	Plant name	Parts used	Extract used	Dose used	Hepatotoxicity-inducing agents	Finding of study	Mechanism of hepatoprotective activity	Reference
1	Phenylethanoid glycoside: acteoside	*Plantago major* L	Aerial parts	Aqueous methanolic	500 mg/kg orally	CCl_4	Inhibited the serum elevation of ALT, AST, ALP, and GGT enzymes as well as total and direct bilirubin. Decrease LPO and increased GSH in the liver	Blocks the P50-mediated CCL4 bioactivation and exhibits superoxide-free radical scavenging effects	[40, 192]
2	Pentacyclic triterpene: alpha-amyrin	*Alstonia scholaris* Linn	Stem bark	Ethanol extract	20 mg/kg/day orally	CCl_4	Decreased serum liver markers like GGT, AST, ALT, LDH, ALP, acid phosphatase (ACP), sorbitol dehydrogenase (SDH), glutamate dehydrogenase (GDH), and total bilirubin, total protein Increased glutathione, ceruloplasmin, β-carotene, vitamin C, and vitamin E Increased hepatic antioxidants like SOD, CAT, GPx, GR, GST, LPO, 5′-ribonucleotidase, acid ribonuclease, succinic dehydrogenase	Exhibits antifibrotic, anti-inflammatory, antiapoptotic, and free radical scavenging effects	[149, 162]
3	Triterpenoid: asiatic acid	*Potentilla chinensis*			4 or 8 mg/kg/day orally	Lipopolysaccharide/D-galactosamine	Decreased the serum ALT and AST and showed improvement of liver pathology	Inhibits MAPK and NF-κB via the partial induction of PDCD4 and upregulation of Nrf2 in an AMPK/GSK3β pathway activation-dependent manner resulting in the inhibition of oxidative stress and inflammation	[91, 126]

Table 2 (continued)

S. no	Name of bioactive phytoconstituent	Plant name	Parts used	Extract used	Dose used	Hepatotoxicity-inducing agents	Finding of study	Mechanism of hepatoprotective activity	Reference
4	Pentacyclic triterpenoid saponin: asiaticoside	*Centella asiatica*			5, 10, and 20 mg/kg/day orally	Lipopolysaccharide/D-galactosamine	Decreased the elevated serum level of ALT, hepatocytes apoptosis, caspase-3, improvement of liver pathological injury in dose-dependent manner. Also reduced the elevation of phospho-p38 MAPK, phospho-JNK, phospho-ERK protein, and TNF-alpha mRNA expression in liver tissue	Inhibits TNF alpha and MAPKs	[13, 191]
5	Saponin: cristatain	*Celosia cristata* L	Seeds	50% ethane	1, 2, and 4 mg/kg/day orally	CCl_4 and N,N-dimethyl formamide	Significantly reduced in the values of AST, ALT and ALP of serum and histopathological examinations compared to controls	Downregulates caspase-3 and caspase-8 activities and prevents hepatic cell apoptosis. Exhibits antioxidant activities through scavenging hydroxyl and DPPH-free radicals	[4, 177]
6	Oleanolic acid saponins: celosin A and celosin B	*Semen celosiae*	Seeds	Ethanolic extract	1, 2, and 4 mg/kg orally	CCl_4	Inhibited the serum elevation of AST, ALT, and ALP while improve the serum level of GSH_PX, MDA, CAT, and SOD	Both have significant hepatoprotective effects due to the antioxidant property by decreasing the serum liver biochemical markers and liver antioxidant enzymes	[183, 184]
7	Sesquiterpene glycoside: cichotyboside	*Cichorium intybus*	Seeds	-		CCl_4	Exhibited a significant anti-hepatotoxic activity by reducing the elevated levels of liver enzymes such as AST and ALT	Reduces liver weight and liver protein; inhibits oxidative stress by increasing reduced glutathione content and decreasing lipid peroxidation	[64, 94]

Table 2 (continued)

S. no	Name of bioactive phytoconstituent	Plant name	Parts used	Extract used	Dose used	Hepatotoxicity-inducing agents	Finding of study	Mechanism of hepatoprotective activity	Reference
8	Flavonol glycoside: visconoside C	*Cleome viscosa* L	Leaves	Methanolic extract	100 µM	CCl_4-induced hepatotoxicity on HepG2 cells	Exhibited a significant hepatoprotective activity by antioxidant mechanism and quercetin taken as standard control	Shows free radical scavenging activity and normalizes impaired membrane function activity	[118, 151]
9	Dehydrocavidine	*Corydalis saxicola*		-	1, 0.5 and 0.25 mg/kg/day intraperitoneally	CCl_4-induced hepatic fibrosis in rats	Inhibited the serum level of ALT, AST, ALP, TB and increased the SOD, CAT, GPx	Alleviates liver damage by reducing the formation of fibrous septa, decreasing the MDA concentration, reducing oxidative stress, promoting collagenolysis, and regulating fibrosis-related genes	[175]
10	Isoflavones: puerarin	Kudzu roots/*Pueraria lobelia*	Roots		30, 60, and 120 mg/kg/day orally	Chronic alcohol-induced liver injury	Decreased the serum levels of ALT, AST, ALP, and intrahepatic contents of alcohol dehydrogenase (ADH); aldehyde dehydrogenase (ALDH) were elevated	Inhibits endogenous activities of CYP2E1, CYP1A2, and CYP3A which potentially sustain metabolic homeostasis	[28, 84]
11	Rubiadin	*Rubia cordifolia* Linn		-	50, 100, and 200 mg/kg orally	CCl_4-induced hepatic damage in rats	Normalized serum level of ALT, AST, ALP, and GGT and decrease activities of glutathione S-transferase and glutathione reductase	Shows glutathione mediated detoxification as well as free radical scavenging effect	[103, 138]

Table 2 (continued)

S. no	Name of bioactive phytoconstituent	Plant name	Parts used	Extract used	Dose used	Hepatotoxicity-inducing agents	Finding of study	Mechanism of hepatoprotective activity	Reference
12	Ursolic acid	*Hedyotis corymbosa* L	Whole plant	Ethane	0.75 mg/ml/kg body weight orally	Paracetamol-induced liver injury	Decreased serum enzyme levels of ALT, AST, ALP, total bilirubin, and also normalized histological architecture of the liver compared to the paracetamol-treated group	Suppresses the nuclear factor-kappa beta (NF-κB) activation, inhibits Cytochrome P4502E1 expression, enhances hepatic-glutathione regeneration capacity, and upregulates metallothionein expression	[56, 157]
13	Coumarin: wedelolactone	*Eclipta prostrata* L	NA	NA	50 and 100 mg/kg intraperitoneally	Concanavalin A-induced hepatitis in mice	Significantly reduced leukocyte infiltration and T-cell activation in liver. Suppress the activity of nuclear factor-kappa B, tumor necrosis factor, interferon gamma, and interleukin (IL)-6	Inhibits the infiltration of leukocytes into the liver via suppression of NF-κB signaling pathway	[89]
14	Betulinic acid and ricinine	*Tetracarpidium conophorum*	Seeds	Hexane fraction	100 mg/kg betulinic acid and 50 mg/kg ricinine orally	CCl_4-induced hepatotoxicity	Both betulinic acid and ricinine exhibited hepatoprotective potential in CCl_4 rat model in vivo. Both possess strong affinity and better interaction in the active sites of hepatitis B virus DNA polymerase	Improves tissue redox system, decrease lipid peroxidation, and maintain antioxidant system	[122, 189]
15	Coumarin analogues: meranzin hydrate I	*Citrus grandis*	Pericarp	70% ethanol and 30% water	20-μM concentration	D-Galactosamine-induced cell survival inhibition in LO2 cells by MTT assay	Increased superoxide dismutase and glutathione peroxidase and decreased the level of malondialdehyde in liver toxic model	Modulates cellular antioxidant pathway and improves the free radical scavenging property	[164]

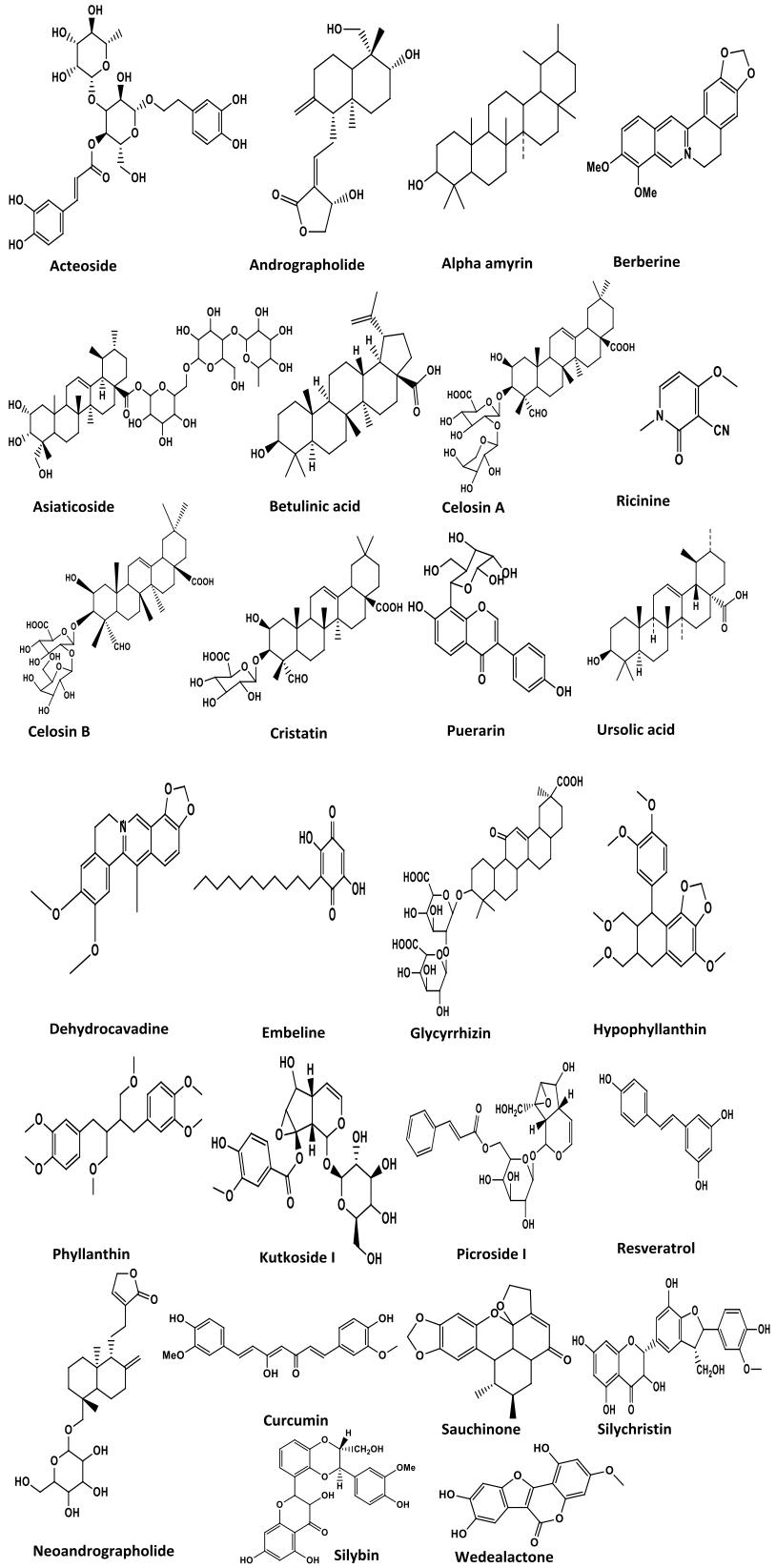

Fig. 1 Chemical structure of some potent bioactive phytochemical with hepatoprotective activity

18β-glycyrrhetinic acid reduces oxidative stress and expression of inflammatory markers which were predicted as a result of the downregulation of NF-κB and upregulation of Nrf2 target genes [59, 87].

Andrographolide and neoandrographolide (family: Acanthaceae)

Andrographolide and neoandrographolide are the active chemical constituents of herbaceous plant of *Andrographis paniculata* Nees. commonly known as "king of bitters" due to its extremely bitter taste and is well-known for liver diseases [134, 172].

The main active chemical constituent is diterpene lactone class which is obtained from the leaves, i.e., neoandrographolide, 14-deoxy-11-dehydroandrographolide, 14-deoxy-11-oxoandrographolide and deoxy-andrographolide, andrographolide, andrographine, panicoline, paniculide-A, paniculide-B, and paniculide-C [129, 136].

Andrographolide inhibits inflammation, angiogenesis, and fibrosis in chemically induced liver injury animal model via antioxidant and anti-inflammatory mechanisms [26, 77]. Oxidative stress-inducible gene such as hypoxia-inducible factor-1 alpha, superoxide dismutase (SOD-1), heme oxygenase-1 (HO-1), and glutathione S-transferase (GST1) which uprise nuclear Nrf2 content and its DNA-binding activity and other upregulated protein and gene are balanced by andrographolide [26, 187]. It also helps in upregulation of HO-1 via the p38 mitogen-activated protein kinase, MAPK/Nrf2 pathway shows anti-HCV activity [77]. Additionally, andrographolide helps in downregulation of hypoxia-inducible genes such as vascular endothelial growth factor (VEGF) and also diminishes TNF-α and cycloxygenase-2 (COX-2) expression and finally reduces liver hypoxia and attenuates hepatic apoptosis and fibrosis in rats [72, 79]. The compound decreases serum levels of TNF-α and interleukin-1 beta (IL-1β) and hepatic expression of TGF-β, cannabinoid receptor type 1 (CBR1), and Bax. The predicted mechanism for the decrement of serum levels of TNF-α and IL-1β is through the downregulation of JNK and ERK phosphorylation. A study in high-fat diet (HFD) fed mice administering andrographolide showed that cellular lipid accumulation is diminished [37, 79].

Picroside I and kutkoside (family: *Scrophulariaceae*)

Picroside and kutkoside are the active chemical constituents of roots and rhizomes of *Picrorhiza kurroa* Royle, commonly known as "Kutki" or "Kutaki," and have been used to treat hepatic disorder since long [58, 140].

The major active constituents are kurkoside, apocynin, drosin, cucurbitacin glycoside, and the iridoid glycoside such as picroside 1, 2, and 3. Kutkin is formed when picroside I and kutkoside are mixed in the ratio of 1:2 [141, 152].

Picroside-I and kutkoside show hepatoprotective effect via membrane stabilizing, hypolipidemic and antioxidant properties, and finally liver regenerative effect in rats via stimulation of nucleic acid and protein synthesis [101, 139, 153]. Picroside-I and kutkoside are free radical scavengers (superoxide anion O2•) and inhibit lipid peroxidation in liver tissue [95]. It also showed restoration of bilirubin and activity of serum liver biomarkers level of AST, ALT, ALP, and LDH against acetaminophen-induced liver toxicity animal model by protecting injury hepatocyte proving its hepatoprotective effect [141]. Moreover, picroside also reduces the lipid peroxidation, normalizes glutathione metabolism, and inhibits hepatocarcinogenesis caused by N-nitrosodiethylamine in rats by increasing the life span of tumor bearing rats [24, 195]. It acts against less expression of LDL receptor on cell surface caused by paracetamol and uprises the conjugated dienes in liver cells as well as maintain of oxidation–reduction balance for healthy liver [108, 152].

Curcumin (family: Zingiberaceae)

Curcumin is the principle curcuminoid found in rhizome of *Curcuma longa* commonly known as "turmeric." Traditional use of turmeric for the treatment of bilirubin-related liver disease such as jaundice and several other hepatic complication is being documented since long [81].

Structurally, similar phenolic compounds found in the rhizomes of turmeric are known as curcuminoids in their mixed form. Three major curcuminoids present in rhizomes of turmeric are curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Chemically, curcumin is a diferuloylmethane which consists of diferulic acid moiety fused with methylene moiety or other carbon group and exists mainly in keto-enol form [83, 130].

Hepatoprotection mechanism of the curcumin may be due to its antioxidant activity and activation of the phase 2 detoxifying/antioxidant enzymes such as HO-1 and NADPH quinone oxidoreductase-1 (NQO1) and Nrf2/Kelch-like ECH-associated protein 1 (Keap1)/antioxidant-responsive element (ARE) pathway [43, 48]. In addition, its administration in diet reduces oxidative stress, decreases Cytochrome P450 2E1 (CYP2E1) and paired-related homeobox 1 (Prx1) expression, while upregulates paired-related homeobox 6 (Prx6) expression [78]. Oxidative stress caused by hepatotoxins is closely associated with activation of some inflammatory mediators such as MAPKs, NF-κB, and signal transducer and activator of transcription-3 (STAT3) via different pathways [5]. Research reported that curcumin can inhibit the expression of toll-like receptor-2 (TLR2), toll-like receptor-4

(TLR4), and HMGB1 in rat suffered with fibrogenesis expression of ligand molecules. Concanavalin A-induced hepatitis in mice via T-cell-mediated pathway become less severe when administered with curcumin which is mainly due to the inhibition of liver inflammation [167, 168]. Likewise, curcumin could diminish liver toxicity cause by lipopolysaccharide (LPS)/D-galactosamine (D-GalN) through inhibition of hepatic mRNA levels of Sirtuin (silent mating type information regulation 2 homolog)-1 (SIRT1) [190]. It also suppresses expression of gene for receptors which are involved in final product of advanced glycation in hepatic stellate cells (HSCs) by uprising the peroxisome proliferator-activated receptor-gamma (PPARγ) activity and subsiding oxidative stress [86]. Moreover, curcumin could protect against paracetamol-induced hepatocyte apoptosis by reducing the availability of proapoptotic genes Bax and caspase-3 while improving antiapoptotic genes [80]. However, curcumin is able to downregulate Bcl-2 mRNA expression and upregulates p53 protein expression in thioacetamide-induced cytotoxicity, facilitating apoptosis in damaged cells which reduces hepatic inflammatory gene and fibrogenesis [174]. Additionally, antioxidant and anti-inflammatory effect of curcumin could protect mice against human cytomegalovirus infection [92].

Phyllanthin and hypophyllanthin (family: Euphorbiaceae)

Phyllanthin is a potent hepatoprotective lignans found in *Phyllanthus niruri* Linn., commonly known as "gale of the wind," is a long established herbal remedy for jaundice and other hepatic diseases [50].

The main active chemical constituents include alkaloids, astragalin, brevifolin, ellagitannins, amariin, repandusinic acid, phyllanthusiin D gallocatechins, geraniin, hypophylanthis, lignans, nirutin, phyllanthin, and phyllanthenol. Chemically, phyllanthin and hypophyllanthin are lignans isolated from the hexane extract and have been established as the hepatoprotective agents [58, 83].

Phyllanthus niruri is effective against infective hepatitis and other liver disease [65, 76]. Ethanolic extract of this plant possesses potent hepatoprotective activity both in vitro and in vivo. In India, it was used to treat jaundice in children because of its liver-protective and detoxifying action [38, 52]. A study in the UK revealed that *Phyllanthus* extract could be effective for treatment of both acute and chronic hepatitis in children [38, 76]. Phyllanthin and hypophyllanthin both can protect rat liver from toxicity induced by carbon tetrachloride and cytotoxicity induced by galactosamine [7, 158].

These lignans also protect against liver damage induced by alcohol and normalize a "fatty liver" condition. The hepatoprotective effects of phyllanthus lignin are achieved with the mechanism of inhibition of superoxide and hydroxyl radicals and lipid peroxidation [16, 67].

Berberine (family: Berberidaceae)

Berberine is an isoquinoline alkaloid which could be isolated from roots, rhizomes, and stem bark of *Berberis aristata* DC, commonly known as "barberry" and has been used as tonic remedy for liver since long ago [98].

The major active chemical constituents present in *Berberis aristata* are berberine, oxyberberine, berbamine, aromoline, karachine, and oxycanthine. Berberine is experimentally proved hepatoprotective phytoconstituent [63, 96].

Berberine shows antioxidant activity which could suppress oxidative stress and attenuates apoptosis through the increment of ratio of Bcl-2/Bax in ischemia-/reperfusion-injured rat liver inhibiting caspase-3 cleavage in the liver [123]. Its mechanism of action is upregulation of Akt and inhibition of mTOR expression [146]. Furthermore, hepatocyte nuclear factor-4 alpha and PPARα/peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α) could be restored with berberine showing hepatoprotective effect in liver ischemia. Experiment in mice with steatosis induced by ethanol showed that berberine protects the liver from ethanol-induced oxidative stress [193]. Berberine even reduces the expression of hepatic proprotein convertase subtilisin/kexin type 9 (PCSK9), a cholesterol homeostasis regulator, and decreases IFN-γ, TNF-α, IL-1α and 8-isoprostane levels in LPS-induced hepatoxicity mouse model [180]. Carbon tetrachloride-induced liver injury is attenuated by berberine via suppression of TNF-α, COX-2, and iNOS expression and oxidative stress [39]. Berberine could diminish liver fibrosis through the activation of AMPK and decreasing the expression of NOX4 and phosphorylated Akt [82].

Embelin (family: Myrsinaceae)

Embelin, chemically known as "2,5-dihydroxy-3-undecyl-1,4-benzoquinone," is an active chemical constituent of leaves of *Embelia ribes* Burm.f. commonly known as "false black pepper" and is known for free radical scavenging and liver protective function [66]. The active constituents are embelin, christembine, quercitol, and resin. Embelin shows its hepatoprotective effect mainly through its free radical scavenging and lipid peroxidation pathway. Embelin can control the liver biomarkers: AST, ALT, ALP, LDH, bilirubin γ-glutamyl transpeptidase, and total protein levels in carbon tetrachloride-treated rats [150]. Study in mitochondria of rat liver showed that embelin could inhibit lipid peroxidation, and impaired superoxide dismutase level was restored with embelin administration. Furthermore, to extraplot mechanism

and rate of reactions of embelin with hydroxyl, way of oxidizing single electron and radical called "organohaloperoxyl" with the technique known as nanosecond pulse radiolysis was studied. Its redox potential was also evaluated, and the study depicted that embelin is a potent-free radical scavenger in physiological conditions [35, 66].

Resveratrol

Resveratrol chemically known as "trans-3,5,4′-trihydroxystilbene" is a naturally occurring polyphenol compound present in *Vitis labrusca* commonly known as "grapes," *Vaccinium myrtillus* L. commonly known as "blueberries" and *Rubus idaeus* L. commonly known as "raspberries" with potent antioxidant properties. Resveratrol, a phytoalexin, is generated in plants when bacteria and fungi attacked it [32].

Resveratrol shows liver protection via reduction of oxidative stress during hepatocyte injury by modifying the expression of nuclear transcription factors Nrf2 and NF-κB and downregulating HO-1 and iONS gene expression [1, 144]. This enhances the free radical scavenging properties as well as phase 2 enzymes [21]. Furthermore, it even inhibits proinflammatory cytokines such as IL-2, IL-6, and TNF-α in concanavalin A-induced autoimmune hepatitis [199]. In liver injury cause by high cholesterol, resveratrol shows protective effect which is mediated by the enhancement of autophagy and downregulation of proapoptotic proteins such as Bax and caspase-3 and caspase-8 [23]. Followingly, hepatotoxicity caused by isoniazid and rifampicin is ameliorated by resveratrol by modulating the expression of SIRT1 mRNA hepatic cells of mice, which finally minimize hepatic oxidative stress in the liver, production of cytokine, and expression of gene called PPARγ [119]. Moreover, resveratrol also prevents hepatotoxicity resulted from higher consumption of acetaminophen by upregulating expression of SIRT1 and downregulating p53 signaling, enhancing the expression of cell nuclear antigen, promoting hepatic cell proliferation, enhancing liver regeneration and inducing uprising the level of cyclin D1 and Cdk4 [53, 176].

Clinical trials of some hepatoprotective leads

During the drug development phase of the clinical trials, potent hepatoprotective phytoconstituents are studied in different human liver disease condition with specified period to curing the liver disease. The summary of the reported clinical trials of major hepatoprotective leads is documented in Table 3.

Possible best mechanism of herbal remedy for the protection of liver against variety of toxins and injury

The study revealed that the most profound hepatoprotective mechanisms of the herbal plants are through the free radical scavenging effect and anti-inflammatory pathway. The hepatic injury perpetually involves per oxidation of fatty acid present in hepatocyte membrane leading to the distortion of the cells and their organelles. Recent studies suggested that oxidative stress has a vital role in the commencement and development of hepatic damage. Role of oxidative stress in viral hepatitis and in liver diseases caused by autoimmune syndrome has been studied and reported significantly [42]. Furthermore, xenobiotics and toxic chemicals damage hepatic cells mainly by the generation of reactive free radicals which form covalent bonding interaction with the amino acid residue of the hepatic cell membranes (Fig. 2). Due to widespread contact to harmful chemicals, sometimes the produced free radicals override the defensive system available naturally causing hepatic injury. Natural phytoconstituents such a vitamin E and silymarin are known for their protective role against liver injury caused by hepatotoxic agent [197]. Inflammation which is the major clinical symptom in hepatotoxin-induced liver damage is cause by toxin or through oxidative stress which leads towards the noteworthy increment of proinflammatory cytokines including TNF-α (tumor necrosis factor-α) and IL-6 (interlukin-6) and hepatocyte inflammation [2]. In brief, minimizing the oxidative stress and inflammatory cytokines is the major mechanism by which herbal remedies act as hepatoprotectant.

Discussion

Global use of herb-based regimen is increasing day by day, and at least one-quarter of patients with liver diseases use natural phytoconstituents for disease therapy. Current research strategies are focused on scientific investigation of herbal-based medicine for their safety and efficacy through huge preclinical studies followed by clinical trials to find the mysteries hidden in medicinal plants [51]. Such approaches ultimately help to find the real potent therapeutic lead and valuable pharmacotherapeutic candidate from the natural sources specially plant origin and standardize the dosage regimen on scientific-based finding [135]. Recently, most of the herbal products are marketed for the purpose of disease prevention, support health, relieve symptoms, and curing of different disease and aliments. Still most of these products lack scientific and pharmacological validation. Most of the experimental model study related to hepatotoxicity using cell culture and animals showed that various plant extracts exert hepatoprotective and curative effects

Table 3 Clinical trial with different promising hepatoprotective leads in patients with different liver diseases

S. no	Name of hepatoprotective lead	Condition	Study design (*n*)	Treatment (*n*)	Duration	Outcome with hepatoprotective leads	References
1	Silymarin	Epileptic children having antiepileptic treatment and experienced drug-induced liver injury (DILI)	Randomized clinical trial (55)	Randomized children were administered either silymarin (5 mg/kg per day) or folic acid (1 mg per day) for 1 month	Three months	Folic acid group had significantly decreased ALT, AST, and GGT levels compared to the patients in the silymarin groups. Both treatments were safe and effective in the management of DILI, but folic acid seems to be superior	[10]
		Patients with severe preeclampsia whose pregnancy was terminated	Randomized clinical trial (30)	Case group received 70 mg of silymarin, and control group received the placebo at 3 and 24 h after the termination of pregnancy	Three days	Hepatic enzymes ALT and AST level decreased significantly during 36 and 60 h after the termination of pregnancy in the study group compared to control group. This indicates that silymarin improves liver disorder in severe preeclampsia	[12]
		Non-cirrhotic patients with non-alcoholic steatohepatitis (NASH)	Randomized double-blind placebo control phase II clinical trial (78)	Silymarin treatment group 400 mg (26 patients) and 700 mg (27 patients) and placebo group (25 patients) in dosing frequency thrice a day	48 weeks	Significant variation was not observed in side effect among the treatment group and patient treated with silymarin in patients. Whether NASH is treated with silymarin is inconclusive due to the lack of substantial number of patients who meet the histological criteria and therefore required additional clinical trial	[115]
		New cases of pulmonary tuberculosis patients	Randomized double-blind clinical trial (70)	Test group received silymarin 140 mg three times a day + standard antituberculosis treatment, and control group received standard antituberculosis treatment only	Two weeks	Silymarin was proved to be safe without adverse event, but measurable hepatoprotective effect was not observed among patients receiving tuberculosis treatment	[99]
		Liver disease (78% with daily alcohol use)	Double-blind control study (97)	Test group (47) received silymarin 420 mg/day, and control group (50) received placebo	4 weeks	Liver function parameters, liver histology, ALT, and AST were observed to be improved	[145]

Table 3 (continued)

S. no	Name of hepatoprotective lead	Condition	Study design (*n*)	Treatment (*n*)	Duration	Outcome with hepatoprotective leads	References
		Alcoholic liver disease (ALD) (50% with cirrhosis)	Double-blind comparative study (116)	Test group (57) received silymarin 420 mg/day, and control group (59) received placebo	3 months	No significant effects	[166]
		ALD or non-alcoholic fatty liver disease (NAFLD) (70% with cirrhosis)	Randomized control trial (170)	Test group (87) received silymarin 420 mg/day, and control group (59) received placebo	Median 41 months	Ameliorate the survival rate, and difference in survival was observed mostly in patients with ALD and liver cirrhosis and those with less serious aliments (Child class A)	[46]
		ALD	36	Test group (17) received silymarin, and control group (19) received placebo	6 months	Decrease in ALT, bilirubin and procollagen synthesis	[45]
		ALD	Double-blind protocol NA (not available)	Test group received silymarin 420 mg/day, and control group received placebo	6 months	Improvement in antioxidative system by decreasing MDA and increasing GSH in liver cell	[113]
		ALD (72% with cirrhosis)	Double-blind randomized control trial (59)	Test group (25) received silymarin 280 mg/day, and control group (34) received placebo	15 months	Blood glucose level was observed to get improved (including fasting); HbAIC and MDA daily dose of insulin administration get decreased in ALT and AST	[18]
		Insulin-treated type 2 diabetic mellitus with alcoholic cirrhosis	Randomized clinical trial (60)	Test group (30) received silymarin 680 mg/day + standard treatment, and control group (30) received standard treatment only	12 months	No measurable effect was observed on progression, and survival of cells involved in liver disease	[171]
		ALD with cirrhosis	Double-blind randomized control multicenter trial (200)	Test group (103) received silymarin 450 mg/day, and control group (97) received placebo	2 years	Decrease MDA and aminoterminal propeptide of procollagen type 3	[127]
		ALD with cirrhosis	Randomized double-blind placebo control clinical trial (49)	Test group (24) received silymarin 450 mg/day, and control group (25) received placebo	6 months	Slight upsurge in the level of glutathione and down surge of lipid peroxidation were observed in the patient with ALD was silymarin administration	[88]

Table 3 (continued)

S. no	Name of hepatoprotective lead	Condition	Study design (*n*)	Treatment (*n*)	Duration	Outcome with hepatoprotective leads	References
2	Picroside	Liver disease patients	Double-blinded placebo randomized clinical trial	Test group received the herbal formulation contains picroside, and control group received placebo	NA	Reduction in bilirubin value by 2.5 mg was achieved by 27.4 days for the picroside herbal formulation treatment group, whereas 75.9 days are required for the placebo group	[6]
		Hypolipidemic patients with liver disease	Double-blind placebo study	Test group receive 2 gm kutaki formulation along with atorvastatin 20 mg two times a day, and control group received 500-mg starch powder with atorvastatin 20 mg in same duration	NA	Test group showed significant increase in the liver function enzyme parameters as compared to the placebo group	[105]
3	Phyllanthin	Oxidative stress, liver damage, and patients with hangover symptoms	Randomized placebo-controlled trial	Test group received 750 mg/day; *Phyllanthus amarus* ethanol extract and control group received placebo (15)	Ten days	*Phyllanthus amarus* treatment group showed significant control over hangover, inflammation, and liver function following intoxication by reducing blood alcohol and upregulating cytokine IL-8 and IL-10 as compared to control group	[49]
		Patients suffering from liver disease	Clinical study (107)	Test group received 3 g of *Phyllanthus amarus* powder for three times for a day orally with water (98)	45 days	Significant decrease in SGPT and bilirubin and increase in hemoglobin with patient treated with test drug	[128]

Table 3 (continued)

S. no	Name of hepatoprotective lead	Condition	Study design (*n*)	Treatment (*n*)	Duration	Outcome with hepatoprotective leads	References
4	Glycyrrhizin	A healthy individual consume alcohol (vodka) nightly for 12 days	Randomized, double-blind, placebo, cross over study (12; six males and six females)	Test group received the glycyrrhizin product with daily alcohol, and control group received alcohol alone daily	12 days	Plasma glutathione level and ALP significantly decreased in alcohol control group suggested that consumption of glycyrrhizin product during the alcohol consumption may improve the liver health compared with the consumption of alcohol alone	[29]
		Digestive tract cancer patients	Clinical trial (84)	Test group treated with the saponin (160 mg i.v once a day) with standard cancer chemotherapy, and control group received only standard cancer chemotherapy alone	NA	Test group showed significantly lower liver transaminase level and higher level of neutrophile, granulocyte, and white blood cells when compared with the standard chemotherapy control group	[55]
		Patients with hepatitis E and severe jaundice	Clinical trial (78)	Test group received magnesium isoglycyrrhizinate, and control group received an intravenous injection of 150 mg of magnesium once a day	6 weeks	Use of magnesium isoglycyrrhizinate in test group showed improved effective against the hepatitis E virus infection with severe jaundice as compared to the control group	[182]
		Patients with chronic hepatitis B	Clinical trial (64)	Test group received magnesium isoglycyrrhizinate, and control group received an intravenous injection of saponin once a day	4 weeks	Liver function was improved in both patients group, but no statistically significant difference observed in test group and control group	[19]

Table 3 (continued)

S. no	Name of hepatoprotective lead	Condition	Study design (*n*)	Treatment (*n*)	Duration	Outcome with hepatoprotective leads	References
5	Curcumin	Patients with liver cirrhosis	Randomized double-blind placebo control trial (70)	Test group (35) received 1000 mg/day curcumin, and control group received the placebo	3 months	Curcumin supplement showed beneficial effect in decreasing disease activity score and severity of cirrhosis in patients with liver cirrhosis as compared to placebo group	[120]
		Chronic alcoholic patients	Randomized double-blind placebo control trial (48)	One group received curcumin-galactomannoside complex 500 mg/day, and another group received placebo drug per day	8 weeks	Curcumin-galactomannoside complex group showed significant decrease in liver function markers such as transaminase and GGT increase in endogenous antioxidant (GSH, SOD, GPx) and decrease in inflammatory markers (IL-6 and CRP) level as compared to placebo group	[159]

Table 3 (continued)

S. no	Name of hepatoprotective lead	Condition	Study design (*n*)	Treatment (*n*)	Duration	Outcome with hepatoprotective leads	References
		Type 2 diabetic mellitus (T2DM) patients and measure glycemic, hepatic, and inflammatory biomarker measure	Randomized double-blind placebo control trial (100)	Test group received standard treatment, dietary advice plus curcuminoids 500 mg/day coadministered with piperine 5 mg/day, and control group received the standard treatment, dietary advice plus placebo drug	3 months	Intervention group showed significant reduction in serum level of glucose, HbA1c, and low serum level of ALT and AST as compared to the placebo group. The study concluded that curcuminoid mixed with piperine when coadministered with diabetic medicine shows improved hepatoprotective and glycemic control in T_2DM patients	[124]
		Patients with non-alcoholic fatty liver disease (NAFLD)	Double-blind randomized clinical trial (46; 21 males and 25 females)	Intervention group received six turmeric capsules containing 500 mg in each, and control group received placebo drug daily	12 weeks	Turmeric consumption decreased the serum level of glucose, insulin, HOMA-IR, and leptin as compared to the placebo group. This may be useful in control of NAFLD complications	[116]
		Patients diagnosed with non-alcoholic fatty liver disease (NAFLD)	Randomized double-blind placebo control trial (102)	Intervention group received 1000 mg/day curcumin in 2 divided dose ($n=50$), and control group received the placebo drug ($n=52$). Both groups received the dietary and lifestyle advice before the start of clinical trial	8 weeks	Curcumin supplement group showed reduction of body mass index, waist circumference, decrease level of AST and ALT as compared to the placebo drug treatment group. This indicated that intervention improve the liver fat and normalize liver biomarker level in patients with NAFLD	[125]
		Non-alcoholic fatty liver disease (NAFLD)	Randomized double-blind placebo control trial (80)	Intervention group received amorphous curcumin powder 500 mg/day (equivalent to 70 mg/day curcumin), and control group received the placebo drug	8 weeks	Curcumin-treated group showed reduction of liver fat, body mass index, total cholesterol, low-density lipoprotein, triglyceride, AST, ALT, glucose, glycated hemoglobin as compared to the placebo drug-treated group. This indicated that curcumin amorphous powder improves liver of patients with NAFLD	[137]

Table 3 (continued)

S. no	Name of hepatoprotective lead	Condition	Study design (*n*)	Treatment (*n*)	Duration	Outcome with hepatoprotective leads	References
6	Berberine	Non-alcoholic fatty liver disease (NAFLD)	Randomized parallel controlled open-label clinical trial (184)	Lifestyle intervention group or placebo group ($n=62$) (60) is lifestyle intervention plus pioglitazone 15 mg qd ($n=60$), lifestyle intervention plus 0.5 g berberine t.i.d. ($n=62$)	16 weeks	As compared to the placebo and pioglitazone treatment group, intervention group showed significant reduction in serum lipid profile, body weight, HOMA-IR which help to ameliorate NAFLD and related metabolic disorder by directly regulating the hepatic lipid metabolism	[185]

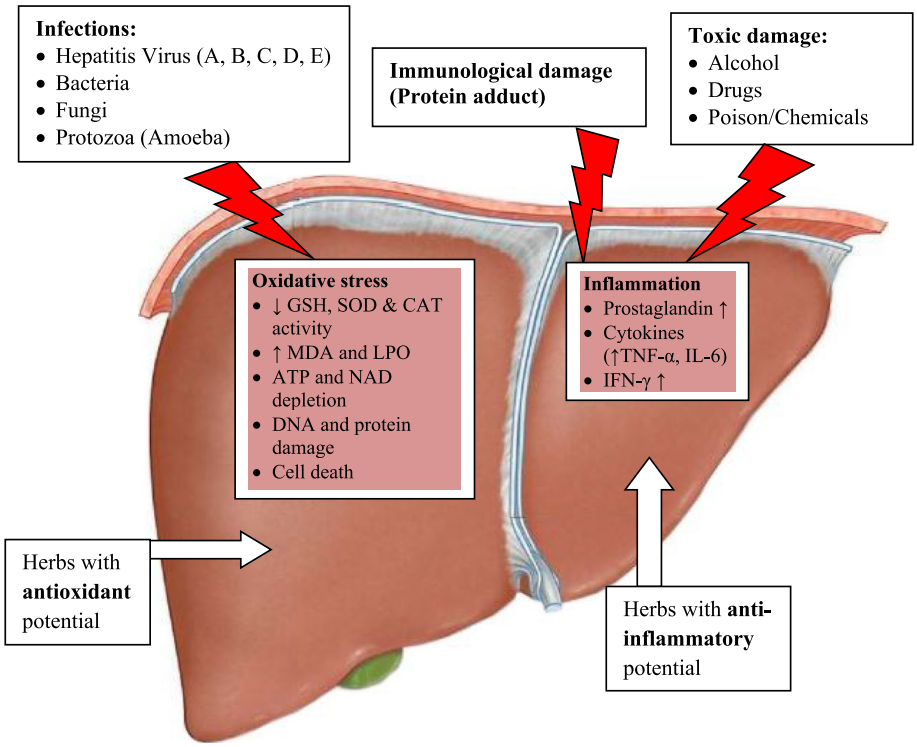

Fig. 2 The mechanism by which herbal remedies protect against liver injury from different toxins and injurious stimuli [3]

which further assist in clinical testing for discovery of hepatoprotective leads. Due to lack of scientific-based pharmacological data, most of the herbal-based formulations cannot be recommended for the treatment of liver diseases [155].

This review gives the clear idea that herbal-based therapy could play a significant role against various liver disorder and disease condition occurring in human. Several herbs from natural sources and plant extracts have measurable hepatoprotective effect in several experimental animal models. Secondary metabolites such as alkaloid, flavonoids, phenolic, tannins, lignins, and resin-based compound are the major active phytocontituents for hepatoprotective effect [9]. The significant portion of the study depicts that extracts of different parts of medicinal plants have potentials to subside hepatic disorder Baral et al. [14]. In addition, this study highlighted scientific evidence and mechanism of hepatoprotection by crude extracts of medicinal plants. The most probable mechanism of action of several plant extracts is through the scavenging effect of harmful free radical generated during infirmities. Several experiments in vivo study showed that phenolic and flavonoid constituents of plant extracts help to upsurge the decrease proportion of blood glutathione, to enhance protein secretion, to minimize lipid peroxidation and to enhance free radical scavenging properties. Furthermore, phytoconstituents lower the hepatic enzymes such as AST, ALT, ALP and arginase and enhance the level of total bilirubin in blood plasma,upsurge antioxidative enzymes such as SOD, GPx, CAT and GST,and lower MDA level [41]. In a nutshell, it could be highlighted that herbal drug possesses significant hepatoprotective properties which could be proved by various preclinical and clinical studies.

Conclusion and future perspective

To recapitulate, numerous research in last few decades have clearly established that herbal lead compounds have significant hepatic injury; the major mechanism for protection of liver cells is eradication of free radicals, reducing oxidative stress and decreasing the proinflammatory cytokine mediators in the body. This ample review will be helpful to begin a new way and to explore additional clinical application of bioactive constituents as liver-protective agents. Significant natural availability and economic and minimum side effect as compared to allopathic medicine have encouraged utilization of bioactive compounds for the treatment of liver disease. Followingly, subsequent preclinical investigations have been directed, and such studies have already proved several remedies as

hepatoprotective agents, and further clinical trials are on demand for authentication. Several in silico studies and compounds from molecular networking have also suggested active phytoconstituents from natural sources as possible hepatoprotective agents. In addition, it is a proper time to uncover the possibility of hepatoprotection potential of new bioactive compounds for human health either through in silico methods such as molecular docking, machine learning, and deep learning or through biophysical and biochemical experimental techniques. Finally, in this review, an attempt has been made to compile the reported hepatoprotective plants and their active phytoconstituents around the globe. These phytoconstituents are claimed to have proved benefit for health professionals, scientists, and scholars working in the field of pharmacology, therapeutics, and pharmacognosy to develop evidence-based alternative medicines to cure different kinds of liver diseases for mankind. This study paved a marvelous path for further scientific validation, research, and investigation to understand the therapeutic potential of these natural lead constituents to discover novel hepatoprotective therapeutics from natural source.

The point is not that natural products will solve all problems. It is that a lot of problems are not being solved because natural products are not being examined.
S. J. Gould, Chem. Eng. News 13 October 2003, p 103

Abbreviations

Akt	Enzyme type of serine/threonine protein kinase
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AMPK	AMP-activated protein kinase
ARE	Antioxidant-responsive element
AST	Aspartate aminotransferase
Bcl-xL	B-cell lymphoma-extra large
CAT	Catalase
Cdk4	Cyclin-dependent kinase 4
COX-2	Cycloxygenase-2
CYP2E1	Cytochrome P450 2E1
ERK2	Extracellular signal-regulated kinase
EGFR	Epithelial growth factor receptor
GGT	Gamma-glutamyl transferase
GPx	Glutathione peroxidase
GR	Glutathione reductase
GSH	Glutathione
GST-1	Glutathione S-transferase
GSTO1	Glutathione transferase omega 1
HAT	Histone acetyltransferase
HDAC2	Histone deacetylase-2
HCV	Hepatitis C virus
HFD	High-fat diet
HMBG1	High mobility group box 1
HO-1	Heme oxygenase-1
HSCs	Hepatic stellate cells (HSCs)
IFN	Interferon
IL-6	Interleukin-6
IL-1β	Interleukin-1β
JNK	Jun N-terminal kinase
LDH	Lactate dehydrogenase
LPO	Lipid peroxidation
LPS/D-GalN	Lipopolysaccharide/D-galactosamine
MAPK	Mitogen-activated protein kinase
MDA	Malonaldehyde
MMP	Mission mode project
NF-κB	Nuclear factor kappa B
Nrf2	Nuclear factor erythroid 2-related factor 2
NQO1	NADPH quinone oxidoreductase-1
PPARγ	Peroxisome proliferator-activated receptor gamma
PGC-1α	Peroxisome proliferator-activated receptor-gamma coactivator 1-alpha
PDGF	Platelet-derived growth factor
Prx	Paired-related homeobox
SIRT1	Sirtuin 1
SOD	Superoxide dismutase
STAT3	Signal transducer and activator of transcription 3
TB	Total bilirubin
TGF-β1	Transforming growth factor beta
TLR	Toll-like receptor
VEGF	Vascular endothelial growth factor

Authors' contributions
BP, RB, and SP wrote and arranged the paper. RB, SP, AK, and BP edited the text and arranged the paper. BP and SP provided supervision and direction. All authors critically read and approved the final manuscript.

Availability of data and materials
The data used to support the findings of this study are available from the corresponding author upon request.

Declarations

Competing interests
The authors declare that they have no competing interests.

Received: 14 November 2022 Accepted: 14 March 2023
Published online: 29 March 2023

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