



# Hepatoprotective potential of selected medicinally important herbs: evidence from ethnomedicinal, toxicological and pharmacological evaluations

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**Abstract** Medicinal herbs are nature's gift to humanity, contributing crucially to the preservation, maintenance and improvement of our health. In order to explore the hepatoprotective potential of prevalent medicinal plants, nine species were selected from different genera based on their ethnomedicinal records in treating different liver-related pathological conditions in South Asia. Besides, the available information was critically analyzed to gain new insights and directions for future investigations towards establishing such natural products as potent hepatoprotective agents or dietary supplements. The hepatoprotective activities of the species have been investigated in a wide variety of in vivo experimental models including

carbon tetrachloride-, paracetamol-, iron-, mercuric chloride-, thioacetamide-, cyclophosphamide-,  $\beta$ -D-galactosamine-, cumene hydroperoxide-,  $\alpha$ -naphthylisothiocyanate-, physical stress- and alcohol-induced hepatotoxicity in rats and mice. All the plants were consistent in their ability to possess hepatoprotective properties. As well, three bioactive isolates namely, schaftoside, echinocystic acid, and eclalbasaponin II were found to have promising hepatoprotective potential. However, extensive comparative studies are warranted in future to establish the relative hepatoprotective potentials of the nine species under discussion. Preparation of poly-herbal formulations from these plants and identification of hepatoprotective phytoconstituents from these plants might open up new avenues in the development of therapeutic hepatoprotective agents.

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## Abbreviations

ACS	American Chemistry Society
ALP	Alkaline phosphatase
AAT	Alpha-1 antitrypsin
ALT	Alanine transaminase
AST	Aspartate transaminase
CYP450	Cytochromes P450
CAT	Catalase

FXR	Farnesoid × receptor
GSH	Reduced glutathione
GPx	Glutathione peroxidase
GST	Glutathione-S-transferase
HSCs	Hepatic stellate cells
HPLC	High-performance liquid chromatography
HepaRG	Hepatic stem cell line
HepG2	Human liver cancer cell line
HCV	Hepatitis C virus
ICR	Institute of Cancer Research
LD <sub>50</sub>	Lethal dose
LC–MS	Liquid chromatography–mass spectrometry
KM	Kunming
LPO	Lipid peroxidation
LDH	Lactate dehydrogenase
MS	Mass spectroscopy
MDA	Malondialdehyde
ROS	Reactive oxygen species
SOD	Superoxide dismutase
TG	Triglyceride
TBARS	Thiobarbituric acid reactive substances
TB	Tuberculosis
WHO	World Health Organization

## Introduction

Liver as the largest gland of the body, is significantly contributory to the maintenance and synchronization of vital physiological functions which eventually lead to the preservation of homeostasis (Haque et al. 2017; Khan et al. 2020). It acts as the major physiological site for almost all of these body's metabolic pathways including the distribution and storage of nutrients and energy, synthesis and regulation of hormones and enzymes, processing of xenobiotics, and neutralization of toxins and pathogens. The liver also serves as an integral component of the digestive system through providing different digestive enzymes at the specific sites as well as the bile juice in duodenum, thus aiding protein and lipid digestion (Kumar et al. 2011). Bile produced in liver is momentarily stored in the gall bladder which later releases it into the duodenum to

assist in lipid digestion. Bile salts, which make up majority of the biliary content, acts as detergent and facilitate the solubilization of highly hydrophobic materials including oils, fats, long chain fatty compounds and fat-soluble vitamins, into the highly hydrophilic and acidified digestive content. Moreover, through similar action, bile salts also enable the elimination of cholesterol and other fat-soluble harmful substances such as environmental toxins, carcinogens drugs, xenobiotics, and toxic metabolites (Trauner and Boyer 2003). Besides, majority of the prodrugs, those are given in their inactive forms for minimizing toxicity or enhancing bioavailability, require hepatic enzyme-mediated activation in order to exert their respective therapeutic action (Ortiz de Montellano 2013). Therefore, a healthy liver is crucial for maintaining homeostasis and optimum health. However, liver is susceptible to infection by hundreds of etiological events including microorganisms (hepatitis viruses, yellow fever viruses, cytomegalovirus, Epstein-Barr virus), metabolic problems (obesity related liver disease, hemochromatosis, Wilson's disease), alcohol, drugs, and chemicals (hepatotoxic substances) as well as different autoimmune diseases (Lavanchy 2009). According to WHO these manifestations contributes to the reduction of working capacities, shortening of life span, and limiting the quality of life, which eventually leads to a high mortality and morbidity rate (Lavanchy 2009; Lok et al. 2001; Waxman and Bulletin 2004). Moreover, oxidative stress has been demonstrated to play a significant role in the etiology and progression of many liver diseases. Oxidative stress signifies an imbalanced oxidative status of cells and tissues as imposed by an over-exposure to free radicals. Many hepatotoxic substances precipitate the formation of powerful free radicals leading to an increased oxidative burden which in turn, may potentially translate into hepatic damage, cirrhosis and hepatitis (Valko et al. 2007; Vrba and Modriansky 2002).

Since ancient days, plant-derived natural products have been used extensively for their medicinal properties, as well as in the form of culinary ingredients and nutritional supplements. Owing to their vast spectrum of dietary values including vitamins,

minerals, phenolics, antioxidant and enzymes, plant materials have asserted significant contributions to the medicinal, nutraceutical, and food industries. Eventually, numerous research studies into the hepatoprotective properties have been conducted from different medicinal plants and herbal preparations, for instance, *Colocasia esculenta* (Chinonyelum et al. 2015a), *Spirulina maxima* (Alvari et al. 2012), *Eclipta alba* (Bedi et al. 2016), *Boehmeria nivea* (Singh et al. 2010a), *Cichorium intybus* (Sultana et al. 1995), *Picrorhiza kurroa* (Thyagarajan et al. 2002), *Mangifera indica* (Hiraganahalli et al. 2012), *Litchi chinensis* (Sagar et al. 2014). Moreover, recent studies have reported that polyherbal preparation from the aqueous extracts of different plants including *Berberis vulgaris* L., *Cucumis sativus* L., *Portulaca oleracea* L., *Rheum palmatum* L. showed promising anti-hepatotoxic effects while used as dietary supplement (Sarhadynejad et al. 2016). Another study reported that a polyherbal hepatoprotective formulation (PHF) containing spray-dried aqueous extracts of *Andrographis paniculata* Nees., *Phyllanthus niruri* Linn., *Phyllanthus emblica* Linn., provided promising hepato-protection owing to the combined activities of the plants (Tatiya et al. 2012). Additionally, approximately 170 phytoconstituents isolated from 110 medicinal plants distributed among 55 families have been reported to exhibit hepatoprotective activities. Nearly 600 commercial herbal supplements are also being marketed worldwide with reported hepatoprotective efficacy. In South Asia, more than 93 medicinal herbs are used in various combinations for the preparation of forty polyherbal formulations. Nevertheless, just a limited number of hepatoprotective herbs as well as their dietary formulations are being endorsed into the conventional medicines due to their safety and efficacy profile (Girish and Pradhan 2017; Stickel and Schuppan 2007).

In this comprehensive review, nine ethnomedicinally significant plant species named *Colocasia esculenta*, *Alstonia scholaris*, *Mangifera indica*, *Hypericum japonicum*, *Kalanchoe pinnata*, *Leucas aspera*, *Litchi chinensis*, *Eclipta prostrata* and *Hybanthus enneaspermus*, which are being widely used for

their hepatoprotective properties, were reviewed covering their distribution, ethnomedicinal significance, hepatoprotective phytoconstituents, and therapeutic potentials in alleviating oxidative and hepatic stress. Although a significantly larger number of plant species have been attributed with hepatoprotective potentials, the selection was established through considerations of their formulation into advanced formulations and subsequent integration into modern medicinal systems. The collected information were also critically reviewed in order to present insights and recommendations for future studies with the ultimate aim of establishing these plants as possible sources of new hepatoprotective herbal preparations.

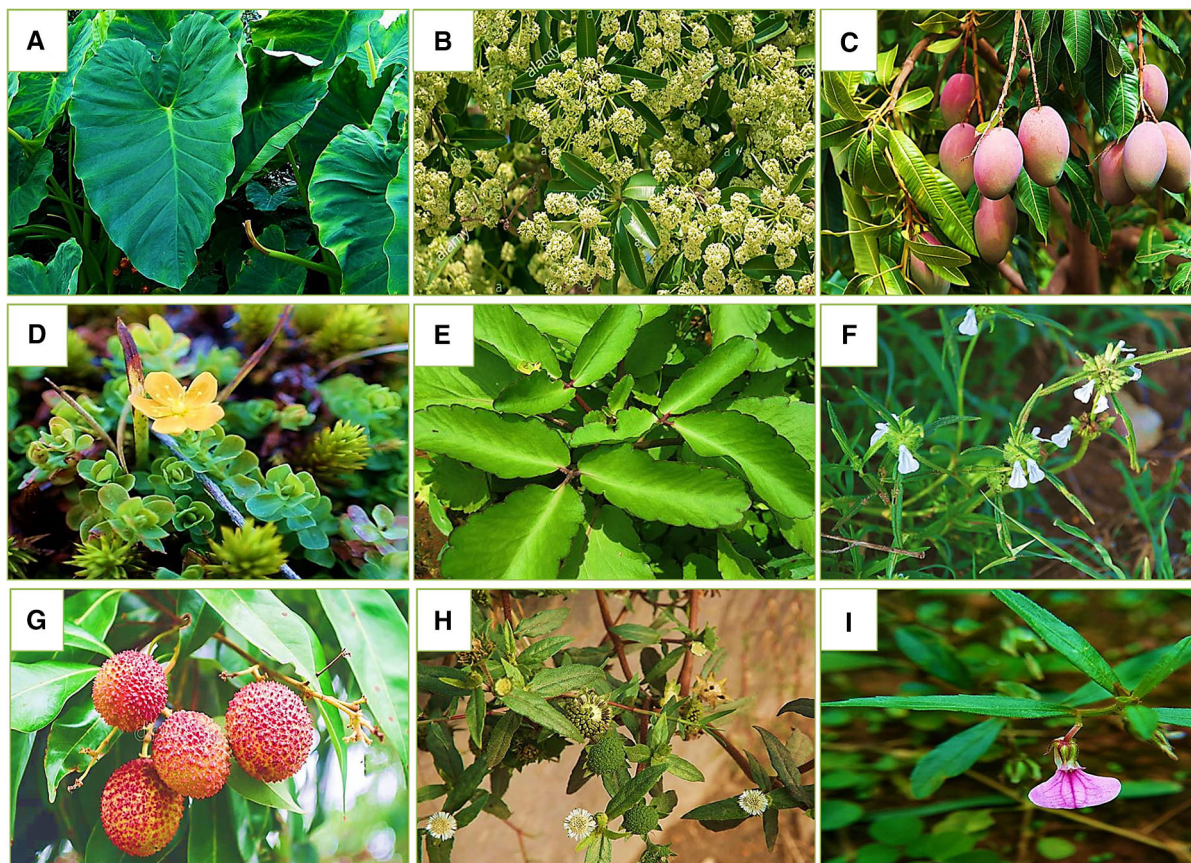
## Methodology

Electronic databases viz. Google Scholar, PubMed, Scopus, ScienceDirect, ACS publications, Wiley online library and SpringerLink, were explored extensively using keywords including “South Asian medicinal plants” “*Colocasia esculenta*”, “*Alstonia scholaris*”, “*Mangifera indica*”, “*Hypericum japonicum*”, “*Kalanchoe pinnata*”, “*Leucas aspera*”, “*Litchi chinensis*”, “*Eclipta prostrata*”, “*Hybanthus enneaspermus*”, “traditional uses”, “ethnomedicinal uses”, “bioactive metabolites”, “hepatoprotective activity” and “toxicological study”. Eventually, relevant literatures published prior to October 2020 were collected, curated and critically evaluated in order to extract necessary information. The recognized accepted plant names and their respective synonyms were validated according to The Plant List (2013). The chemical structures of different phytochemicals were illustrated in accordance with PubChem with the help of ChemDraw Ultra 15.0.

## Distribution and ethnomedicinal applications

Throughout the history of the Indian subcontinent, records of various ethnomedicinal practices have been abundant which have managed to remain relevant and





**Fig. 1** Major South Asian medicinal plants with hepatoprotective effects; (A) *Colocasia esculenta*, (B) *Alstonia scholaris*, (C) *Mangifera indica*, (D) *Hypericum japonicum*, (E) *Kalanchoe pinnata*, (F) *Leucas aspera*, (G) *Litchi chinensis*, (H) *Eclipta prostrata* and (I) *Hybanthus enneaspermus*

effective to this day. Different traditional medicinal systems including the Ayurveda, Unani, Homeopathy and Shiddah have attained significant institutional recognitions and are contributing to the healthcare system to an outstanding extent comparable to the modern system of medicine. Moreover, around 40–50 million people from the rural areas of the subcontinent are still primarily dependent on these systems for their healthcare (Mazid et al. 2012). This review has mainly focused on medicinal plants (Fig. 1) which have experienced extensive utilizations under different ethnomedicinal systems of South Asia, especially for their hepatoprotective potentials. However, a majority of them are distributed worldwide and are recognized for their contribution to the regional medicinal systems as well as the culinary cultures. Therefore, the relevant general information of these plants

including their accepted scientific names, recognized synonyms, complete taxonomical classifications, geographical distribution patterns and common local names (mainly within the subcontinent) have been summarized in Table 1. Moreover, based on extensive literature review on different parts (leaves, stem, bark, rhizome, roots, flowers and fruits) as well as the phytochemistry of the nine species under discussion, their ethnomedicinal significance have been enumerated in Table 2.

### Phytochemistry

With the blessings of urbanization and modern technology, the crude extracts as employed in the traditional medicinal systems are now being harnessed

**Table 1** General information and taxonomical distribution of the selected species

Species	Accepted name	Synonyms	Taxonomy	Local/common names	Geographical distribution	References
<i>Colocasia esculenta</i>	<i>Colocasia esculenta</i> (L.) Schott	<i>Colocasia esculenta</i> f. <i>ebimo</i> Makino, <i>Colocasia esculenta</i> f. <i>rotundifolia</i> Makino	Kingdom: Plantae Phylum: Tracheophyta Class: Liliopsida Order: Alismatales Family: Araceae Genus: <i>Colocasia</i> Species: <i>Colocasia esculenta</i>	Kachu, Alupam, Dasheen, Ashukachu, Taro	Southeast Asia, Srilanka, Bangladesh, India, China, Burma, Nigeria, Indonesia, West Indies, Africa, Philippines and South America	(Lee 1999; Wang and Higa 1983)
<i>Alstonia scholaris</i>	<i>Alstonia scholaris</i> (L.) R. Br	<i>Echites scholaris</i> L., <i>Alstonia kurzii</i> Hook.f	Kingdom: Plantae Phylum: Tracheophyta Class: Magnoliopsida Order: Gentianales Family: Apocynaceae Genus: <i>Alstonia</i> Species: <i>Alstonia scholaris</i>	Satiani, Chattin, Chatium, Dita Bark, Chitvan, Saptaparna,	South Asia, India, Srilanka, Bangladesh, Western Himalayas, Western Ghats and Southern region	(Baliga 2012; Meena et al. 2011)
<i>Mangifera indica</i>	<i>Mangifera indica</i> L.	<i>Mangifera austroyunnanensis</i> Hu, <i>Mangifera amba</i> Forsk	Kingdom: Plantae Phylum: Tracheophyta Class: Magnoliopsida Order: Sapindales Family: Anacardiaceae Genus: <i>Mangifera</i> Species: <i>Mangifera indica</i>	Mango tree, Cuckoo's joy, Mango, Aam, Aama	Bangladesh, Malaysia, Philippines, Thailand, India	(Guha et al. 2020)
<i>Hypericum japonicum</i>	<i>Hypericum japonicum</i> Thunb	<i>Hypericum japonicum</i> var. <i>australe</i> R. Keller, <i>Hypericum japonicum</i> var. <i>kainantense</i> Masam	Kingdom: Plantae Phylum: Tracheophyta Class: Equisetopsida Order: Malpighiales Family: Hypericaceae Genus: <i>Hypericum</i> Species: <i>Hypericum japonicum</i>	Swamp hypericum, Sonaphuli	India, China, Bangladesh, Japan, South Korea, Thailand, Nepal, Vietnam and Philippines	(Liu et al. 2014b; Samaga and Rai 2016b)
<i>Kalanchoe pinnata</i>	<i>Bryophyllum pinnatum</i> (Lam.) Oken	<i>Crassula pinnata</i> (Lam.) L.f., <i>Bryophyllum calycinum</i> Salisb	Kingdom: Plantae Phylum: Tracheophyta Class: Magnoliopsida Order: Saxifragales Family: Crassulaceae Genus: <i>Kalanchoe</i> Species: <i>Kalanchoe pinnata</i>	Kop Pata, Amar Poi, Leaf of Life, Air Plant, koppata	Bangladesh, India, Africa, Australia and America, Nigeria	(Pattewar 2012; Phatak and Hendre 2014; Quazi Majaz et al. 2011)

continued

Species	Accepted name	Synonyms	Taxonomy	Local/common names	Geographical distribution	References
<i>Leucas aspera</i>	<i>Leucas aspera</i> (Willd.) Link	<i>Leucas aspera</i> var. <i>wightiana</i> (Wall. ex Benth.) Benth., <i>Leucas plukenetii</i> (Roth) Spreng	Kingdom: Plantae Phylum: Tracheophyta Class: Magnoliopsida Order: Lamiales Family: Lamiaceae Genus: <i>Leucas</i> Species: <i>Leucas aspera</i>	Ghal Ghase, Thumba, Chota Halkusa, Dronapushpi	Bangladesh, India, Philippines	(Rahman et al. 2014a, b)
<i>Litchi chinensis</i>	<i>Litchi chinensis</i> Sonn	<i>Litchi chinensis</i> var. <i>euspontanea</i> H.H. Hsue	Kingdom: Plantae Phylum: Tracheophyta Class: Magnoliopsida Order: Sapindales Family: Sapindaceae Genus: <i>Litchi</i> Species: <i>Litchi chinensis</i>	Lichi, Litchi, Litsu	China and Vietnam, India, Bangladesh, Indonesia, Nepal, South Africa, Thailand	(Soni and Agrawal 2017)
<i>Eclipta prostrata</i>	<i>Eclipta prostrata</i> (L.) L	<i>Eclipta prostrata</i> f. <i>aureoreticulata</i> Y.T.Chang, <i>Eclipta prostrata</i> var. <i>undulata</i> (Willd.) DC	Kingdom: Plantae Phylum: Tracheophyta Class: Magnoliopsida Order: Asterales Family: Asteraceae Genus: <i>Eclipta</i> Species: <i>Eclipta prostrata</i>	Keshuti, Kesharaja, Madhukar, False daisy, Babri	Asia, Africa, Australia, India, Arabia, Sri Lanka, Philippines, Indochina, Taiwan	
<i>Hybanthus enneaspermus</i>	<i>Hybanthus enneaspermus</i> (L.) F.Muell	<i>Hybanthus enneaspermus</i> f. <i>angustifolius</i> Domin <i>Hybanthus enneaspermus</i> var. <i>latifolius</i> (De Wild.) Engl	Kingdom: Plantae Phylum: Tracheophyta Class: Equisetopsida Order: Malpighiales Family: Violaceae Genus: <i>Hybanthus</i> Species: <i>Hybanthus enneaspermus</i>	Munbora, Spade Flower, Rathnapurusha, Ratan Purush	Sri Lanka, tropical Asia, Africa and Australia	(Rajsekhar et al. 2016)

for exact bioactive molecules contributory to their respective bioactivities. The secondary metabolite pool of the plants not only act as the principal source of these bioactive molecules, but also provide humankind with a continuous stream of significant structural diversity to work with (Saxena et al. 2013). Such molecules, in turn have illustrated significant contribution either directly as the drug molecule or indirectly as the lead compound, in the treatment of a

wide variety of diseases. Furthermore, specific classes of compounds have been shown to be consistent in exhibiting specific types of pharmacological potentials viz. hepatoprotective activity of phenolics, flavonoids and tannins (Aneja et al. 2013; Rehman et al. 2015), anti-inflammatory property of flavonoids (Olaokun et al. 2017), antioxidative potential of polyphenols (Zhang et al. 2015), and antiproliferative properties of polyphenols and flavonoids (Saxena et al.

**Table 2** Ethnomedicinal uses of the selected medicinal plants

Species	Plant parts used	Uses	Mode of use	References
<i>Colocasia esculenta</i>	Corms, leaves, stem, rhizomes	To treat peptic ulcer, chronic liver problems, inflammatory bowel disease, gall bladder disease, antidiabetic, hypoglycemic, hypolipidemic, anti-inflammatory, antioxidant, anti-cancer, antifungal and antibacterial activities	Snacks, baby foods	(Chinonyelum et al. 2015a; Rashmi et al. 2018; Wang and Higa 1983)
<i>Alstonia scholaris</i>	Bark, leaves, roots, whole plant	To treat diarrhea, malaria, diabetes, hemorrhoids, chronic skin ulcers, jaundice, asthma, chronic cough, liver disorders, toothache. Used as contraceptive. Helps post-delivery weakness. Useful against snake-bite		(Baliga 2012; Meena et al. 2011)
<i>Mangifera indica</i>	Bark, Fruits, Seeds, Leaves	To cure mouth infections in children, diarrhea, syphilis, iron deficiency, ringworm, leprosy, dysentery, skin abscesses and infections  To ailment diarrhea, gastrointestinal tract disorders, dysentery, sore throat, typhoid fever, and scurvy, for treating stroke, relief from pains and exhaustion, Sources of vit-A, Ant diabetic  Medication of indigestion, astringency, cholera, Gastrointestinal motility, hepatoprotective activity, anthelmintic and wounds	Drink as tea As fruits	(Doughari and Manzara 2008; Shah et al. 2010; Wauthoz et al. 2007)
<i>Hypericum japonicum</i>	Plant	Used to treat bacterial diseases, infectious hepatitis, acute and chronic hepatitis, gastrointestinal disorder, internal hemorrhage and tumor, dysentery, diarrhea, appendicitis, abscess of lung, aphtha, swelling and pain of eyes, venomous snake bite, wounds and bruises		(Liu et al. 2014a; Samaga and Rai 2016a, b; Zhang et al. 2007)
<i>Kalanchoe pinnata</i>	Leaves, barks	To prolong gestation in pregnant women, childbirth, treat ulcers, liver toxicity, skin diseases, to treat stones in the gall bladder and rheumatism, sedative, wound-healer, diuretic, anti-inflammatory and cough suppressant, edema of the legs  Leaves juice are used for headaches, psoriasis, toothaches, earaches, eye, infection, ulcer, rheumatism, wounds, boils, burns, and insect bites  As analgesic and carminative, for curing diarrhea and vomiting	Infusion	(Biswas et al. 2011; Enjamoori et al. 2019; Quazi Majaz et al. 2011; Rajsekhar et al. 2016; Jaiswal et al. 2014)

**Table 2** continued

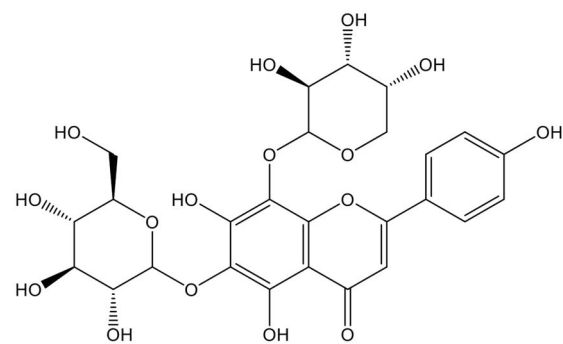
Species	Plant parts used	Uses	Mode of use	References
<i>Leucas aspera</i>	Plant, leaves, flowers	As antipyretic and insecticide, helminthic manifestation, treating jaundice, anorexia, dyspepsia, skin disease. Remedy for chronic skin eruptions, psoriasis and chronic rheumatism  To process insecticide, stimulant, diaphoretic, expectorant, and aperient	Juice externally (topical)	(Annapandian and Rajagopal 2017; Prajapati et al. 2010; Rahman et al. 2014a, b)
<i>Litchi chinensis</i> Sonn	Fruits, seeds, fruit skin, leaves	To cure hepatotoxicity, as antibacterial, hypoglycemic, to alleviate intestinal troubles and to relieve neuralgic pain and nerve inflammation, as anti-hyperlipidemic, antiplatelet, anticancer and antiviral, to cure orchitis, hernia, lumbago, ulcers, and for intestinal troubles, diarrhea, animal bites		(Ibrahim and Mohamed 2015a, b; Soni and Agrawal 2017)  (Ibrahim and Mohamed 2015a, b)
<i>Eclipta prostrata</i>	Fresh leaves, roots and stems, flowers	In the therapy of hemorrhagic diseases, respiratory disorders, skin diseases, microbial infections, heart disease, vitiligo, respiratory disorders, snake bite, hair loss, hepatic disorders, dizziness, renal diseases, antispasmodic whitening of hair, amoebiasis, analgesic, fungicidal	Oral administration of herb juice combined with other herb, rubbed to the site of bite	(Feng et al. 2019; Rajakumar et al. 2016)
<i>Hybanthus enneaspermus</i>	Roots, whole plant seeds	To treat diuretic, gonorrhea, cholera, urinary infections, syphilis and dysentery  Used as antidiabetic, aphrodisiac, tonic, anticonvulsant, nephroprotective, hepatoprotective, diuretic	Infusion, topically, orally	(Du et al. 2020; Patel et al. 2013)

2013). The plants under discussion have been illustrated with a wide variety of secondary metabolites covering major phytochemical classes including alkaloids, flavonoids, glycosides, oils and fats, gums, terpenoids, steroids and vitamins. The major bioactive metabolites isolated from these plants with prominent hepatoprotective potentials include schaftoside, echinocystic acid and eclalbasaponin II (Fig. 2). Moreover, thirteen polyphenolic and flavonoid molecules including catechin, epicatechin, kaempferol, quercetin, quercitrin, isoquercitrin, anthocyanins, procyanidin A2, quercetin-7-O-rhamnoside, pelargonidin-3-O-glucoside, quercetin 3-O-rutinoside-7-O- $\alpha$ -L-rhamnoside, gallic acid and hyperin have been chemically characterized as the major phytoconstituents of different extracts from these plants which have been found to exert noteworthy hepatoprotective activities.

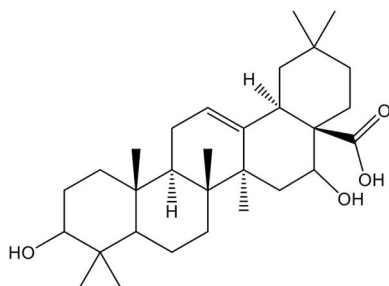
### Pharmacological properties

All the nine species selected in this review possess diverse pharmacological potentials including significant hepatoprotective properties with traditional uses. The plants both as whole and individual parts (leaves, stems, roots, rhizomes) have been investigated substantially through in-vitro assays and in-vivo experimentations in order to evaluate the extent of hepatoprotective potential, to ascertain the responsible phytochemicals and to enumerate their apparent pharmacology as well as respective mechanisms. Such information has been elaborated in the following sub-sections and summarized in Table 3.

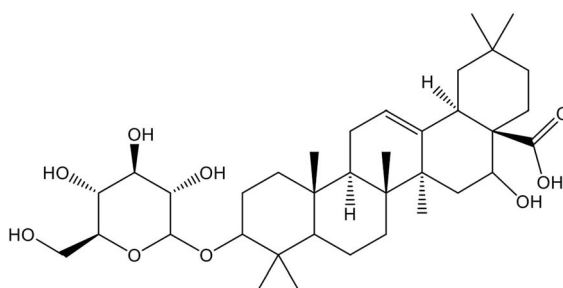




Schaftoside



Echinocystic acid



Eclalbasaponin II

**Fig. 2** Structure of the major hepatoprotective secondary metabolites

### *Colocasia esculenta* (L.) Schott

*C. esculenta* have been recognized as a traditional remedy owing to its hepatoprotective properties which have been further validated through pharmacological studies. The methanol extract of the aerial parts of *C. esculenta* have been reported to reverse iron-induced hepatotoxicity in Swiss albino mice to a significant

extent, indicating potent hepatoprotective property. The extract at a dose of 200 mg/kg body weight, suppressed iron-induced elevated serum concentrations of alanine transaminase (ALT) and aspartate transaminase (AST) by 41.7% and 50.6%, respectively, compared to the standard desirox (20 mg/kg body weight) which suppressed the enzymes by 47.7% and 52.5%, respectively. The extract also potentiated hepatic antioxidants viz. superoxide dismutase (SOD), catalase, glutathione-*S*-transferase (GST) and reduced glutathione (GSH) by 289.6%, 103.8%, 144.1% and 20.3%, respectively. Furthermore, the hepatoprotective potential of the extract was attributed to its capacity to neutralize iron through chelation and reduction. Interestingly, microscopic examination of mice liver sections stained with hematoxylin and eosin at 400 $\times$  zoom, showed a significant reduction in hepatocellular necrosis and increase in the number of hepatocyte cells. This, in turn, suggested the possible efficacy of the extract in reversing any metal overload-based hepatotoxicity which should be subjected to future investigation. However, such justification also challenges the hepatoprotective potential of the extract in case of any chemically induced hepatotoxicity (Saikia et al. 2018a, b). Recent in-vivo investigation of the aqueous extract of the leaves in thioacetamide-induced male Wistar rats demonstrated remarkable hepatoprotective activity. The extract at the dose of 250 mg/kg reversed the hepatotoxicity-associated elevation of ALT, AST and alkaline phosphatase (ALP) activities by 33.2%, 47.4% and 20.9%, respectively, compared to the standard silymarin exerting 60%, 64.8% and 21.8% suppressions of the enzymes, respectively, at a dose of 100 mg/kg body weight. The extract also maintained the regular level of serum albumin against hepatotoxic reduction of the same. (Chinonyelum et al. 2015a). Schaftoside available in *C. esculenta* has been demonstrated to attenuate paracetamol-induced hepatotoxicity in mice at doses of 40, 80 and 160 mg/kg. Intracellular investigation revealed that the compound was capable of activating the farnesoid X receptor (FXR) in hepatocytes which, in turn, potentiated the hepatic antioxidative system and diminished the generation of pro-inflammatory eicosanoids as well as the activation of nuclear factor kappa B (NF- $\kappa$ B) signaling pathway (Guo et al. 2010; Liu et al. 2020a, b). The leaf juice of the plant rich in

**Table 3** Hepatoprotective potentials of the selected medicinal plants

Species	Extracts/fractions/compounds	Screening model/hepatotoxic induced substances	Types of study (in vivo/ in vitro?)	Doses	Key findings/Mode of action or Biochemical and Histopathological Parameters studied	References
<i>Colocasia esculenta</i>	Methanol extract of aerial parts	Iron	In vivo (Swiss albino mice)	50, 100 and 200 mg/kg	↓ Plasma ALT and AST ↑ Hepatic SOD, CAT, GST and GSH	(Saikia et al. 2018a, b)
	Schaftoside	Paracetamol	In vivo (Male rats)	40, 80 and 160 mg/kg	↑ FXR ↓ Pro-inflammatory eicosanoids, nuclear factor kappa B (NF-κB) activation, hepatic inflammation	(Liu et al. 2020a, b)
<i>Astonia scholaris</i>	Aqueous extract of leaves	Thioacetamide	In vivo (Male Wistar rats)	250 and 500 mg/kg	↓ Plasma AST, ALT, ALP and albumin	(Chinonyelum et al. 2015b)
	Leaf juice (Anthocyanins)	Paracetamol and carbon tetrachloride	In vitro (Liver slice method)	5 and 10 µl/ml	↓ Plasma ALT and AST	(Patil et al. 2011)
	Methanol extract of stem	Carbon tetrachloride, β-D-galactosamine and paracetamol	In vivo (male Wistar rats)	200, 300 and 600 mg/kg	↓ Plasma ALT and AST	(Lin et al. 1996a, b, c)
	Methanol extract of stem barks	Carbon tetrachloride	In vivo (Swiss albino mice)	200 mg/kg	↓ Plasma ALT, AST, ALP and total bilirubin	(Kumar et al. 2012b)
<i>Mangifera indica</i>	Ethanol extract of fruits	Carbon tetrachloride	In vivo (albino rats)	150 and 300 mg/kg	↓ Plasma ALT, AST, TG	(Shankar et al. 2012)
	Aqueous extract of fruits	Cumene hydroperoxide	In vivo (Male Sprague-Dawley rats)	20, 50 and 100 µg/ml	↓ ROS generation, hepatocyte lysis, lipid peroxidation and glutathione depletion	(Pourahmad et al. 2010)
	Ethanol and aqueous extracts of stem barks	Paracetamol	In vivo (male Wistar albino rats)	200 mg/kg	↓ Plasma ALT, AST, ALP and albumin ↑ Hepatic SOD, CAT and GSH	(Omotayo et al. 2015)
	Acetone extract of fruit pulp	Carbon tetrachloride	In vivo (male Wistar albino rats)	250 and 500 mg/kg	↑ Catalase ↓ Lipid peroxidation	(Singh et al. 2010b)
	Aqueous extract of stem barks	Carbopn tetrachloride in olive oil	In vivo (male Wistar rats)	250 and 500 mg/kg	↓ Plasma ALT, AST, ALP and total bilirubin ↑ Hepatic SOD, CAT, GSH and MDA	(Adewusi and Afolayan 2010)
	Methanol and ethanol extract of leaves	Mercuric chloride	In vivo (male Swiss albino mice)	25 and 50 mg/kg	↓ Plasma ALT and AST ↑ Hepatic SOD, CAT, GST & GPx	(Adewusi and Afolayan 2010; Karuppanan et al. 2014)
	Polysaccharide extract from fruit pulp	Cyclophosphamide	In vivo (male albino rats)	500 and 1000 mg/kg	↓ Plasma ALT and AST ↑ Hepatic SOD, GST, GSH and MDA	(Fahmy et al. 2016; Vargas-Mendoza et al. 2014)

Table 3 continued

Species	Extracts/ fractions/compounds	Screening model/ hepatotoxic induced substances	Types of study (in vivo/ in vitro?)	Doses	Key findings/Mode of action or Biochemical and Histopathological Parameters studied	References
<i>Hypericum japonicum</i>	Total aqueous extract and aqueous fraction	Carbon tetrachloride and $\alpha$ -naphthyl-isothiocyanate	In vivo (Kunming mice)	500, 1500 and 4500 mg/kg	↓ Plasma ALT and AST	(Wang et al. 2008)
	Ethanol and ethyl acetate extract of whole plant	D-aminogalactose	In vivo	200, 600 and 1200 mg/kg	↓ Plasma ALT and AST	(Su et al. 2016)
	Total flavonoid extract of whole plant	Carbon tetrachloride	In vivo	20 mg/kg	↑ SOD, GSH and MDA	(Liu et al. 2014b; Zhang et al. 2012)
<i>Kalanchoe pinnata</i>	Fresh juice and ethanol extract of leaves	Carbon tetrachloride	In vitro	100 $\mu$ L	↓ Plasma ALT and AST	(Adewusi and Afolayan 2010; Yadav and Dixit 2003)
	Aqueous extract of whole plant	D-galactosamine	In vivo (female Wistar albino rats)	200 mg/kg	↓ Plasma ALT, AST and total bilirubin	(Banu et al. 2012)
	Methanol extract of whole plant	Carbon tetrachloride	In vivo (male Wistar rats)	100 and 200 mg/kg	↑ Hepatic SOD, CAT and GPx	(Latha et al. 2012)
	Hydroalcoholic (70:30) extract of leaves	Lead acetate	In vivo (male Wistar albino rats)	400 mg/kg	↓ Plasma ALT, AST and ALP	(Thenmozhi et al. 2013)
<i>Litchi chinensis Sonn</i>	Concentrate of the fresh juice of fruit pulps	Carbon tetrachloride	In vivo (Male Sprague-Dawley rats)	100 and 500 mg/kg	↓ Plasma ALT, AST and ALP	(Bhoopat et al. 2011)
	Phenolic extract of the fruit pulp	Physical stress	In vivo (male Kunming mice)	50, 100 and 200 mg/kg	↓ Plasma ALT and AST	(Su et al. 2016)
	Methanol extract of fruit pulp	Carbon tetrachloride	In vivo (male ICR mice)	20, 100 and 200 mg/kg	↑ Hepatic SOD, CAT, GSH and GPx	(Chen et al. 2017a, b)
<i>Eclipta prostrata</i>	Aqueous extract of whole plant	Carbon tetrachloride, Paracetamol and D-galactosamine	In vivo (male ICR mice)	300 mg/kg	↓ Plasma ALT and AST	(Lin et al. 1996a, b, c)
	Ethanol extract of leaves	Alcohol	In vivo (male Wistar albino rats)	200 mg/kg	↑ Hepatic SOD, CAT, GSH and GPx	(Arun and Balasubramanian 2011; Lin et al. 1996a, b, c)
	Echinocystic acid and eclalbasaponin II		Rat hepatic stellate T6 cell line		↓ Hepatic fibrosis	(Lee et al. 2008b; Rathore et al. 2014a, b)

Table 3 continued

Species	Extracts/fractions/compounds	Screening model/hepatotoxic induced substances	Types of study (in vivo/in vitro?)	Doses	Key findings/Mode of action or Biochemical and Histopathological Parameters studied	References
<i>Hybanthus enneaspermus</i>	Aqueous extract of leaves	Carbon tetrachloride	In vivo (male Wistar rats)	200 and 400 mg/kg	↓ Plasma ALT, AST, ALP and total bilirubin	(Vuda et al. 2012a, b)
	Ethanol extract of leaves	Paracetamol	In vivo (male albino mice)	100 and 200 mg/kg	↑ SOD, CAT, GST, GPx and GR ↓ Hepatic lipid peroxidation	(Bhanu et al. 2011)

anthocyanins was evaluated for its hepatoprotective potential through the administration of 5 µl/ml and 10 µl/ml of the extract in in-vitro liver slice method. The extract boosted the activities of ALT and AST in liver while restricting their availability in plasma (Patil et al. 2011). All of these experimental demonstrations are testament to the powerful hepatoprotective activity of the plant as projected by its ethnomedicinal claims. However, further in-depth and more focused investigations following the known hepatotoxicity-associated biochemical pathways, are warranted. Although many bioactive isolates have been reported from this plant, only one compound was characterized with hepatoprotective activity. Eventually, other phytochemicals from the plant should be investigated for their hepatoprotective potentials along with the characterization of their exact pharmacological and biochemical responses. Moreover, any clinical study is yet to be attempted for the assessment of its capacity to maintain optimum liver function in the presence and absence of hepatotoxic inducers. Therefore, this systematic review suggests pharmacokinetics study followed by clinical investigation of its potential for hepatoprotection.

#### *Alstonia scholaris* (L.) R. Br.

*A. scholaris* have been characterized with a diverse range of pharmacological activities including anti-inflammatory, anticoagulant, and antidepressant (Khan et al. 2020), anti-asthmatic (Shang et al. 2010), antibacterial and synergistic (Wang et al. 2016), anti-proliferative (Wang et al. 2017), antidiabetic and antihyperlipidemic (Arulmozhi et al. 2010), anti-arthritic and antioxidant activities (Arulmozhi et al. 2011). Apart from these, prominent hepatoprotective activity has also been demonstrated in favor of this plant in agreement with its ethnomedicinal claims. A study investigated hepatoprotective potential of the methanol extract of *A. scholaris* in carbon tetrachloride-, β-D-galactosamine- and paracetamol-induced hepatotoxic model in male Wistar rats. The extract at the dose of 300 mg/kg body weight suppressed the hepatotoxicity-induced enhancements of ALT (80.7%, 80.9% and 97.1%, respectively) and AST (77.4%, 33.0% and 82.5%, respectively) plasma levels in all three models. It was evident through histopathological analysis that *A. scholaris*-administered cells showed minimum inflammatory infiltration and

microvascular cell degeneration while also reducing cellular necrosis (Lin et al. 1996a, b, c). Another in-vivo study in carbon tetrachloride-induced Swiss albino mice further reinforced this claim as methanol extract of the stem barks (dose of 200 mg/kg body weight) reduced plasma concentrations of ALT, AST, ALP and bilirubin by 42.2%, 12.3%, 45.7% and 18.3%, respectively, compared to standard silymarin (25 mg/kg body weight) which exhibited 61.7%, 27.2%, 61.4% and 29.6% reductions, respectively. In the pathological examination, the extract-treated liver cells showed a low number of damaged hepatocytes and fatty degeneration (Kumar et al. 2012a). Similarly, the ethanol extract of the fruits of this plant at the dose of 300 mg/kg body weight was demonstrated to suppress plasma concentrations of ALT, AST, ALP and bilirubin in albino rats by margins of 32.6%, 26.1%, 65.5% and 50.8%, respectively (Shankar et al. 2012). Although the hepatoprotective activity of *A. scholaris* has been substantiated by few studies, any attempt on the identification of the responsible bioactive molecule is yet to be reported. Hence, extensive studies are still needed to assure its hepatoprotective potential in terms of individual phytochemicals. Furthermore, thorough clinical studies are also required to strengthen its traditional application and establish its stature as a suitable hepatoprotective agent.

#### *Mangifera indica* L.

From an ethnomedicinal perspective, *M. indica* is one of the most widely used plant used for its hepatoprotective properties in the rural areas of South Asian countries (Shah et al. 2010). Extracts of different parts of the plant including stem, leaves, aerial parts, fruits and pulps have been subjected to hepatoprotective investigation against the synthetic compound silymarin (Ediriweera et al. 2017). (Pourahmad et al. 2010) claimed that, the aqueous extract of the fruits was capable of reversing cumene hydroperoxide-induced oxidative stress-mediated hepatotoxicity in male Sprague–Dawley rats. Further biochemical characterization illustrated reduced rates of reactive oxygen species (ROS) generation, lipid peroxidation, hepatocyte lysis and intracellular glutathione depletion. Another in-vivo study investigated

the aqueous extract of the stem barks of *M. indica* for hepatoprotective potential at the doses of 125, 250 and 500 mg/kg body weight in male Wistar rats. The hepatoprotective properties were assessed both in pre-treatment and post-treatment models where the extract was administered before and after the administration of 30% carbon tetrachloride in olive oil, respectively. In pre-treatment model, the extract at the doses of 250 and 500 mg/kg body weight produced comparable effects as the standard ascorbic acid (10 mg/kg) as they prominently suppressed ALT (58.0%, 72.6% and 58.2%, respectively), AST (72.4%, 77.9% and 67.6%, respectively), ALP (62.1%, 57.0% and 37.2%, respectively) and total bilirubin (52.9%, 48.1% and 29.6%, respectively). The extract at both doses as well as the standard also elevated hepatic concentrations of SOD (110.9%, 148.5% and 37.1%, respectively), catalase (107.1%, 162.1% and 23.2%, respectively), GSH (149.6%, 260.8% and 42.4%, respectively) and diminished hepatic concentration of malondialdehyde (MDA) (71.1%, 89.5% and 78.9%, respectively) significantly. A similar trend was observed in the post-treatment model for both the plasma and hepatic markers (Adeneye et al. 2015). Another paracetamol-induced hepatotoxic study model in male Wistar albino rats demonstrated the hepatoprotective properties of both the ethanol and aqueous extract of the stem barks. Both the extracts at a dose of 200 mg/kg body weight reversed paracetamol-induced elevation of ALT, AST and ALP whereas the hepatic concentrations of antioxidants viz. SOD, catalase and GSH were remarkably improved (Omotayo et al. 2015). Similarly, both the methanol and ethanol extract of *M. indica* leaves (25 and 50 mg/kg body weight) were reported to suppress plasma ALT and AST and to cause hepatic enhancements of SOD, catalase, GST and glutathione peroxidase (GPx) in mercuric chloride-induced male Swiss albino mice, indicating prominent hepatoprotective capacities (Adewusi and Afolayan 2010; Karuppanan et al. 2014). An in-vivo carbon tetrachloride-induced hepatotoxic model in male Wistar albino rats demonstrated that the acetone extract of the fruit pulp of *M. indica* at the doses of 250 and 500 mg/kg body weight, was capable of elevating catalase activity and reducing the extent of lipid peroxidation, compared to the standard silymarin (25 mg/kg) (Singh et al. 2010b). The polysaccharide



content from the pulp of unripe fruits of *M. indica* was investigated for its potential anti-hepatotoxic activity against cyclophosphamide-induced liver damage in male albino rats. Compared to the standard silymarin (150 mg/kg body weight), the polysaccharide extract administered at doses of 500 and 1000 mg/kg body weight, significantly diminished plasma concentrations of ALT (40.4%, 44.7% and 47.5%, respectively) and AST (43.0%, 36.3% and 19.4%, respectively). Furthermore, the extract also enhanced hepatic levels of SOD, GST and GSH while diminishing hepatic MDA concentration. Liver tissue sections stained with hematoxylin and eosin were compared with control group tissues. The oral administration of MPS extract improved the hepatic architecture when compared to the control group, apparently indicating the regeneration of liver cells (Fahmy et al. 2016; Vargas-Mendoza et al. 2014). However, the study illustrated enhancement of plasma ALP both in the presence of the standard and the extracts which is quiet contradictory to positive hepatoprotective activity. Any hepatoprotective agent is ought to suppress the plasma ALP level parallel to plasma ALT and AST levels.

Although, several studies have been conducted on the activity of this plant, hepatoprotective properties have been characterized for different extracts only. Therefore, major hepatoprotective isolates need to be identified and elaborative studies need to be performed to find out the cellular mechanism on systemic level.

#### *Hypericum japonicum* Thunb.

*H. japonicum* is distributed throughout the Asia and some parts of Europe. The plant has an extensive history of being utilized for ethnomedicinal purposes. Phytochemical investigations into this plant have afforded a wide variety of bioactive molecules which have been further characterized with prominent pharmacological potentials through appropriate studies. Eventually, the hepatoprotective properties of the plant have also been traced to individual secondary metabolites (Liu et al. 2014a). The hepatoprotective effects of the total aqueous extract of *H. japonicum* and its different fractions were investigated against carbon tetrachloride-induced hepatitis and  $\alpha$ -naphthyl-isothiocyanate-induced cholestasis in Kunming (KM) mice. The study demonstrated that, the total aqueous extract as well as the aqueous fraction at doses of 0.5, 1.5 and 4.5 g/kg body weight suppressed

several serum markers in both models following a dose-dependent manner. In carbon tetrachloride-induced hepatotoxicity, the standard biphenyldicarboxylate (200 mg/kg body weight) reduced the plasma concentration of ALT and AST by 69.2% and 29.7%, respectively. Comparably, both the aqueous extract and fraction at the dose of 4.5 g/kg, reduced plasma ALT by 63.0%, 66.7%, respectively and plasma AST by 53.8%, 51.4%, respectively. Similarly, in the  $\alpha$ -naphthyl-isothiocyanate-induced cholestatic model, standard Yin-Zhi-Huang oral solution at the dose of 15 ml/kg diminished total bilirubin and ALT levels in plasma by 34.4% and 27.8%, respectively, whereas the aqueous extract and fraction (4.5 g/kg) suppressed total bilirubin by 60.2%, 62.6%, respectively, and plasma ALT by 54.0%, 56.0% respectively (Wang et al. 2008). The ethanol and ethyl acetate extracts of the plant were also demonstrated to suppress D-aminogalactose-induced elevation of ALT and AST at the doses of 0.2, 0.6 and 1.8 g/kg body weight (Su et al. 2016). The total flavonoid extract of the plant was investigated for its hepatoprotective potential against carbon tetrachloride-induced hepatic injury where it potentiated SOD, GSH and MDA in hepatic tissue. Chromatographic analysis into the extract had revealed quercetin, kaempferol, quercitrin, isoquercitrin, hyperin and quercetin-7-O-rhamnoside as the major flavonoid constituents (Liu et al. 2014a; Wang et al. 2009). On a separate study, quercetin and its glycoside rutin (quercetin-rutinoside) were subjected to an in-vivo study involving male BALB/cN mice. Both the compounds were demonstrated to reverse carbon-tetrachloride-induced elevation of serum ALT and AST as well as the hepatotoxic reduction of SOD and GSH levels. Rutin at the dose of 150 mg/kg body weight suppressed serum ALT and AST levels by 87.3% and 93.1%, respectively, and elevated hepatic SOD and GSH levels by 67.9% and 56.8%, respectively. On the other hand, quercetin at the dose of 50 mg/kg body weight enhanced hepatic SOD and GSH levels by 76.5% and 70.3%, respectively, and diminished serum ALT and AST by 25.3% and 50.3%, respectively (Domitrović et al. 2012). Since pharmacokinetic profiling of these phytochemicals has already been established (Wang et al. 2009), clinical studies in the future is definitely warranted in order to evaluate their therapeutic potential.

*Kalanchoe pinnata* (Lam.) Pers.

The hepatoprotective potentials of the fresh juice and the ethanol extract of *K. pinnata* leaves were investigated against carbon tetrachloride-induced hepatotoxicity in-vitro and in-vivo. In-vitro assay involving rat hepatocyte culture revealed more prominent hepatoprotective activity in favor of the fresh juice concentrate (10  $\mu$ L) than the ethanol extract (10  $\mu$ L) as they suppressed plasma ALT by 52.7%, 29.3%, respectively, and plasma AST by 34.7%, 22.8%, respectively. The similar pattern was reflected by the in-vivo experimentation in Wistar albino rats as both the samples (200 mg/kg body weight) suppressed serum concentrations of ALT (68.8%, 60.5%, respectively), AST (25.0%, 14.3%, respectively), ALP (37.7%, 23.8%, respectively) and total bilirubin (52.1%, 24.2%, respectively). Additionally, when subjected to histopathological analysis, extract-treated liver cells of rats intoxicated with carbon tetrachloride appeared to be slightly unclear as in normal hepatocytes. However, compared to the carbon tetrachloride damaged ones, the number of hepatocytes with normal nucleus was much higher (Adewusi and Afolayan 2010; Yadav and Dixit 2003). Methanol extract of *K. pinnata* leaves along with its ethyl acetate and butanol fractions exhibited potent anti-viral activities in-vitro against hepatitis C virus (HCV) as evident from their IC<sub>50</sub> values of 17.2, 9.3 and 7.1  $\mu$ g/mL, respectively. Further investigation involving isolated secondary metabolites viz. quercetin, gallic acid and quercitrin revealed prominent anti-HCV activities in favor of the first two with IC<sub>50</sub> values calculated at 1.5 and 6.1  $\mu$ g/mL, respectively (Aoki et al. 2014). Further in-vivo investigations are necessary so as to ascertain their efficacy in the treatment of hepatitis C. Moreover, with more than 100 compounds isolated from the plant, prospective pharmacological studies of the isolated compounds can provide supportive evidence to confirm exact therapeutic efficacy hereafter for next step clinical investigation.

*Leucas aspera* (Willd.) Link

*L. aspera*, commonly known as ‘Thumbai’ is extensively utilized by the ethnomedicinal healers of Himalayan regions of Southeast Asia for providing hepato-protection. Alongside other biological activities, its hepatoprotective potential has also been

explored scientifically (Prajapati et al. 2010). The possible effect of the aqueous extract of *L. aspera* was investigated against D-galactosamine-induced hepatotoxicity in female Wistar albino rats. The extract at the dose of 400 mg/kg body weight suppressed pathological elevation of ALT, AST, ALP and total bilirubin by 35.5%, 60.9%, 54.5% and 50.0%, respectively, compared to the standard silymarin (100 mg/kg) which diminished the same markers by 40.4%, 68.2%, 62.5% and 61.9%, respectively. Furthermore, the extract as well as the standard also potentiated hepatic antioxidative enzymes including SOD (256.0%, 238.8%, respectively), catalase (152.9%, 134.6%, respectively) and GPx (102.2%, 80.4%, respectively) while diminishing the rate of hepatic lipid peroxidation (50.4%, 46.0%, respectively) (Banu et al. 2012). Another study revealed the hepatoprotective properties of the methanol extract of the plant in carbon tetrachloride-induced male Wistar rats as the extract at a dose of 100 and 200 mg/kg reduced plasma concentrations of ALT, AST and ALP significantly. The extract at both doses also effectuated comparable level of enhancements as the standard silymarin (50 mg/kg) to the levels of hepatic antioxidants including SOD (21.4%, 82.0% and 65.5%, respectively), catalase (26.7%, 91.7% and 69.0%, respectively), GST (300.0%, 485.7% and 328.6%, respectively), GSH (259.1%, 384.1% and 356.8%, respectively) and GPx (65.2%, 140.5% and 78.9%, respectively). When compared to the carbon tetrachloride-treated group, the pre-treatment animals administered with plant sample and reference drug showed promising protection from carbon tetrachloride-induced liver damage as evident from the prevalence of improved hepatic architectural pattern (Latha et al. 2012). The hydroalcoholic (70:30) extract of the leaves of *L. aspera* was investigated for potential hepatoprotective activity in lead acetate induced-male Wistar albino rats. After 21 days of daily extract administration (400 mg/kg body weight), significant reductions of plasma ALT, AST and ALP concentrations by 27.4%, 20.9% and 9.3%, respectively, was indicative of noteworthy anti-hepatotoxic activity (Thenmozhi et al. 2013). Since any pharmacological study is yet to be illustrated involving the isolated phytochemicals, future in-vivo and in-vitro investigations are strongly recommended using fractions and bioactive isolates. Furthermore, detailed biomolecular characterizations are also necessary to ascertain the particular mechanism of action.

*Litchi chinensis* Sonn.

*L. chinensis* is a popular plant of the South Asian region whose leaves, fruits and seeds have experienced extensive traditional applications against a wide variety of pathological conditions including hepatotoxicity. Concentrate of the fresh juice of fruit pulps of two varieties of the plant named Chakapat and Gimjeng were evaluated for their potential hepatoprotective effects against carbon tetrachloride-induced liver damage in male Sprague–Dawley rats at the doses of 100 and 500 mg/kg body weight. The concentrates were also characterized with the presence of ascorbic acid, trans-cinnamic acid and pelargonidin-3-*O*-glucoside as the major phytochemical constituents. Earlier investigation revealed that polyphenolic compounds of litchi leaf augment kidney and heart functions in 2K1C rats (Mamun et al. 2020). However, following the carbon tetrachloride administration both the concentrates were able to reverse hepatotoxic elevation of plasma ALT, AST and ALP levels as well as the rate of hepatic lipid peroxidation to significant extents as compared to the standard silymarin (100 mg/kg). According to histopathological analysis, animals' pretreatment with plant extract resulted in lesser extent of pathological damage in their livers. In carbon tetrachloride-intoxicated rats, histopathologic changes included centrilobular damage, including Kupffer cell hyperplasia. Moreover, elevated level of serum hepatic markers, extent of apoptosis, and centrilobular damage in rat livers as caused by carbon tetrachloride, were significantly restored by pretreatment with plant extract (Bhoopat et al. 2011). Another study demonstrated that the phenolic extract of the fruit pulp of *L. chinensis* was capable of exerting prominent dose-dependent (50, 100 and 200 mg/kg body weight) hepato-protection against physical stress-induced liver damage in male Kunming mice. The extract at the dose of 200 mg/kg enhanced the hepatic activities of SOD, catalase, GSH and GPx by 19.0%, 6.0%, 107.2% and 18.5%, respectively. The extract also significantly diminished plasma ALT and AST levels indicating potent hepatoprotective properties. Eventually, chromatographic investigation into the phenolic extract with the help of HPLC revealed quercetin 3-*O*-rutinoside-7-*O*- $\alpha$ -L-rhamnoside, rutin and (–)-epicatechin as the major bioactive components. The microscopic examination of animal mitochondria demonstrated that nearly all

the mitochondria became blue-green in color in the normal control group animals. The restraint-stressed group had significantly fewer blue-green mitochondria than the usual control group. After pretreatment with lychee pulp extract, the number of blue-green mitochondria which dropped in response to restraint stress, was partially and dose-dependently restored (Su et al. 2016). As mentioned earlier, both quercetin and rutin have been individually characterized with prominent hepatoprotective potential in-vivo. Animals pretreated with the bioactive compound rutin at different doses were examined for histopathological changes. The doses of 50 mg/kg showed a markedly reduced size of the hepatic necrotic areas. Notably, at the higher dose (150 mg/kg), there was a complete reversal of carbon tetrachloride-induced hepatocellular damage (Domitrović et al. 2012). A recent study illustrated that the methanol extract of *L. chinensis* fruit pulp improved in-vitro cellular viability of BNL hepatocytes to a greater extent than standard silymarin. Furthermore, bioactivity-guided phytochemical investigation into the extract afforded epicatechin and procyanidin A2 as the major polyphenolic constituents. The hepatoprotective effect of the extract was also replicated in-vivo in carbon tetrachloride-induced male ICR mice at the doses of 20, 100 and 200 mg/kg body weight. At the end of 3rd week of administration, the extract at the dose of 100 mg/kg diminished plasma levels of ALT and AST by 78.5% and 77.6%, respectively. However, the effect was found to be abrupt, inconsistent and even reversed in some cases for the dose of 200 mg/kg and at the end 6th week, thus limiting the efficacy of the extract within certain dose and time period. During histopathological examinations performed at  $\times 40$  zoom, the number of lipid droplet holes or voids was reduced in the high-level LPE group compared to all other groups. In all treatment groups, the hexagonal portal area generated by aligning hepatocyte edges were preserved. The LPE group with the higher doses had fewer eosinophilic infiltrations than the other groups. The portal vein area of the intermediate and high-level LPE groups had less macro steatosis than the other groups (Chen et al. 2017a, b). Another study demonstrated a similar pattern of hepatoprotective potential in favor of the aqueous extract of the its flowers as the extract was capable of reversing high calorie diet-induced elevation of plasma ALT, AST and hepatic cytokines (viz. tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$  and interleukin-6) as well as plasma

concentrations of triacylglycerol and cholesterol in male Wistar rats (Park et al. 2007; Wu et al. 2013). Future pharmacological studies and pharmacokinetic profiling are necessary for the major bioactive molecules including epicatechin, procyanidin A2 and pelargonidin-3-*O*-glucoside, available in the fruit pulp of *L. chinensis* as well as the major phytoconstituents of the flower extract viz. gentistic acid, catechin, epicatechin and proanthocyanidins, in order to ascertain their individual potential as hepatoprotective agents.

#### *Eclipta prostrata* (L.) L.

*E. prostrata* is an important ethnomedicine mainly used in the Uttar Pradesh of India and few other South Asian countries for treating different diseases, especially a wide range of bacterial infection and liver damage (Khan and Khan 2008). Carbon tetrachloride-, paracetamol- and D-galactosamine-induced hepatotoxic model in male ICR mice was treated with the aqueous extract of the plant at a dose of 300 mg/kg body weight and the hepatoprotective potentials were evaluated based on plasma ALT and AST levels as well as subsequent histopathological changes. Although significant levels of ALT and AST suppressions were achieved in the carbon tetrachloride- and D-galactosamine-induced mice, the same was not observed for the paracetamol-induced model. As seen in the microscopic images, post-treatment of carbon tetrachloride-intoxicated mice with *E. prostrata* greatly reduced the severity of the histopathological lesions (sub massive centrilobular necrosis, ballooning degeneration, and cellular infiltration in the liver) (Lin et al. 1996a, b, c). Thus, further biochemical analyses are necessary in order to identify the exact underlying mechanisms leading to the hepatoprotective activities. Another study investigated the ethanol extract of *E. prostrata* leaves for its hepatoprotective potential in alcohol induced-male Wistar albino rats. The extract at the dose of 200 mg/kg body weight elevated the concentrations of hepatic antioxidants namely SOD, catalase, GSH and GPx by 124.7%, 51.7%, 111.0% and 113.7%, respectively, compared to the standard silymarin (2.5 mg/kg) which enhanced the same markers by 28.5%, 31.2%, 77.9% and 72.3%, respectively. The extract as well as the standard was also reported to increase plasma concentrations of vitamin E (128.1% and 56.1%, respectively) and

vitamin C (118.5% and 66.2%, respectively) which are the first line of antioxidative defense of the body (Arun and Balasubramanian 2011; Lin et al. 1996a, b, c). This, in turn, was suggestive of the fact that the hepatoprotective property of the extract could be attributed to its capacity to act as antioxidants itself in neutralizing the toxic metabolites. A later in-vitro study identified bioactive triterpenoids from the methanol extract of the aerial parts of *E. prostrata* named echinocystic acid and eclalbasaponin I–III and V, which were then evaluated for their potential anti-fibrotic activities in rat hepatic stellate cells (HSCs) containing solution. Echinocystic acid and eclalbasaponin II was reported to exert prominent time- and dose-dependent antiproliferative effects over the T6 cell line which was further linked to their potential to suppress hepatic fibrosis in vivo (Lee et al. 2008a; Rathore et al. 2014a, b). However, such in-vivo studies in appropriate animal models are warranted in future to ascertain their hepatoprotective potential in biological systems. Moreover, biochemical characterization of respective plasma and hepatic markers are also required for the illustration of underlying mechanisms.

#### *Hybanthus enneaspermus* (L.) F. Muell.

Hepatoprotective properties of the ethanol extract of *H. enneaspermus* leaves was demonstrated against paracetamol-induced hepatotoxicity model in adult male albino rats. The extract at the dose of 200 mg/kg body weight diminished plasma concentrations of ALT, AST and ALP by 23.1%, 13.2% and 17.7%, respectively. Furthermore, the extract also potentiated hepatic antioxidative enzymes named SOD, catalase, GST, GPx and glutathione reductase (GR) to extents of 24.4%, 52.7%, 41.1%, 6.7% and 155.8%, respectively, while decreasing hepatic lipid peroxidation by 19.5%. In paracetamol-treated mice, histological examinations revealed significant necrosis with the loss of nuclei. In the experimental animals treated with plant extract, all of these alterations were reduced dramatically as normal hepatic architecture, normal hepatic central vein, regular hepatocytes with nuclei, and sinusoidal gaps were observed predominantly (Bhanu et al. 2011). In another study, aqueous extract of *H. enneaspermus* at the doses of 200 and 400 mg/kg body weight was investigated for potential hepatoprotective activities against carbon tetrachloride-induced male Wistar rats through both pre-treatment and post-

treatment models. In the later model, the extract at both doses as well as the standard silymarin (100 mg/kg) suppressed plasma levels of ALT (70.3%, 78.7% and 84.9%, respectively), AST (43.5%, 56.6% and 68.9%, respectively), ALP (39.5%, 54.7% and 61.0%, respectively) and total bilirubin (45.8%, 79.2% and 79.2%, respectively) significantly. The hepatoprotective potential of the extracts followed a similar pattern in the pre-treatment model as well. Furthermore, in histological investigation, carbon tetrachloride-treated rat liver sections showed massive changes throughout the lobules, including fatty accumulations, cellular distensibility, and necrosis, as well as dilation of Disse spaces with focal disruption of the sinusoidal endothelium, inflammatory incursions of the portal triads, and distortion of the central venules. Animals treated with an aqueous extract of *H. enneaspermus* and the control showed lower hepatic vacuolation and better maintenance of normal liver architecture, as well as moderate hepatocyte plate disorganizations and smaller dilations of interstitial spaces. In the hepatic lobules of the treated animals, periportal inflammatory infiltrates were infrequent or absent (Vuda et al. 2012a, b). In order to validate and reinforce these initial findings, more in-vivo studies involving the extract, their subsequent fractions as well as isolated phytochemicals are required. In addition, extensive molecular experimentation on diverse hepatocytic cell lines is also warranted to affirm the exact mechanism of action.

### Safety and toxicity

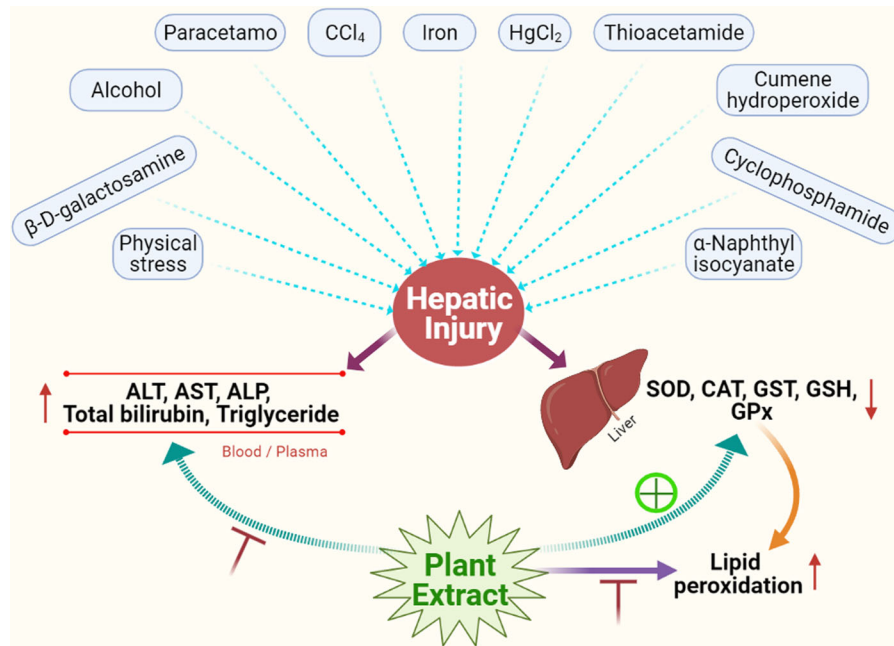
Although a large number of pharmacological investigations have enumerated the hepatoprotective potentials of the nine selective plants, safety profiling and relevant toxicological investigations have not been conducted for all these species extensively. A study investigated the acute toxicity of *Colocasia esculenta* aqueous extract in female Wistar rats. The extract at the maximum dose of 4000 mg/kg body weight maintained normal levels of plasma markers viz. ALT, AST, creatinine, cholesterol and triglycerides indicating an absence of toxicity. However, in the sub-acute toxicity study, the extract at the dose of 800 mg/kg enhanced hepatic AST in female while diminishing the same in male rats at the end of twenty days. Moreover, the extract also suppressed platelet count in

female rats only, therefore limiting the continuous administration of the extract at larger doses (Nzebang et al. 2018). Methanol extract of the leaves and stems of *Alstonia scholaris* administered in female Sprague Dawley rats at the maximum dose of 2000 mg/kg body weight demonstrated the absence of any observable toxicity rendering a safer profile in favor of the extract. In sub-acute toxicity test, both male and female rats exhibited signs of toxicities in the form of lethargy, diminished motor reflexes, heavy breathing and fur loss after continuous administration of the extract at the doses of 500 and 1000 mg/kg body weight for at least 14 days straight. The toxicity was also translated at organ level as the weight of lungs decreased in both male and female whereas weight of liver diminished only in male (Bello et al. 2016). A 90 days long oral toxicity study of *Mangifera indica* involving repeated doses of 2000 mg/kg body weight revealed that the experimental mice did not show any adverse effect or death (Reddeman et al. 2019). Correspondingly, another study reported that the administration of the aqueous extract of stem bark were found to exert no adverse or lethal reactions in Sprague Dawley rats at the doses of 2000 mg/kg. The extract was also found to be non-irritant towards skin, ocular and renal mucosa following single dose administration in rabbits (Garrido et al. 2009). Although the aforementioned study revealed relative safety for three species under limited doses, these data are very still insufficient in terms of establishing absolute safety for all these plants. Thus, further comprehensive toxicological studies are warranted taking into account all plants fractions and their active bioactive metabolites.

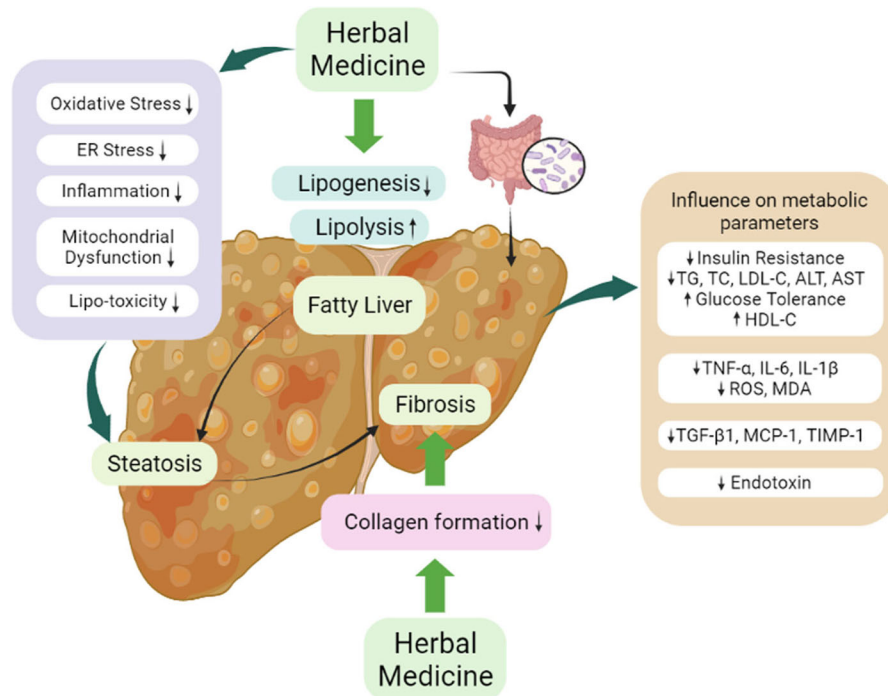
### Conclusion and future prospects

Herbal medicines have the potential to offer an effective mean towards the treatment of liver diseases. The present comprehensive review was focused on nine selective South Asian herbs which have extensive traditional applications based on their hepatoprotective potentials. The effects of these plants at cellular levels which lead to their hepatoprotective effects have been converged and depicted in Fig. 3 and the effects of herbal medicines in the treatment of hepatotoxicity have been illustrated in Fig. 4. The primary obstacle towards the utilization of these plants





**Fig. 3** Mechanistic pathways involved in the hepatoprotective effects of South Asian medicinal plants. The blunt line indicates downregulation and plus sign indicates upregulation of the markers



**Fig. 4** The mechanistic pathways by which herbal medicine plays its role in the protection of hepatotoxicity

in the preparation of hepatoprotective formulations can be referred to the unavailability of sufficient safety reports at acute, sub-acute and chronic levels. Therefore, toxicological studies into these plants in terms of cellular, hepatic and hematological markers are necessary on an extensive scale. Secondly, a relative evaluation of these plants should be attempted in identical experimental animal model addressing individual plant-based as well as poly-herbal formulations. Although hepatoprotective properties of different plant extracts have been illustrated at biochemical level, the information is still insufficient as single or multiple relevant markers are yet to be explored in some of the plants. A comparative investigation should allow for the evaluation of their hepatoprotective properties based on all relevant markers and might also lead to the designing of a more efficient poly-herbal formulation with the presence of individual plants in relatively minor quantities where individual plant-associated toxicities could be minimized completely. Finally, identification of bioactive molecules from these plants must be undertaken in future followed by pharmacological evaluation of the promising molecules for hepatoprotective activities. The availability of modern hepatoprotective drugs with realistic clinical utility is still very limited and identification of new molecules with similar potentials will surely advocate the process of novel drug discovery as well as development.

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#### Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

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