



Hepato Protective Activity – A Review

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ABSTRACT

The liver is one of the most important organs in the body, performing a fundamental role in the regulation of diverse processes, among which the metabolism, secretion, storage, and detoxification of endogenous and exogenous substances are prominent. Due to these functions, hepatic diseases continue to be among the main threats to public health, and they remain problems throughout the world. Despite enormous advances in modern medicine, there are no completely effective drugs that stimulate hepatic function, that offer complete protection of the organ, or that help to regenerate hepatic cells. Thus, it is necessary to identify pharmaceutical alternatives for the treatment of liver diseases, with the aim of these alternatives being more effective and less toxic. The use of some plants and the consumption of different fruits have played basic roles in human health care, and diverse scientific investigations have indicated that, in those plants and fruits so identified, their beneficial effects can be attributed to the presence of chemical compounds that are called phytochemicals.

Keywords: Alcoholic liver disease, Decompensated liver disease, Chronic liver disease, Liver abscess, Hepatoprotective agents, Antibiotics.

Introduction

Liver

The liver is the largest organ, accounting for approximately 2% to 3% of average body weight. The liver has 2 lobes typically described in two ways, by morphologic anatomy and by functional anatomy. Located in the right upper quadrant of the abdominal cavity beneath the right hemidiaphragm, it is protected by the rib cage and maintains its position through peritoneal reflections, referred to as ligamentous attachments. Although not true ligaments, these attachments are avascular and are in continuity with the Glisson capsule or the equivalent of the visceral peritoneum of the liver.

Function of Liver

- Bile production and excretion.
- Excretion of bilirubin, cholesterol, hormones, and drugs.

- Metabolism of fats, proteins, and carbohydrates.
- Enzyme activation.
- Storage of glycogen, vitamins, and minerals.
- Synthesis of plasma proteins, such as albumin, and clotting factors.

Hepatic Diseases

- **Fatty Liver Disease:** liver disease is an excess buildup of fat in the liver – or more than 5 to 10 percent of the liver's total weight. This condition is most common in those who are overweight, diabetic or have metabolic syndrome. If unrelated to alcohol consumption, it is known as nonalcoholic steatohepatitis, or NASH. Otherwise, it is known as alcoholic liver disease. Excess liver fat can lead to inflammation, progressing to scarring (or cirrhosis)

in 20 percent of patients. Treatment includes weight loss, exercise, diabetes control, regulating blood pressure and cholesterol, limiting or eliminating alcohol consumption and not smoking.

- **Hepatocellular Carcinoma:** At Cleveland Clinic, liver cancer is diagnosed and treated by a multidisciplinary team that includes our hepatologists and experts from a number of other departments, including hepato-pancreato-biliary surgery, interventional radiology and medical oncology. As with any cancer, early diagnosis is critical. Patients with certain liver diseases are susceptible to liver cancer and should be screened regularly. Cleveland Clinic hepatologists have experience in determining who needs to be screened and how often. In collaboration with Cleveland Clinic Taussig Cancer Institute, patients are provided a wide variety of treatment options, including access to appropriate clinical trials.^[4]

- **Liver Cirrhosis:** The liver, the largest internal organ in the body, is essential in keeping the body functioning properly. It removes or neutralizes poisons from the blood, produces immune agents to control infection, and removes germs and bacteria from the blood. It makes proteins that regulate blood clotting and produces bile to help absorb fats and fat-soluble vitamins. You cannot live without a functioning liver. In cirrhosis of the liver, scar tissue replaces normal, healthy tissue, blocking the flow of blood through the organ and preventing it from working as it should. Cirrhosis is the twelfth leading cause of death by disease, killing about 26,000 people each year. Also, the cost of cirrhosis in terms of human suffering, hospital costs, and lost productivity is high.^[1]

- **Hepato Toxicity**

Hepatotoxicity is related to mitochondrial dysfunction, inhibition of cellular respiration or alteration in β oxidation of fatty acids. These result in apoptosis, necrosis, autophagy and, therefore, cell death. The main clinical-pathological manifestations of hepatotoxicity and its histological findings are

- Acute hepatitis (characterized by parenchymal inflammation, necrosis and Kupffer cells in the sinusoids).
- Chronic hepatitis (fibrosis).
- Fulminant hepatitis (necrosis and inflammation).
- Cholestatic hepatitis (inflammation and liver damage).
- Cholestasis (biliary plugs in zone 3).
- Vanishing bile duct syndrome (damage to the bile ducts, cholestasis and inflammation).
- Granulomatous hepatitis (granulomas in portal tracts or parenchyma).
- Macrovesicular steatosis (lipid droplets in the cytoplasm of the hepatocyte).
- Microvesicular steatosis (tiny drops of lipids in the cytoplasm of the hepatocyte).
- Steatohepatitis (steatosis, lobular inflammation, engorged hepatocytes and pericellular fibrosis).

Sign and Symptoms

- Stomach pain.
- Nausea and vomiting and fatigue.
- Dark-colored urine.
- Light-colored bowel movements.
- Jaundice (yellow skin and eyes).
- Loss of appetite.
- People taking HIV medicines that may cause hepatotoxicity should know about the possible symptoms of hepatotoxicity.^[2]

Complications

Complications of alcoholic liver disease include Oesophageal variceal bleed are dilated oesophageal veins secondary to portal hypertension. When fluid accumulates in the abdomen, between two membrane layers that together make up the peritoneum develops ascites. An ascitic fluid infection without an obvious intra-abdominal medically curable source develops in patients with cirrhosis and ascites is characterized as spontaneous bacterial peritonitis (SBP).

Hepatorenal syndrome (HRS) is a condition in which people with severe liver disease suffer renal failure. Hepatic encephalopathy, also known as portosystemic encephalopathy (PSE), is a reversible brain dysfunction disease that

occurs in people with extensive liver failure. Hepatocellular carcinoma (HCC) is a kind of liver cancer that most commonly affects people who have cirrhosis or chronic liver disease.

Symptoms

- Nausea.
- Vomiting.
- Fever.
- Fatigue.
- Loss of weight.

Risk Factor:

- Tattoos or body piercings.
- Blood transfusion.
- Exposure to chemicals or toxins.
- Family history of liver disease.
- Heavy alcohol intake.
- Obesity.
- Type 2 diabetes.
- Injecting drugs using shared needles.
- Exposure to blood and body fluids.^[3]

Prevention

- Stop drinking alcohol: Once you develop symptoms of chronic alcoholism, symptoms of liver failure or pancreatitis – absolutely stop taking alcohol in any form, join deaddiction centre if not able to stop alcohol intake with self-determination.
- Avoid risky behavior: Use a condom during sex. If you choose to have tattoos or body piercings, be picky about cleanliness and safety when selecting a shop. Seek help if you use illicit intravenous drugs, and don't share needles to inject drugs.
- Get vaccinated: If you're at increased risk of contracting hepatitis or if you've already been infected with any form of the hepatitis virus, talk to your doctor about getting the hepatitis B vaccines.
- Use medications wisely: Take prescription and nonprescription drugs only when needed and only in recommended doses. Don't mix medications and alcohol. Talk to your doctor before mixing herbal supplements or prescription or nonprescription Drugs.
- Avoid contact: with other people's blood and body fluids. Hepatitis viruses can be spread by accidental needle sticks or improper cleanup of blood or body fluids Keep your food safe :

Wash your hands thoroughly before eating or preparing foods. If traveling in a developing country, use bottled water to drink, wash your hands and brush your teeth.

- Take care with aerosol sprays: Make sure to use these products in a well-ventilated area, and wear a mask when spraying insecticides, fungicides, paint and other toxic chemicals.
- skin Protect your skin : When using insecticides and other toxic chemicals, wear gloves, long sleeves, a hat and a mask so that chemicals aren't absorbed through your skin.
- Maintain a healthy weight: Obesity can cause nonalcoholic fatty liver disease (NAFLD) that may progress to steatohepatitis and alater to Cirrhosis of liver. Details of Metabolic syndrome.
- Low sodium diet: decreases water / fluid retention.
- Adequate protein: Keeps fluid in arteries & veins rather than leaking into tissues.
- Avoid Excessive fluid intake.
- Small Frequent meals are useful if patients feel full quickly or if appetite has decreased.
- Muscle wasting can be controlled by continues energy supply.
- Reduce nausea.
- Control blood sugar level.

Hepatoprotective Drugs

- N-Acetylcysteine and Glutathione.
- Glycyrrhizin Acid Preparation.
- Polyene Phosphatidylcholine.
- Bicyclol.
- Silymarin.
- Ursodeoxycholic Acid.
- S-Adenosylmethionine.
- Cholestyramine.

Other drugs that can lead to liver injury include:

- Amiodarone.
- Anabolic steroids.
- Birth control pills.
- Chlorpromazine.
- Erythromycin.
- Halothane (a type of anesthesia)
- Methyldopa.
- Isoniazid.^[4]

Herbal Treatment for Hepato Protective Activity

S.No	Description of plant	Result and discussion
1	<i>Amaranthus spinosus</i> L. Plant part used- Whole plant	Similarities were observed in the root type (having a taproot with many lateral roots as dicotyledonous plants), possession of simple leaves. ^[5]
2	<i>Artemisia absinthium</i> L. Plant part used- Aerial parts	The three essential oils from Tajikistan, sample #1 from the Muminobod region collected at the budding (pre-flowering) stage, and two samples from the Yovon region, collected during the budding (pre-flowering) period and the full flowering period, #2 and #3, respectively, showed qualitative similarities. ^[6]
3	<i>Astragalus membranaceus</i> (Fisch.) Bunge., Plant part used- Whole plant	This perspective review discussed the botanical, geographical, historical, and the therapeutic properties of <i>A. membranaceus</i> , with a special focus on its health improving effects and medicinal applications both in vitro and in vivo. ^[7]
4	<i>Calotropis procera</i> (Aiton) Dryand. Plant part used- Flowers	<i>Calotropis procera</i> is a shrub or small tree 2–4 m tall (rarely up to 6 m tall), with distinctive grey-green waxy leaves (Figure 1). As described by Grace (2006, 2009), the stems are greygreen, smooth, somewhat crooked and covered with a soft, thick, corky bark. ^[8]
5	<i>Clerodendrum abilioi</i> R. Fern Plant part used- Leaves	which in turn has accelerated the scientific research regarding the hepatoprotective activity. In this overview, the globe due to their wide applicability and therapeutic efficacy coupled with least side effect. ^[9]
6	<i>Ficus carica</i> L. Plant part used- Leaves	Phytochemical research carried out on <i>F. carica</i> has led to the isolation of few classes of plant metabolites. Most of the phytochemical works have been employed on leaves and fruits of <i>F. carica</i> . ^[10]
7	<i>Glycyrrhiza uralensis</i> . Plant part used- Leaves	These traditional medicine practices include the wider range of health care practices that includes folk or tribal's rituals as well as Chinese, Ayurveda, Korean, Siddha medicine, Japanese, Iranian medicine, Unani, ancient traditional African medicine. ^[11]
8	<i>Orthosiphon stamineus</i> Plant part used- Leaves	Treatment with EOS resulted in dose-dependent inhibition of paw edema in acute and chronic models of inflammation. It also inhibited significantly the production of TNF- α , IL-1 COX-1, and COX-2 ^[13]
9	<i>Baliospermum montanum</i> Plant part used- Root	Liver is an important part in human beings and plays a very important and major role in metabolism and excretion of xenobiotics from the body. ^[14]
10	<i>Tridax procumbens</i> Plant part used- Leaves	It is a small, semi prostrate, annual or perennial and herbaceous creeper weed having short, hairy blade-like leaves. Corolla is yellow color. The stem is elongated to the height of 20-60 cm tall, branched, sparsely hairy, rooting at nodes. ^[15]
11	<i>Allium hirtifolium</i> Alliaceae Plant part used- Flower	Based on available pharmaceutical investigations, antioxidant and hepatoprotective effects of <i>A. hirtifolium</i> have been also demonstrated. ^[16]

12	<i>Apium graveolens</i> <i>Apiaceae</i> Plant part used-Seeds	<i>A. graveolens</i> has many pharmacological properties such as antifungal, antihypertensive, antihyperlipidemic, diuretic, and anticancer. ^[17]
13	<i>Cynara scolymus</i> (artichoke) <i>Apiaceae</i> Plant part used-Leaf	In <i>C. scolymus</i> leaf extract, there are compounds such as cynarin, luteolin , chlorogenic acid , and caffeic acid, other flavonoids, and polyphenol compounds. ^[18]
14	<i>Berberis vulgaris</i> (<i>barberry</i>) <i>Berberidaceae</i> Plant part used-Fruit	Berberine, oxyacanthine, and other alkaloids such as berbamine, palmatine, columbamine, malic acid , jatrorrhizine, and berberrubine comprise some other compound. ^[19]
15	<i>China officinalis</i> (<i>marigold</i>) <i>Asteraceae</i> Plant part used-Flower	It has been taken in order to treat fevers and jaundice and to promote menstruation. Extracts, tinctures, balms, and salves of <i>C. officinalis</i> have been applied directly to heal wounds and soothe inflamed and injured skin. ^[20]
16	<i>Nigella sativa</i> (<i>garlic</i>) <i>Alliaceae</i> Plant part used-Root	<i>N. sativa</i> contains more than 30 fixed oils. The volatile oil has been proved to contain thymoquinone and many monoterpenes such as p-cymene and α -pinene. ^[21]
17	<i>Taraxacum officinale</i> <i>Asteraceae</i> Plant part used-Root	The treatment of hepatobiliary problems, its root has been shown to have sesquiterpene lactones, triterpenes, carbohydrates, fatty acids (myristic), carotenoids (lutein), flavanoids (apigenin and luteolin). ^[22]
18	<i>Taraxacum. porrifolius</i> , <i>Asteraceae</i> Plant part used-Root	Beginners can often be bewildered by the number of rather similar species with yellow dandelion-like flowers. Even experienced botanists can be deceived by the enormous variability shown by some common species. ^[23]
19	<i>Prangos ferulacea</i> <i>Apiaceae</i> Plant part used-Leaf	The genus of <i>Prangos</i> with the common Persian name of Jashir includes 15 species, occurring widely in many regions of the country. ^[24]
20	<i>Marrubium vulgare</i> , <i>Lamiaceae</i> Plant part used-Seeds	The plant possesses antihypertensive, analgesic, anti-inflammatory, and hypoglycemic effect, antidiabetic activity, and antioxidant properties. ^[25]
21	<i>Citrullus lanatus</i> <i>Cucurbitaceae</i> Plant part used-Fruit	Its fruits are eaten as a febrifuge when fully ripe or almost putrid. The fruit is also diuretic and helpful for the treatment of dropsy and renal stones. ^[26]
22	<i>Prunus armeniaca</i> <i>Rosaceae</i> Plant part used-Fruit	It has organic acids, salicylic acid, tannins and potassium salts, p-coumaric acid, and protocatechuic, ferulic, and diferulic acids. ^[27]
23	<i>Sterculia setigera</i> <i>Del</i> Plant part used -Seeds	<i>Sterculia Setigera</i> stem bark that belongs to the family of Sterculiaceae was evaluated for its hepatoprotective activity in albino with liver damage induced. ^[28]
24	<i>Ocimum basilicum</i> <i>L.</i> Plant part used-Whole plant	The hepatoprotective activity of <i>Ocimum basilicum</i> L. whole plant ethanolic extract was evaluated. The study concluded that <i>O. basilicum</i> ethanolic extract has a potential hepatoprotective activity. ^[29]
25	<i>Acacia mellifera</i> (Vahl) . Plant part used -Leaves	Leaves: rachis 2-5 cm long, slender, sparsely puberulous to glabrous; glands more or less midway on petioles, circular, sessile, ca 0.5 mm diameter, pinna. ^[30]
26	<i>Adansonia digitata</i> <i>L</i>	The leaves have high beta-carotene and iron content and

	Plant part used-Fruit pulp	are eaten fresh as leafy vegetables or dried and powdered as a soup ingredient. They are also used to treat kidney and bladder diseases, asthma, general fatigue, diarrhea, insect bites and guinea worm. ^[32]
27	<i>Argemone mexicana L</i> Plant part used-Seeds	The hepatic injury was achieved by injection of CCl ₄ 3 ml/kg s.c in olive oil (1 : 1 v/v). The extracts were given at different doses, 100, 200, and 400 mg/kg/day for methanolic extract and 400 mg/kg/day. ^[32]
28	<i>Anogeissus leiocarpus (DC) Wall.</i> Plant part used-Bark	Oral administration of the ethanolic extract of the plant at a dose of 200 mg/kg displayed a significant hepatorenal protective effect against CCl ₄ by lowering liver biomarkers (AST, ALT, and ALP). ^[33]
29	<i>Balanites aegyptiaca L</i> Plant part used-Stem bark	The extracts were administered at the same time with CCl ₄ at a dose of 250 to 500 mg/kg orally for 10 days. Significant decreases in AST, ALT, and ALP activities. ^[34]
30	<i>Cannabis sativa L</i> Plant part used-Bark	The hepatotoxicity induced by injecting CCl ₄ in paraffin oil (1 : 9 v/v) at a dose of 0.2 ml/kg for 10 days was found to be inhibited by simultaneous oral administration of <i>C. sativa</i> oil of at a dose of 1 and 0.5 ml/kg. ^[35]
31	<i>Capparis decidua (Forsk.)</i> Plant part used-Stem	The hepatotoxicity produced by administration of CCl ₄ in paraffin oil (1 : 9 v/v) at a dose of 0.2 ml·kg ⁻¹ for 10 days was found to be inhibited by simultaneous oral administration of aqueous and methanolic extracts. ^[36]
32	<i>Combretum hartmannianum (Schweinf)</i> Plant part used-Leaves	The hepatoprotective effect of this plant may be due to high antioxidant activity in DPPH free radical scavenging assay and flavonoid content. ^[37]
33	<i>Dobera glabra (Forsk)</i> Plant part used- Leaves	The preliminary phytochemical screening of the powdered plant showed the presence of alkaloids, flavonoids, tannins, sterols, saponins, cyanogenic glycosides, and coumarins as major constituents of the studied extracts. ^[38]
34	<i>Khaya senegalensis (Desr.)</i> Plant part used-Bark	The hepatoprotective effect of the methanolic extract of the bark of Sudanese plant <i>Khaya senegalensis</i> , which is used in folk medicine for treatment of jaundice, was investigated. ^[39]
35	<i>Kigelia africana (Lam.)</i> Plant part used- Leaves	The study revealed that, administration of the two extracts (aqueous and methanol) of the plant seeds has toxic effects which resulted in alterations in haematological parameters (Hb, WBCs MCH, MCHC). ^[40]
36	<i>Lawsonia inermis L</i> Plant part used-Leaves	The two doses of the plant extract showed dose-dependent hepatoprotective effects, as evident by the significant reduction in serum levels of AST, ALT, ALP, and bilirubin along with the improvement in histopathological liver sections compared with CCl ₄ . ^[41]

Conclusion:

It can be concluded that there are a variety of phytochemicals in plant products with hepatoprotective activity against CCl₄-induced toxicity in animal models. The studied fractions show hepatoprotective potential with promising value as hepatoprotective drugs of natural origin in comparison with silymarin as the standard hepatoprotective drug. glucoside, arabinoside and rhamnoside) and kaempferol glycoside derivatives were highly abundant in Administration of thioacetamide resulted in marked elevation in liver enzymes, elevation of lipid profile and alteration in oxidative stress parameters. It can be concluded from the results of the present study that AHPL/AYTAB/0613 tablet possesses hepatoprotective activity in high, medium and low doses in CCl₄, ethanol and paracetamol-induced hepatotoxicity in rats. No signs and symptoms of toxicity in any group were observed, and all the formulations tested were well tolerated by the rats. Although high- and low-dose formulations are also effective as hepatoprotective agents, medium dose formulation of AHPL/AYTAB/0613 is recommended for potent hepatoprotective effect in humans.

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