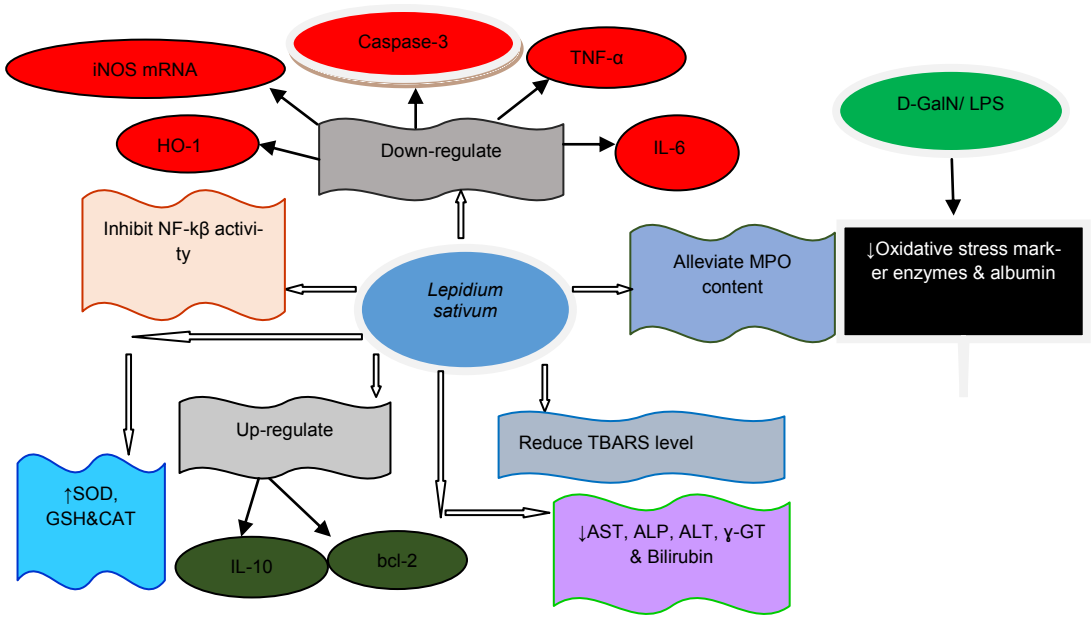


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# Mini Review

## Advances in hepatoprotective medicinal plants research

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# 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 12$^{th}$ 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

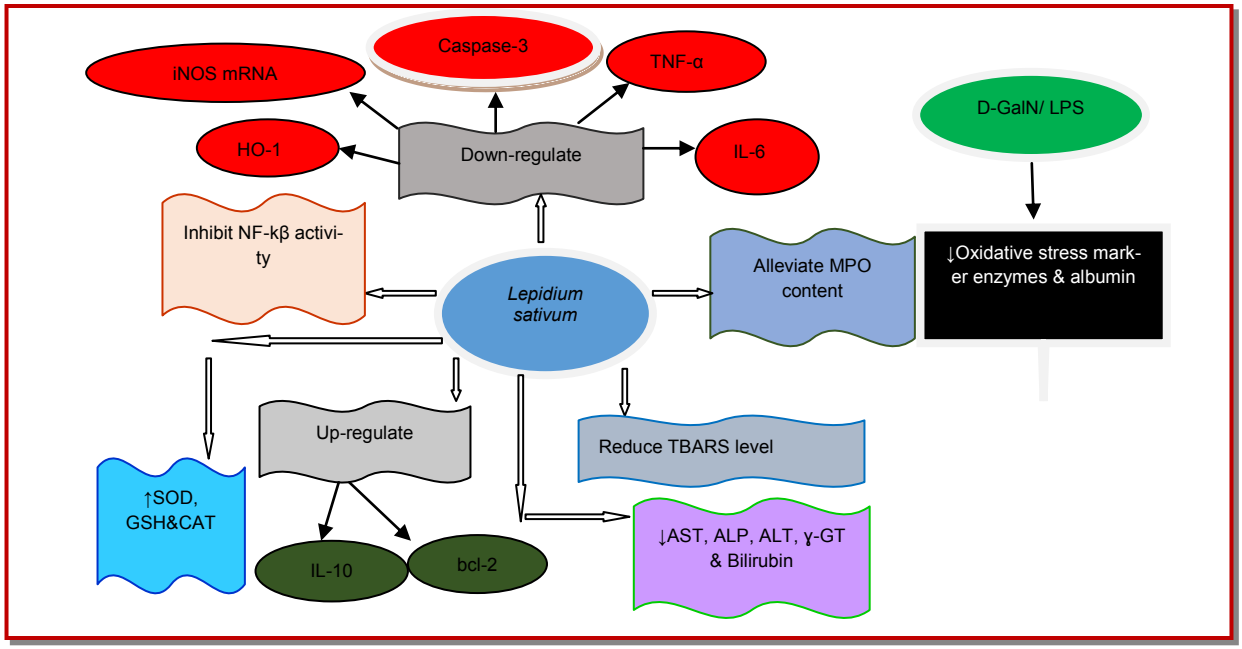


Figure 1: D-GalN/LPS (D-galactosamine/lipopolysaccharides) decrease oxidative stress marker enzymes and albumin. *Lepidium sativum* ethanolic extract has shown hepatoprotective activity by decreasing AST (aspartate aminotransferase), ALP (alkaline phosphatase), ALT (alanine aminotransferase), ɣ-GT (gamma 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,

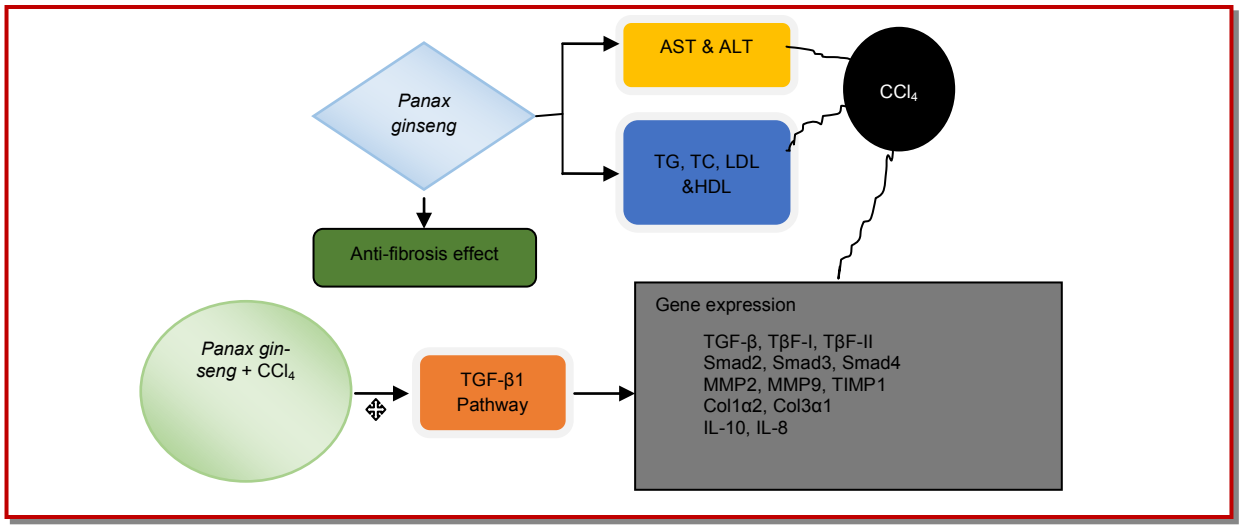


Figure 2: *Panax ginseng* has shown anti-fibrosis effect via TGF-β1 signaling pathway in $CCl_4$ induced liver fibrosis model. The administration of ginseng in combination with $CCl_4$ significantly decreased the expression of TGF-β; its receptors, Smad2, Smad3, Smad4, MMP2, MMP9 and TIMP1 genes expression. 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<br>Restored collagen and hydroxyproline levels<br>↓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<br>↑TP, CAT, GSH-Px | Ubhenin et al., 2016 |
| *Caesalpinia gilliesii* (Yellow bird of paradise) | Flower | Dichloromethane | Carbon tetrachloride | Rat | ↓AST, ALT<br>↑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<br>Paracetamol | Rat | ↓AST, ALT, ALP, bilirubin, UA, MDA<br>↑GSH, SOD, CAT | Awodele et al., 2016 |
| *Cassia fistula* (Golden shower tree) | Fruit seed | Methanol | No | Chick | ↓AST, ALT, ALP, urea, CRE<br>↑plasma protein | Iqbal et al., 2016 |
| *Cassia tora* (Coffee cassia) | Leaf | Methanol | Carbon tetrachloride | Rat | ↑TP, ALB, GSH<br>↓AST, ALT, ACP, ALT, AST, MDA | Saravanan and Malarvannan, 2016 |
| *Centratherum anthelminticum* (Banjira) | Seed | Ethanol | Carbon tetrachloride | Rat | ↓AST, ALP ALT, IBR, bilirubin, UA<br>↑TP, ALB<br>↓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<br>↑TPN, ALB | Gnanadesigan et al., 2016 |
| *Citrus macroptera* (Satkara/wild orange) | Fruit | Ethanol | Paracetamol | Rat | ↓ALT, GGT, LDH, AST, ALP, TB, TG, TC<br>Improved serum CRE, urea, UA, $Na^+$, $K^+$, $Cl^-$<br>↓MDA | Paul et al., 2016 |
| *Coreopsis tinctoria (Golden tickseed)* | Flowers | Ethanol | Carbon tetrachloride | Rat | ↓ALT, AST, MDA,NO, TNF-α, IL-6, IL-1β<br>↑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, $Na^+$<br>↑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<br>↑GSH (liver) | Saenthaweesuk et al., 2017 |
| *Eclipta alba* (Bhangra) | Leaf | Aqueous | Carbon tetrachloride | Rat | ↓ALT, AST, ALP, SB<br>↑SP | Beedimani and Shetkar, 2015 |
| *Elettaria cardamomum* (True cardamom) | Seed | Aqueous | Gentamicin | Rat | ↓AST, ALT, BR, CHL, TG, LDL-C<br>↑SB, HDL-C | Aboubakr and Abdelazem, 2016 |
| *Eriocaulon quinquangulare* (Eriocaulonsp Australia Red) | Whole plant | Aqueous | Ethanol | Porcine liver slices | ↓ALT, AST, LDH<br>↓Lipid peroxidation | Fernando and Soysa, 2016 |
| *Ferulago angulata* (Chavir) | Flower | Methanol | N-nitroso-dimethylamine | Rat | ↓SOD, CAT, GSH-Px<br>↓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,<br>↑GSH, SOD, CAT, GPx expression<br>↑anti-apoptotic protein Bcl2<br>↓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<br>↑ TP | Yang et al., 2017 |
| *Helicanthus elastica* (Mango Mistletoe) | Whole plant | Ethanol | Paracetamol | Mouse | ↓AST, ALT<br>↑ALPase activity<br>↓Serum TB<br>↑Serum TP | Kumar et al., 2016 |
| Grapefruit<br>Lemon<br>Orange<br>(Hesperidin) | No | No extract | Carbon tetrachloride | Rat | ↑GSH, CAT, SOD<br>↓TBARS synthesis,<br>Reduced caspase-3 activation | Çetin et al., 2016 |
| *Holostemma ada-kodien* (Holostemma creeper) | Whole plant | Alcohol | Paracetamol | Rat | ↓ALT, ASP, ALP, SB, MDA<br>↑GSH | Sunil et al., 2015 |
| *Homalium letestui* (Makoli) | Stem | Ethanol | Paracetamol | Rat | ↓ALT, AST, ALP, bilirubin<br>↑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<br>↑ 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<br>Up-regulate IL-10, mitigate MPO, NF-kβ | Raish et al., 2016 |
| *Lawsonia inermis* (Henna) | Leaf | Methanol | Carbon tetrachloride | Rat | ↓AST, ALT, ALP, bilirubin<br>Hepatocytes regeneration | Mohamed et al., 2016 |
| *Mammea africana* (African mammee apple) | Stem bark | Ethanol | Paracetamol | Rat | ↓AST, ALT, ALP, bilirubin<br>↑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<br>↑TC, TG, HDL-C, TP, ALB<br>↑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<br>Normalize G-Px<br>↑GSH, CAT, SOD<br>↓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<br>↑SP, GSH | Reddy and Urooj, 2017 |
| *Murraya koenigii* (Curry tree) | Leaf | Ethanol | Carbon tetrachloride and paracetamol | Rat | ↓AST, ALP, ALT, LPO<br>↑SOD, CAT, GSH | Sangale and Patil, 2017 |
| *Nymphaea lotus* (White water lily) | Whole plant | Methanol | Carbon tetrachloride | Rat | ↓AST, ALT, bilirubin, TBARS (liver)<br>↑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<br>↓LDH leakage and cell necrosis<br>Prevent GSH (liver) depletion | González-Ponce et al., 2016 |
| *Otostegia persica* (Goldar) | Aerial parts | Ethanol | Carbon tetrachloride | Rat | ↓AST, ALT, ALP, bilirubin, MDA<br>↑SP | Toori et al., 2015 |
| *Oudemansiella radicata* (Mushroom/ Rooting shank fungus) | Dried fruiting bodies | Ethanol | Carbon tetrachloride | Mouse | ↓ALT, AST<br>MDA (liver) suppression,<br>↑SOD, GSH-Px<br>Prevent ↑ in liver wt,<br>↓Lipid droplet accumulation | Liu et al., 2017 |
| *Oxalis stricta* (Pickle plant) | Whole plant | Ethanol | Paracetamol | Rat | Prevent GSH depletion<br>↓lipid peroxidation, AST, ALT, ALP, bilirubin | Patel et al., 2016 |
| *Panax ginseng* (Ginseng) | Root | Aqueous | Carbon tetrachloride | Rat | ↓Hepatic fat, reticular fiber deposition,<br>↓AST, ALT, LDL, TGF-β, Smad2, Smad3, Smad4, MMP2, MMP9, TIMP-1, Col1α2, Col3α1<br>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<br>↓ALT, AST, ALP, bilirubin | MacDonald et al., 2016 |
| *Piper trioicum* | Aerial part | Ethanol | Carbon tetrachloride | Rat | ↓AST , ALT, bilirubin, MDA<br>↑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<br>↑SOD, CAT, GPx | Rajeshkumar and Kayalvizhi, 2015 |
| *Pterospermum acerifolium* (Karnikara tree) | Leaf | Petroleum ether, alcohol | Paracetamol | Rat | ↓ALP, AST, ALT, LPO<br>↑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<br>↑SP, SOD, CAT, GSH | Kandimalla et al., 2016 |
| *Rosa canina* (Dog-rose) | Fruit | Ethanol | Carbon tetrachloride | Rat | ↓AST, ALT, ALP, MDA<br>↑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<br>↑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<br>↑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<br>↑SP | Islam et al., 2015 |
| *Terminalia catappa* (Sea almond tree) | Bark | Alcohol | Isoniazid | Rat | ↓AST, ALT, ALP, bilirubin<br>↑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<br>↓AST, ALT, ALP, MDA | Syed et al., 2017 |
| *Vernonia amygdalina* (African bitter leaf) | Leaf | Ethanol | Dimethylnitrosamine | Rat | ↓AST, ALT, ALP, GGT<br>Improved TG, MDA, necrosis<br>↑SOD, CAT, GSH | Usunobun et al. 2015 |
| *Veronica ciliata* (Dongdongchi) | Whole plant | Ethanol, petroleum ether | Paracetamol | Mouse | ↑SOD, GSH<br>↓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<br>↑CAT, SOD<br>Restored SP | Khan et al., 2017 |
| *Zizyphus jujube cv. Huanghetanzao* (Red date) | Whole plant | Ethanol | Paracetamol, carbon tetrachloride | Mouse | ↓AST, ALT, LDH, MDA<br>↑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. More studies to find out the scientific basis of herbal treatment can open the new era in developing the drugs which are not only effective but also free from side effects.

## Conflict of Interest

All authors have completed the ICMJE uniform disclosure form and declare no support from any organization for the submitted work.

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