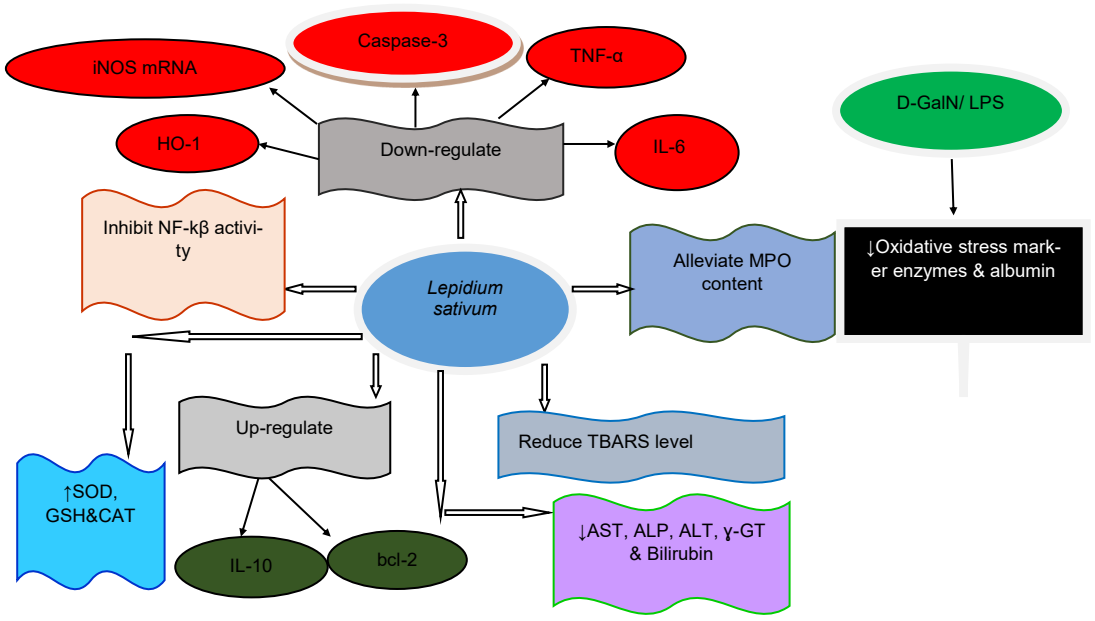

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Mini Review

Advances in hepatoprotective medicinal plants research

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Mini-review

Advances in hepatoprotective medicinal plants research

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Abstract

Hepatic dysfunction is a major catastrophe that challenges the health concern researchers. Multiple factors such as biological, chemical and drug overdose are associated with liver disorders. Man-made pharmaceutical preparations, which are usually used for the treatment, further accelerate the toxification of the liver. In this situation, a great reliance has been evident on natural products which seem promising in dealing with liver diseases effectively. Plants are the basis of innate products, or dynamic constituents named as phytochemicals, which have been analyzed for their hepatoprotective potential and a review article on hepatoprotective plants was published in 2014 in Bangladesh Journal of Pharmacology. After that, a number of researches have been completed to identify new hepatoprotective medicinal plants. The purpose of this review was to update the information until now.

Introduction

Different medicinal plants are used for the protection and treatment of liver diseases and a review article on hepatoprotective plants was published in 2014 (Saleem and Naseer, 2014). After that, a number of researches have been completed to identify new hepatoprotective medicinal plants. The purpose of this review was to update the information regarding medicinal plants used in the protection and treatment of liver diseases, until now.

Liver Diseases

The liver is one of the most rudimentary organs that engage in the biotransformation of nutrients; provide protection to the body against foreign agents, detoxification as well as the excretion of drugs and xenobiotics from the body (Sagar et al., 2014). Thus, it is requisite to protract liver strength for overall body's health and safety. Unluckily, environmental toxins, meager eating habits, alcohol and over-the-counter drug use are recurrent ill-treatments which can weaken the liver (Murugaian et al., 2008). National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (CDC) considered chronic liver disease and cirrhosis; as the 12th foremost basis of death which are asserting 30,000 lives in the United States per year (Gupta et al., 2015).

Liver diseases possibly classified as inflammatory liver diseases (acute/chronic hepatitis), non-inflammatory diseases (hepatosis) and liver fibrosis (also called cirrhosis) (Asadi-Samani et al., 2015). The main cause of pathogenesis of liver injury is the involvement of a deadly agent or the bio-activation of free radicals that elicits an immune response or protein dysfunction, lipid peroxidation, DNA damage, oxidative stress and depletion of reduced glutathione (Bedi et al., 2016). All liver cells including hepatocytes, kupffer and endothelial cells are involved in the pathogenesis of hepatic injury by programmed cell death, necrosis, ischemia and renewal, leading to tainted gene expression. Jaundice, hepatomegaly, hepatic encephalopathy, cirrhosis and obtrusive jaundice are well-known liver disorders (Saleem and Naseer, 2014). Liver damage can be caused by many factors such as biological, autoimmune diseases, some drugs e.g. high dosage of paracetamol, antitubercular drugs, lethal compounds (such as carbon

tetrachloride, thioacetamide, diethylenitrosamine, 4-D-glucosamine/lipopolysaccharides) and overdose of alcohol (Khan et al., 2016); leads to the elevation of serum biochemical markers like serum aminotransaminases, alkaline phosphatase and bilirubin (Chaudhari et al., 2009). Tissue thiol depletion, lipid peroxidation, plasma membrane damage are the indicators of reactive species depletion (Shaik et al., 2012). A number of inflammatory and liver diseases are mediating to oxidative stress and oxidative chain reaction inhibitory compounds have been reported against hepatotoxicity (Pithayanukul et al., 2009). By virtue of the severe hepatotoxic effect of chemicals in humans and animals, carbon tetrachloride is one of the well-known xenobiotics (Parmar et al., 2009) which after reductive halogenations ultimately leads to liver damage. An overdose of paracetamol (also known as acetaminophen) causes oxidative stress and glutathione depletion by its activation and then transformed by cytochrome P_{450} enzymes to NAPQI (*N*-acetyl-*p*-benzoquinoneimine); a deadly metabolite (Parmar et al., 2010).

Medicinal Plants to Treat Liver Disease

It is a challenge to find the ways of treatment for the common liver diseases. Although, there is best incompatibility among effectiveness of treatment such as colchicine, corticosteroid, interferon and penicillamine but the incidence of adverse effect is severe (Jain et al., 2013). For the management of hepatic diseases, there is a need to innovate alternative pharmaceuticals having more effectiveness and less toxicity. Chiefly, about 80% of the world's population has employed plant material as traditional medication for health care. A variety of chemical compounds such as coumarins, essential oils, glycosides, carotenoids, organic acids, alkaloids, lignin's, phenols, xanthenes, flavonoids and monoterpenes are present in the plant as well as fruits for liver protection (Madrigal-Santillán et al., 2014). Many fields such as botany, chemistry, biotechnology, pharmacognosy and pharmacology are doing a massive effort on herbal remedies using statistical methods to assess the reliability of claims (Roy et al., 2014). Although numerous herbal medicines have universal status significantly but there are some limiting factors behind their usage including inconsistency of the herbal drugs, lack of recognition of active constituents, randomized controlled tentative trials, and lack of toxicological review (Saleem et al., 2010). Besides all the above-mentioned restrictions, the researchers are probing some valuable treatments for the liver disorders. Plant-derived natural products and herbs have gained significant considerations in recent years due to their various pharmacological properties; anti-oxidant, anti-inflammatory, etc for hepatoprotective effect. Some examples of medicinal plants with hepatoprotective effect through different mechanisms are explained here briefly:

Berberies aristata, belongs to family the Berberidaceae has hepatoprotective activity against carbon tetrachloride-induced hepatic damage by inhibiting lipid peroxidation. Plant bark extract (at a dose of 100 and 300 mg/kg) inhibits the hepatic damage by decreasing the AST, ALT, ALP and bilirubin (total and direct) which increased after carbon tetrachloride administration (Rathi et al., 2015).

Boerhaavia diffusa (at a dose of 250 and 500 mg/kg) prevents the hepatic cells death and lipid peroxidation by free radical scavenging activity and has a stimulatory effect on hepatic regeneration against carbon tetrachloride-induced hepatotoxicity. It also decreases the serum levels of alanine transferases, aspartate transferases, alkaline phosphatase, total serum bilirubin and serum proteins which significantly increased after carbon tetrachloride administration (Beedimani and Jeevangi, 2015).

Canna indica is effective against hepatic necrosis and NAPI-mediated paracetamol-induced hepatic damage. The plant rhizome extract exerts an inhibitory effect on hepatocytes necrosis by hepatocytes regeneration, decreased serum alanine transaminase and shows anti-inflammatory activity against NAPQI mediated paracetamol poisoning (Longo et al., 2015).

Mangifera indica (mango) belonging to family Anarcardiaceae and has hepatoprotective action by anti-oxidative and anti-lipoperoxidative mechanisms. *Mangifera indica* aqueous stem bark extract at dose of 150-500 mg/kg has hepatoprotective activity against carbon tetrachloride-induced hepatic necrosis via inhibiting increased level of serum aminotransferases, alkaline phosphatase, bilirubin (total and conjugated), fasting blood glucose and malondialdehyde and by increasing total protein, albumin, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), superoxide dismutase, reduced glutathione (GSH) and catalase activity which might attributed to anti-oxidant and anti-lipoperoxidative potential (Adeneye et al., 2015).

The crude powder of *Mimosa pudica* prevents liver cell necrosis and lysosomal latency by normalizing serum biochemical parameters against carbon tetrachloride-induced hepatotoxicity (Kumaresan et al., 2015).

Juice of *Ananas comosus* (family Bromeliaceae), commonly known as pineapple, has liver protective action (Mohamad et al., 2015) by controlling different protein expression, anti-oxidant levels and liver marker enzymes against paracetamol-induced toxicity. Fruit seeds of *Cassia fistula* (golden shower tree of family Fabaceae) have protective potential against hepatotoxins-induced liver damage and have non-significant effect on hematological parameters (Iqbal et

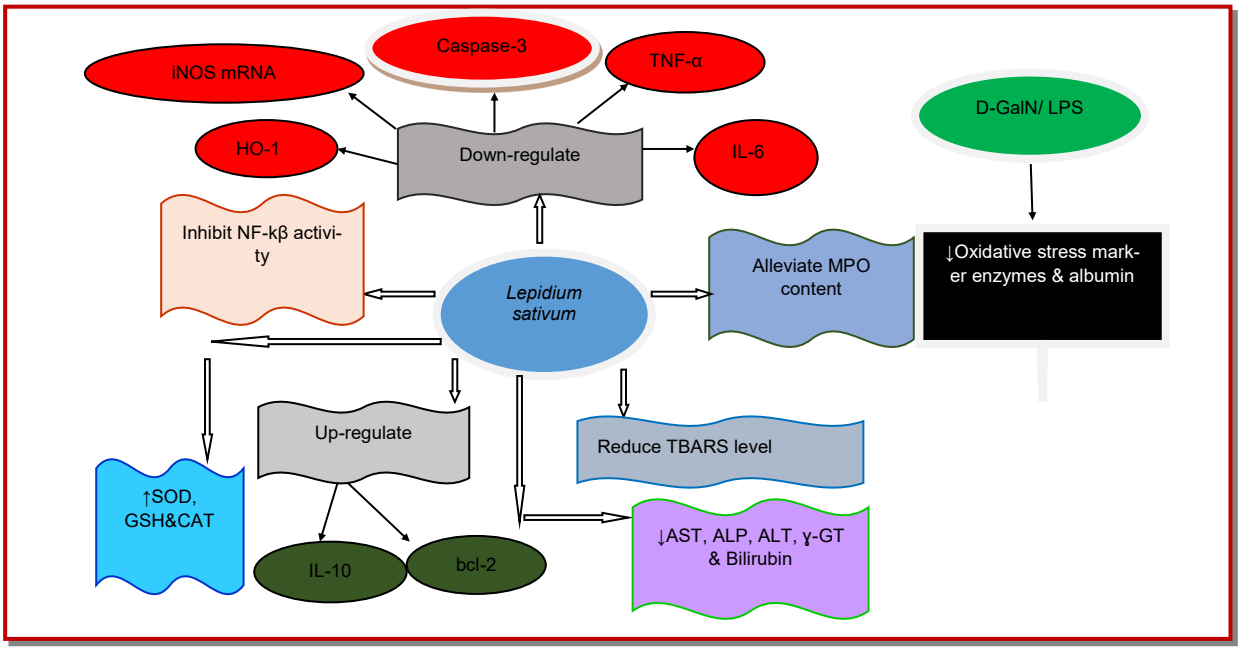

Figure 1: D-GalN/LPS (D-galactosamine/lipopolysaccharides) decrease oxidative stress marker enzymes and albumin. *Lepidium sativum* ethanolic extract has shown hepatoprotective activity by decreasing AST (aspartate aminotransferase), ALP (alkaline phosphatase), ALT (alanine aminotransferase), γ-GT (gamma glutamyl transferase) and bilirubin, inhibiting NF-κβ activity, alleviating MPO (myeloperoxidase) content, reducing TBARS (thiobarbituric acid reactive substance), down-regulating IL-6 (interleukin -6), TNF-α (tumor necrosis factor), caspase-3, iNOS and HO-1, up-regulating IL-10 (interleukin-10) and bcl-2 expression

al., 2016). Figure 1 has presented hepatoprotective action of *Lepidium sativum* (known as garden cress) belongs to family Crucifereae by up-regulating and down-regulating the enzymes, inflammatory genes expression, serum biochemical markers etc (Raish et al., 2016). Plant seeds extract mitigate hepatic injury and structural damage via inhibiting oxidative stress. Numerous plants have been reported against hepatic damage because of their role in hepatic gene regulation. For example, *Panax ginseng* belongs to family Araliaceae also named as 'ginseng'. Roots of ginseng inhibit toxin-induced hepatic damage by decreasing vital genes expression which is essential for normal liver functions (Hafez et al., 2017) as shown in Figure 2.

In Table I, different medicinal plants, fruits, and herbs,

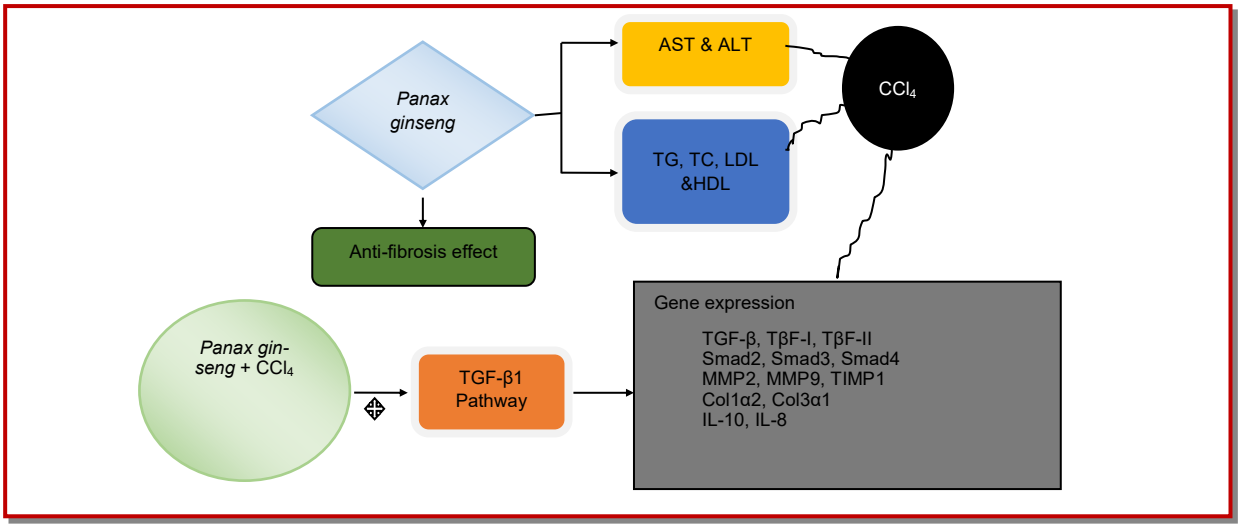

Figure 2: *Panax ginseng* has shown anti-fibrosis effect via TGF-β1 signaling pathway in CCl_4 induced liver fibrosis model. The administration of ginseng in combination with CCl_4 significantly decreased the expression of TGF-β; its receptors, Smad2, Smad3, Smad4, MMP2, MMP9 and TIMP1 genes expression. It also reduced AST (aspartate aminotransferase), ALT (alanine aminotransferase), TG (triglyceride), TC (total cholesterol), and LDL (low density lipids) levels as well as increased HDL (high density lipids)

Table I

Medicinal plants having hepatoprotective potential

Plants with common name	Parts used	Extract	Hepatotoxic agent	Model	Results	References
Acantholimon gilliati	Aerial part	Methanol	Formaldehyde	Mouse	↓AST, ALT, ALP	Lashgari et al., 2017
Acrocarpus fraxinifolius (Shingle tree)	Leaf	*n*-Hexane	Paracetamol	Rat	↓AST, ALT, ALP, lipid, bilirubin, LPO ↑body wt, SP, HAC	Abd El-Ghffar et al., 2017
Acalypha indica (Indian nettle) and *Centella asiatica* (Centella)	Leaf, whole plant	Methanol	Hypoxia	Rat	↓MDA, prevention from hypoxia	Dwijayanti et al., 2015
Adansonia digitata (Baobab tree)	Fruit pulp	Methanol	Paracetamol	Rat	↓AST, ALT, ALP, MDA ↑SOD, GSH, CAT, parenchyma preservation of hepatocytes	Hanafy et al., 2016
Aloe vera (Ghee gangwar)	Stem	Ethanol	Paracetamol	Rat	↓AST, ALT, SALP, bilirubin	Hena et al., 2016
Ananas comosus (Pineapple)	Fruit	No extract	Paracetamol	Male mouse	↓AST, ALT, ALP, TG, restored SOD, SH, LPO, FRAP, ↓NF-kβ, NO, iNOS and liver p450 protein expression	Mohamad et al., 2015
Andographis alata (Justicia alata)	Leaf	Aqueous	Carbon tetrachloride	Rat	↓AST, ALT Prevents histopathological changes	Nagaraja and Krishna, 2016
Annona muricata (Soursop)	Leaf	Ethanol	No	Rat	↑body wt, ↓AST, ALT, ALP	Okoye et al., 2016
Aquilaria agallocha (Agarwood)	Leaf	Ethanol	Paracetamol	Rat	↓AST, ALT, ALP, LDH, CHL, bilirubin, relative liver wt, ↑final body wt, SP	Alam et al., 2017
Artemisia absinthium (Sweet wormwood)	Aerial part	Alcohol	No	Rat	↓AST, ALT, TTG Non-significant ↓ in TAP	Mohammadian et al., 2016
Artemisia capillaries (Yin Chen Hao)	Oil	No extract	Carbon tetrachloride	Mouse	↓AST, ALT, MDA Prevent decrease in SOD, GSH, GSH-Px	Gao et al., 2016
Artemisia dracunculus (Tarragon)	Leaf	Ethanol	Carbon tetrachloride	Rat	↓AST, ALT, ALP, bilirubin ↑SP	Sultana and Ahmed, 2017
Azadiracta indica (Neem)	Leaf	Aqueous	Paracetamol	Rat	↓AST, ALT, ALP ↑Vitamin C & E in liver homogenate	Nwobodo et al., 2016
Bauhinia purpurea (Purple bauhinia)	Leaf	Methanol	Paracetamol	Rat	↓AST, ALT, LDH, ↓liver/body wt ratio ↑SP	Zakaria et al., 2016
Berberis aristata (Chitra)	Stem bark	Ethanol	Carbon tetrachloride	Rat	↓AST, ALT, ALP, bilirubin	Rathi et al., 2015
Bidens pilosa (Blackjack)	Aerial part	Methanol	Carbon tetrachloride D-galactosamine	Mouse	↓ALT, AST, ALP, ↑SP, GSH	Abdel-Ghany et al., 2016
Boerhaavia diffusa (Punarnava)	Root	Aqueous	Carbon tetrachloride	Rat	↓AST, ALT, ALP, SB ↑TP	Beedimani and Jeevangi, 2015
Brassica oleracea var. capitata f. alba (White cabbage)	Aerial part (oil)	No extract	Carbon tetrachloride	Rat	↓GGTP, ALT, bilirubin Prevents glycogen depletion	Morales-López et al., 2017

Table I

Medicinal plants having hepatoprotective potential (Cont..)

Plants with common name	Parts used	Extract	Hepatotoxic agent	Model	Results	References
Butea monosperma (Parrot tree)	Bark	Ethyl acetate	Thioacetamide	Rat	Stabilized AST, ALT, ALB, ALP, SOD, CAT, GSH, GR Restored collagen and hydroxyproline levels ↓expression of p-P13K, p-Akt, p-mTOR	Kaur et al., 2017
Caesalpinia bonduc (Grey nicker)	Leaf	Ethanol	Carbon tetrachloride	Rat	↓AST, ALT, ALP, bilirubin, MDA ↑TP, CAT, GSH-Px	Ubhenin et al., 2016
Caesalpinia gilliesii (Yellow bird of paradise)	Flower	Dichloromethane	Carbon tetrachloride	Rat	↓AST, ALT ↑GSH	Osman et al., 2016
Canna indica (Achira)	Rhizome	Aqueous	Paracetamol	Rat	Normalized rat behavior, ↓relative liver wt and ALT	Longo et al., 2015
Canscorra decussate (Shankhpushpi)	Whole plant	Methanol	Paracetamol	Rabbit	↓AST, ALT, ALP, bilirubin	Akhtar et al., 2015
Carica papaya (Papaya/pawpaw)	Leaf, Unripe fruit	Aqueous	Carbon tetrachloride Paracetamol	Rat	↓AST, ALT, ALP, bilirubin, UA, MDA ↑GSH, SOD, CAT	Awodele et al., 2016
Cassia fistula (Golden shower tree)	Fruit seed	Methanol	No	Chick	↓AST, ALT, ALP, urea, CRE ↑plasma protein	Iqbal et al., 2016
Cassia tora (Coffee cassia)	Leaf	Methanol	Carbon tetrachloride	Rat	↑TP, ALB, GSH ↓AST, ALT, ACP, ALT, AST, MDA	Saravanan and Malarvannan, 2016
Centratherum anthelminticum (Banjira)	Seed	Ethanol	Carbon tetrachloride	Rat	↓AST, ALP ALT, IBR, bilirubin, UA ↑TP, ALB ↓in %inhibition of SOD, CAT, GSH	Qureshi et al., 2016
Ceriopsdecandra (Mangrove plant)	Leaf, Bark, Collar, Hypocotyl, Flower	Petroleum ether, ethanol	Carbon tetrachloride	Rat	↓AST, ALT, ALP, BR, CHL, LDH ↑TPN, ALB	Gnanadesigan et al., 2016
Citrus macroptera (Satkara/wild orange)	Fruit	Ethanol	Paracetamol	Rat	↓ALT, GGT, LDH, AST, ALP, TB, TG, TC Improved serum CRE, urea, UA, Na^+, K^+, Cl^- ↓MDA	Paul et al., 2016
Coreopsis tinctoria (Golden tickseed)	Flowers	Ethanol	Carbon tetrachloride	Rat	↓ALT, AST, MDA,NO, TNF-α, IL-6, IL-1β ↑GRd, SOD, GSH-Px	Tsai et al., 2017
Coriandrum sativum (Coriander)	Fruit	No extract	Ibuprofen	Rat	↓ALT, AST	Baghdadi et al., 2016
Crocus sativus (Saffron)	Dried red stigmas	Ethanol	Amiodarone	Male rabbit	↓ALT, ALP, AST, LDH, BR, UA, Na^+ ↑ALB synthesis	Saleem et al., 2016

Table I

Medicinal plants having hepatoprotective potential (Cont..)

Plants with common name	Parts used	Extract	Hepatotoxic agent	Model	Results	References
Cucumis sativus (Cucumber)	Juice	No extract	Lead	Rat	Pb detoxification, positive effect on RBCs count and food intake	Bajpai et al., 2017
Cymbopogon citratus (Lemon grass)	Whole plant	Aqueous	Paracetamol	Rat	↓AST, ALT, MDA, BUN, CRE ↑GSH (liver)	Saenthaweesuk et al., 2017
Eclipta alba (Bhangra)	Leaf	Aqueous	Carbon tetrachloride	Rat	↓ALT, AST, ALP, SB ↑SP	Beedimani and Shetkar, 2015
Elettaria cardamomum (True cardamom)	Seed	Aqueous	Gentamicin	Rat	↓AST, ALT, BR, CHL, TG, LDL-C ↑SB, HDL-C	Aboubakr and Abdelazem, 2016
Eriocaulon quinquangulare (Eriocaulonsp Australia Red)	Whole plant	Aqueous	Ethanol	Porcine liver slices	↓ALT, AST, LDH ↓Lipid peroxidation	Fernando and Soysa, 2016
Ferulago angulata (Chavir)	Flower	Methanol	N-nitroso-dimethylamine	Rat	↓SOD, CAT, GSH-Px ↓Liver hyperemic	Kiziltas et al., 2017
Ficus religiosa (Peepal tree)	Latex	Methanol, petroleum ether	Cisplatin	Rat	↓ALT, AST, ALP	Yadav, 2015
Fragaria ananassa (Garden strawberry)	Juice	No extract	Carbon tetrachloride	Rat	↓AST,ALT, TBARS, nitrate, ↑GSH, SOD, CAT, GPx expression ↑anti-apoptotic protein Bcl2 ↓pro apoptotic proteins bax, caspase-3	Hamed et al., 2016
Gentianella turkestanerum	Whole plant	GPE, GEA, GBA, GW	Carbon tetrachloride	Male mouse	↓ALT, AST, ALP, TB, GSH, CAT, SOD, MDA ↑ TP	Yang et al., 2017
Helicanthus elastica (Mango Mistletoe)	Whole plant	Ethanol	Paracetamol	Mouse	↓AST, ALT ↑ALPase activity ↓Serum TB ↑Serum TP	Kumar et al., 2016
Grapefruit Lemon Orange (Hesperidin)	No	No extract	Carbon tetrachloride	Rat	↑GSH, CAT, SOD ↓TBARS synthesis, Reduced caspase-3 activation	Çetin et al., 2016
Holostemma ada-kodien (Holostemma creeper)	Whole plant	Alcohol	Paracetamol	Rat	↓ALT, ASP, ALP, SB, MDA ↑GSH	Sunil et al., 2015
Homalium letestui (Makoli)	Stem	Ethanol	Paracetamol	Rat	↓ALT, AST, ALP, bilirubin ↑CAT, SOD, GPx, GSH, TP, ALB, hematological parameters	Okokon et al., 2017
Indocalamus latifolius	Whole plant	Ethanol	Carbon tetrachloride	Rat	↓ALT, AST, ALP	Tan et al, 2015

Table I

Medicinal plants having hepatoprotective potential (Cont..)

Plants with common name	Parts used	Extract	Hepatotoxic agent	Model	Results	References
Juniperus communis (Juniper)	Leaf	Ethanol	Paracetamol	Rat	↓ALT, AST, ALP, bilirubin	Ved et al., 2017
Lagerstroemia speciosa (Queen's flower)	Flower	Ethanol	Carbon tetrachloride	Mouse	↓ACP, ALT, AST, ALP, MDA ↑ in %inhibition of LPO, CAT, GSH	Tiwary et al., 2017
Lepidium sativum (Garden cress)	Seed	Ethanol	D-galactosamine/Lipopolysaccharides	Rat	Down regulate TNF-α, IL-6,HO-1, iNOS, m-RNA expression Up-regulate IL-10, mitigate MPO, NF-kβ	Raish et al., 2016
Lawsonia inermis (Henna)	Leaf	Methanol	Carbon tetrachloride	Rat	↓AST, ALT, ALP, bilirubin Hepatocytes regeneration	Mohamed et al., 2016
Mammea africana (African mammee apple)	Stem bark	Ethanol	Paracetamol	Rat	↓AST, ALT, ALP, bilirubin ↑TP, ALB, SOD, CAT, GPx, GSH	Okokon et al., 2016
Mangifera indica (Mango)	Stem bark	Aqueous	Carbon tetrachloride	Rat	↓ALT, AST, ALP, FBG, TB, CB, LDL-C, MDA ↑TC, TG, HDL-C, TP, ALB ↑SOD, CAT, GSH (liver)	Adeneye et al., 2015
Melothria perpusilla (Lamthabi)	Aerial parts	Aqueous	Carbon tetrachloride	Rat	↓ALT, AST, ALP, bilirubin	Yengkhom et al., 2017
Mimosa pudica (Touch-me-not)	Whole plant	Crude extract	Carbon tetrachloride plus paraffin	Rat	↓AST, ALT, SB, MDA (serum and tissue), γ-GT, ALP, ACP	Kumaresan et al., 2015
Monotheca buxifoli	Fruit	Ethanol	Isoniazid plusrifampicin	Rat	Restored ALT, AST, ALP, SP, bilirubin	Ullah et al., 2016
Moringa peregrina (Ben tree)	Leaf	Ethanol	Paracetamol	Rat	Suppress MDA Normalize G-Px ↑GSH, CAT, SOD ↓DNA fragmentation	Azim et al., 2017
Moringa oleifera (Sohanjana)	Leaf	Gum acasia plus alcohol	Cadmium	Rat	↓AST, ALT, ALP, LPO ↑SOD	Toppo et al., 2015
Morus indica (Mulberry)	Leaf	Aqueous and dechlorophyllised	Carbon tetrachloride	Rat	↓AST, ALT, ALP, TG, LPO ↑SP, GSH	Reddy and Urooj, 2017
Murraya koenigii (Curry tree)	Leaf	Ethanol	Carbon tetrachloride and paracetamol	Rat	↓AST, ALP, ALT, LPO ↑SOD, CAT, GSH	Sangale and Patil, 2017
Nymphaea lotus (White water lily)	Whole plant	Methanol	Carbon tetrachloride	Rat	↓AST, ALT, bilirubin, TBARS (liver) ↑GSH, GSH-Px	Oyeyemi et al., 2017
Opuntia monacantha (Chnutarthar)	Whole plant	Methanol, chloroform	Paracetamol	Rabbit	↓AST, ALT, ALP, bilirubin	Saleem et al., 2015

Table I

Medicinal plants having hepatoprotective potential (Cont..)

Plants with common name	Parts used	Extract	Hepatotoxic agent	Model	Results	References
Opuntia robusta (Wheel cactus) and *Opuntia streptacantha* (Prickly pear cactus)	Fruits (juice)	No extract	Paracetamol	Rat	↓AST, ALT, ALP ↓LDH leakage and cell necrosis Prevent GSH (liver) depletion	González-Ponce et al., 2016
Otostegia persica (Goldar)	Aerial parts	Ethanol	Carbon tetrachloride	Rat	↓AST, ALT, ALP, bilirubin, MDA ↑SP	Toori et al., 2015
Oudemansiella radicata (Mushroom/ Rooting shank fungus)	Dried fruiting bodies	Ethanol	Carbon tetrachloride	Mouse	↓ALT, AST MDA (liver) suppression, ↑SOD, GSH-Px Prevent ↑ in liver wt, ↓Lipid droplet accumulation	Liu et al., 2017
Oxalis stricta (Pickle plant)	Whole plant	Ethanol	Paracetamol	Rat	Prevent GSH depletion ↓lipid peroxidation, AST, ALT, ALP, bilirubin	Patel et al., 2016
Panax ginseng (Ginseng)	Root	Aqueous	Carbon tetrachloride	Rat	↓Hepatic fat, reticular fiber deposition, ↓AST, ALT, LDL, TGF-β, Smad2, Smad3, Smad4, MMP2, MMP9, TIMP-1, Col1α2, Col3α1 Restored IL-8, IL-10	Hafez et al., 2017
Pandanus odoratissimus (Umbrella tree)	Root	Ethanol	Paracetamol	Rat	↓AST, ALT, ALP, bilirubin, TG	Mishra et al., 2015
Picralima nitida (Abeere)	Seed	Methanol	Carbon tetrachloride	Rat	↑CAT, GSH ↓ALT, AST, ALP, bilirubin	MacDonald et al., 2016
Piper trioicum	Aerial part	Ethanol	Carbon tetrachloride	Rat	↓AST , ALT, bilirubin, MDA ↑TP, SOD, CAT, GPx	Lakshmi et al., 2016
Phyllanthus emblica (Amla)	Bark	Alcohol	Ethanol	Rat	Restored ALT, AST, ALP, SP	Chaphalkar et al., 2017
Prunus armeniaca (Apricot)	Leaf	Methanol	Paracetamol	Rat	↓AST, ALT, SALP, TBARS, GGT, LDH, SP, SB, ALB	Raj et al., 2016
Pongamia pinnata (Indian beech tree)	Leaf	Ethanol	Paracetamol	Rat	↓ALT, AST, ALP, GT, SP, bilirubin ↑SOD, CAT, GPx	Rajeshkumar and Kayalvizhi, 2015
Pterospermum acerifolium (Karnikara tree)	Leaf	Petroleum ether, alcohol	Paracetamol	Rat	↓ALP, AST, ALT, LPO ↑GSH, SOD, CAT	George et al., 2016
Randia dumetorum (Emetic nut)	Leaf Bark	Methanol	Carbon tetrachloride	Rat	↓AST, ALT, ALP, LDH, ALB, TB, DB, TBARS, TNF-α, IL-1β ↑SP, SOD, CAT, GSH	Kandimalla et al., 2016
Rosa canina (Dog-rose)	Fruit	Ethanol	Carbon tetrachloride	Rat	↓AST, ALT, ALP, MDA ↑SP	Sadeghi et al., 2016
Salix subserrata (Flute willow)	Flower	Ethanol	Carbon tetrachloride	Rat	↓AST, ALT, ALP, LDH, S-chol, TG, MDA, bilirubin, expression of TNF-α, NF-kβ ↑SP, GSH	Wahid et al., 2016
Sapium sebiferum	Leaf	Methanol	Paracetamol	Mouse	↓AST, ALT, ALP, bilirubin	Hussain et al., 2015

Table I

Medicinal plants having hepatoprotective potential (Cont..)

Plants with common name	Parts used	Extract	Hepatotoxic agent	Model	Results	References
Simaroua glauca (Paradise tree)	Leaf	Ethanol and chloroform	Paracetamol	Rat	↓AST, ALT, ALP	John et al., 2016
Solanum melongena (Eggplant)	Ripe fruit	Methanol	Carbon tetrachloride	Rat	↓ALT, AST, ALP, MDA ↑SOD, CAT	Hamzah et al., 2016
Solanum nigrum (Black nightshade)	Aerial parts	Aqueous	Carbon tetrachloride	Rat	↓ALT, ALP, bilirubin	Goyal and Sharma, 2016
Sonchus asper	Whole plant	-	Paracetamol	Rabbit	↓ALT, ALP, bilirubin	Aftab-Ullah et al., 2015
Sphaeranthus amaranth ides (Sivakaranthai) and *Oldenlandia umbellate* (Chay root)	Whole plant	Methanol	Carbon tetrachloride	Rat	↓AST, ALT, ALP, bilirubin, necrosis	De et al., 2017
Syzygium cumini (Jamun)	Seed	Methanol	Carbon tetrachloride	Rat	↓AST, ALT, BiT, ALP ↑SP	Islam et al., 2015
Terminalia catappa (Sea almond tree)	Bark	Alcohol	Isoniazid	Rat	↓AST, ALT, ALP, bilirubin ↑SP	Vahab and Harindran, 2016
Tinospora cordifolia (Heart-leaved moonseed)	Aerial part	Aqueous	Carbon tetrachloride	Rat	↓ALT, ALP, bilirubin	Goyal and Kumar, 2016
Valeriana wallichii (Mushkbala)	Root	Aqueous	Carbon tetrachloride	Rat	↑CAT, GSH ↓AST, ALT, ALP, MDA	Syed et al., 2017
Vernonia amygdalina (African bitter leaf)	Leaf	Ethanol	Dimethylnitrosamine	Rat	↓AST, ALT, ALP, GGT Improved TG, MDA, necrosis ↑SOD, CAT, GSH	Usunobun et al. 2015
Veronica ciliata (Dongdongchi)	Whole plant	Ethanol, petroleum ether	Paracetamol	Mouse	↑SOD, GSH ↓ALT, AST, MDA, TNF-α, NF-kβ	Tan et al., 2017
Viola canescens (Banafsha)	Whole plant	Methanol, Ethyl acetate	Carbon tetrachloride	Mouse	↓ALT, ALP, bilirubin, MDA ↑CAT, SOD Restored SP	Khan et al., 2017
Zizyphus jujube cv. Huanghetanzao (Red date)	Whole plant	Ethanol	Paracetamol, carbon tetrachloride	Mouse	↓AST, ALT, LDH, MDA ↑SOD, GSH-Px	Liu et al., 2015

Abbreviations: AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GSH: Reduced glutathione, GSH-Px: Glutathione peroxidase, CAT: Catalase, SOD: Superoxide dismutase, ROS: Reactive oxygen species, STP: Total protein, TB: Total bilirubin, CB: Conjugate bilirubin, SB: Serum bilirubin, DB: Direct bilirubin, TG: Triglyceride, MDA: Malondialdehyde, LDH: Lactate dehydrogenase, CCl_4: Tetra chloromethane/carbon tetrachloride, GGT: Gamma glutamyl transferase, LPO: Lipid peroxide, TC: Total cholesterol, TP: Total protein, ALB: Albumin, FBS: Fasting blood sugar, BUN: Blood urea nitrogen, UA: Uric acid, TBARS: Thiobarbituric acid reactive substance, LDL-c: Low density lipoprotein cholesterol, HDL-c: High density lipoprotein cholesterol, TNF-α: Tumor necrosis factor-α, IL-6: Interleukin-6, NO: Nitric oxide, FRAP: Ferric reducing ability plasma, NF-kβ: Nuclear factor kappa β, HO-1: Heme oxygenase-1, iNOS: Inhibitory nitric oxide synthase, ACP: Acid phosphatase, CHL: Cholesterol, CRE: Creatinine, MPO: Myeloperoxidase, TPN: Total protein, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, TLC: Total leukocyte count, DLC: Differential leukocyte count, TAP: Total antioxidant power, TTG: Total thiol groups, GGPT: Gamma glutamyl transpeptidase, IBR: Indirect bilirubin, MMPT: Matrix metalloproteinase, TGF-β: Transforming growth factor beta, TIMP: Tissue inhibitor matrix metalloproteinase, Col1α2: Collagen 1a2, Col3α1: Collagen 3a1, Smad2: Mothers against decapentaplegic homologue 2, B.wt: Body weight, SP: Serum protein, HAC: Hepatic anti-oxidant capacity

etc are compiled which have been reported for their hepatoprotective activity against various hepatotoxins.

Amiodarone causes hepatotoxicity with a characteristic prototype of enzyme turbulence. One study was reported on amiodarone-induced liver toxicity in rabbits. Gentamicin, an aminoglycoside antibiotic is used for treatment of bacterial infections. One of the side effects of gentamicin usage is its potential to induce hepatotoxicity. One study was performed on rat to examine the ameliorative effect of plant extract on gentamicin-mediated hepatotoxicity.

Among the entire listed plants, only a few severe toxicity studies were carried out. For example, *Acrocarpus fraxinifolius* did not show any sign of toxicity up to oral dose of 250 and 500 mg/kg in rats (Abd El-Ghffar et al., 2017) and ethanolic extract of *Pandanus odoratissimus* at a particular dose, LD_{50} was found to be 3,000 mg/kg when injected in rats (Mishra et al., 2015).

Botanical plants have been used for anticipation and management of hepatic disorders due to the charisma of chemical constituents. For instance, polyphenolic compounds have an imperative function in alleviating lipid oxidation as well as anti-oxidant activity. Sigmasterol, β-sterol and flavonoids from *Acalypha indica*, phenol and triterpenoids from *Centella asiatica* have provided defensive consequence in rat liver against hypoxia by means of lipid peroxidation (Dwijayanti et al., 2015). 70% ethanolic extract of *Oxalis stricta* has shown a higher concentration of polyphenolic components that was beneficial for therapy of liver disease by anti-lipoperoxidative activity (Patel et al., 2016). Phytochemical investigation of *Melothria perpusilla* extract revealed the presence of flavonoids, tannins and steroids that have a role in ameliorating hepatic damage by anti-oxidant mechanisms (Yengkhom et al., 2017). Citrus species containing flavonoids also play a crucial role in plant defense scheme. Hesperidin, a bioflavonoid present in citrus fruits, has pharmacological properties and control hepatic cholesterol production via inhibiting the 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase activity (Çetin et al., 2016). Fungal species have gained importance in the prevention of liver diseases.

Fruiting bodies of *Oudemansiella radicata,* an edible mushroom and belong to the family Physalacriaseae has hepatoprotective activity by anti-oxidant mechanisms attributed to heteropolysaccharides (mannose, glucose and galactose) prepared from the mushroom (Liu et al., 2017).

Heteropolysaccharides (arabinose and galactose) from *Zizyphus jujube*, commonly known as red date belongs to the family Rhamnaceae has been involved in liver protective activity via alleviating liver marker enzymes (Liu et al., 2015). Plants containing volatile or essential oils also are main pharmacological active compounds and confers positive effect from the medicinal point of view.

Essential oils of *Artemisia capillaries* has been investigated against carbon tetrachloride-induced hepatotoxicity and has approved protective potential on liver histology, hepatic profile and serum profile (Gao et al., 2016). Anti-oxidant compounds play the significant role in liver protection.

Phyllanthus emblica, due to its anti-oxidant compounds like ellagic acid and gallic acid, has approved hepatoprotective activity in alcohol induce toxicity model (Chaphalkar et al., 2017). Liver protection is also associated with control of protein and gene expression.

Fragaria ananassa (commonly called strawberry, family: Rosaceae) has anti-oxidant, anti-apoptotic and anti-fibrotic properties by gene expression regulation (Hamed et al., 2016)

Conclusion

This study signified the probable hepatoprotective effects of therapeutic plants. It can be concluded that plants have verified hepatoprotective potential which can be utilized in outlook to prepare valuable hepatoprotective drugs. There is still necessitating scrutinizing the hepatoprotective potential of plants on molecular stage so that authentic method of phytochemical action can be explored.

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Authors declare no conflict of interest

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