Herbals in Hepatology

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Abstract

Medicinal herbs are significant source of hepatoprotective drugs. Mono and poly-herbal preparations have been used in various liver disorders. According to one estimate, more than 700 mono and poly-herbal preparations in the form of decoction, tincture, tablets and capsules from more than 100 plants are in clinical use. A drug having beneficial affect on the liver is known as hepatoprotective drug. On the other hand, drugs having toxic affect on the liver are better known as hepatotoxic drugs. Clinical research has also shown that herbals have genuine utility in the treatment of liver diseases. The article deals with investigative work done on herbals beneficial in liver and gall bladder ailments.

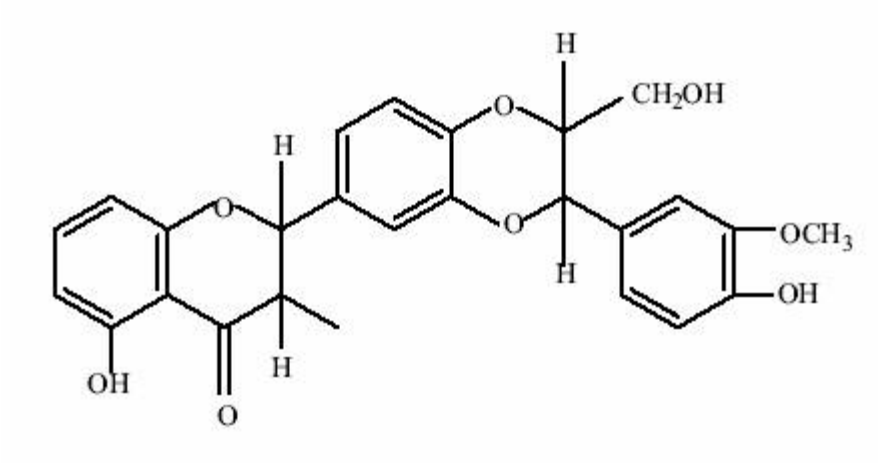
Introduction

The liver performs number of important functions, including Bile production and excretion, excretion of bilirubin (bile pigment), cholesterol (a form of fat), hormones, and drugs. metabolism of fats, proteins, and carbohydrates, enzyme activation, storage of glycogen (stored form of glucose), vitamins, and minerals, synthesis of plasma proteins, such as albumin and globulin, and clotting factors and blood detoxification and purification.

Some functions are not affected by any medicinal preparation to be much of therapeutic value. Hepato-biliary drugs are used for increasing biliary secretions. These groups of drugs are also known as cholagouges which are believed to increase the secretion of bile. Precisely speaking, cholagouges help in better emptying out of the biliary tract rather then increasing bile formation and emptying.

The main function of bile is stimulation of normal bile flow (also known as choleresis). For achieving this affect, drugs derived from plant source are frequently used and are popularly known as choleretics. Cholagouges hasten the gall-bladder emptying whereas choleretics act specifically on liver. Bile is hurried down before it finds time to be altered in the gut. This is affected by group of drugs known as cholagouge purgatives.

Silymarin is a potent hepatoprotecive drug having established place in hepatology practice. Silymarin is a flavonol-lignan mixture obtained from seeds of *Silybum marianum*. Silymarin is a mixture of silybin, isosilybin, silychristin and silydianin. Research on Indian medicinal herbs like *Picrorhiza kurroa* (Kutki) and *Andrographis paniculata* (kalmegh) has thrown light on hepatoptotective activity and it is more promising than silymarin.



Structure of Silybin (Silymarin)

The hepatoprotective activity of the drug is said to be based on two mechanisms:

1. Silymarin alters the structure of the outer membrane of the hepatocytes in such a way as to prevent penetration of the liver toxin into the interior of the cell.

2. Silymarin stimulate the action of nucleolar polymerase A, resulting in ribosomal protein synthesis and, thus stimulates the regenerative ability of the liver and formation of new hepatocytes.

Ayurveda and Liver

Ayurveda is the oldest healthcare system. As far as diagnosis and treatment of liver diseases is concerned, Ayurveda has its own concept. The three biological humors (*vata*, *pitta* and *kapha*) are considered to play major role in pathogenesis as well as treatment of all diseases. In Ayurveda, liver is known as *ykritta*. It has been described as one of the chief organ of the human body. The major disease described in Ayurvedic texts is *Kamla,* which is compared with jaundice.

According to Charka Samhita, *Pandu* (anemia) and *kamla* are related to each other. In fact if a patient suffering from *pandu* keeps on consuming *pitta* aggravating foods, the already disturbed *pitta* further affects blood and skin resulting in *kamla*. The eyes, skin, mucus membrane and nails are yellow coloured. In addition the patient has general debility, indigestion and anorexia.

Ayurvedic texts have described three types of *kamla*.

1. *Kostha-ashrita*: *Kostha* refers to the abdomen. *Kamla* confined to abdominal cavity is known as kostha-ashrita kamla.
2. *Shakha-ashrita*: *Shakha* refers to arms and legs. *Kamla* appearing in extremities is known as *shakha-ashrita kamla*.
3. *Ubhya-ashrita*: When *kamla* is found both in abdomen and extremities it is known as *ubhya-ashrita kamla*.

Although the Ayurvedic texts have not described liver diseases in detail but still number of formulations have been mentioned which have been used successfully by practitioners of Ayurveda. These formulations are of diverse origin and may be derived from plant source alone or herbs in combination with minerals. In following pages we will discuss popular Ayurvedic medicinal herbs used in the treatment of liver diseases.

S.No	Name of formulation	Dose	Vehicle (if any)
1.	*Amlakadi avleha.*	1-2 teaspoonfuls.	
2.	*Astadasang lauha*.	250 mg.	Buttermilk.

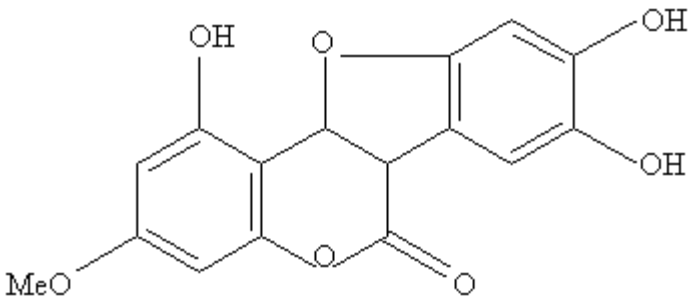
3.	*Darvyadi leha*	600 mg.	Honey and ghee.
4.	*Dhatri-lauha*.	250 mg.	Honey, ghee and sucrose.
5.	*Kamlataka lauha*.	125-600mg.	Honey.
6.	*Navayash lauha*.	125mg-600mg.	Honey and ghee.
7.	*Nisha lauha*.	250 mg.	Honey and ghee.
8.	*Panchamrita lauha mandoora*	75 mg- 250 mg.	*Talamahkana* (*Euyrale ferox*).
9.	*Parpata arista*.	3-6 teaspoonfuls.	Water.
10.	*Phalatrikadi quatha*.	3-6 teaspoonfuls.	Honey.
11.	*Poonarnava mandoora*.	375 mg.	Buttermilk.
12.	*Triushna mandoora*.	375 mg.	Buttermilk.
13.	*Vajravataka mandoora*	1-2 tablets.	Buttermilk.
14.	*Vishaladi churna*.	20G (4 teaspoonfuls)	Lukewarm water.

Table 1: It shows formulations mentioned in Charaka Samhita used in the treatment of jaundice.

Herbals/ botanicals as hepatoprotective agents

***Eclipta alba* (L.) Hassk (bhringraja)**

Eclipta alba is popularly known as trailing eclipta. *Eclipta alba* grows wild in moist places or on the sides on the sides of water channels. It contains resin, alkaloid (eclipticine), and Wedelolactone ($C_{15}H_{10}O_7$). Another alkaloid, 25-ß-hydroxyverazine has been reported from alcoholic extract of the *Eclipta alba*



Structure of Wedelolactone

Saxena, Singh and Anand (1993) studied the hepatoprotective effect of ethanol/ water (1:1) extract of *Eclipta alba* in rats against carbon tetrachloride induced hepatotoxicity. The researchers concluded that *Eclipta alba* prevented carbon tetrachloride induced hepatotoxicity by regulating the levels of hepatic microsomal drug metabolizing enzymes. Singh, Chandan, Agarwal and Anand (2001) studied in vivo hepatoprotective activity of active fractions from ethanolic extract of *Eclipta alba* leaves. The extract was further fractionized and agent with potent hepatoprotecvtive activity was looked for. One fraction was containing wedelolactone and other fraction was containing apigenin, 4-hydroxybenzoic acid and protocatcheuic acid. The second fraction was found to be more active hepatoprotective. Dixit and Achara studied the hepatoprotective activity of *Eclipta alba* in guinea pigs against carbon tetrachloride induced hepatotoxicity. It was concluded that *Eclipta alba* has significant hepatoprotective activity against carbon tetrachloride induced hepatotoxicity.

***Picrorhiza kurroa* Royle (Kutki)**

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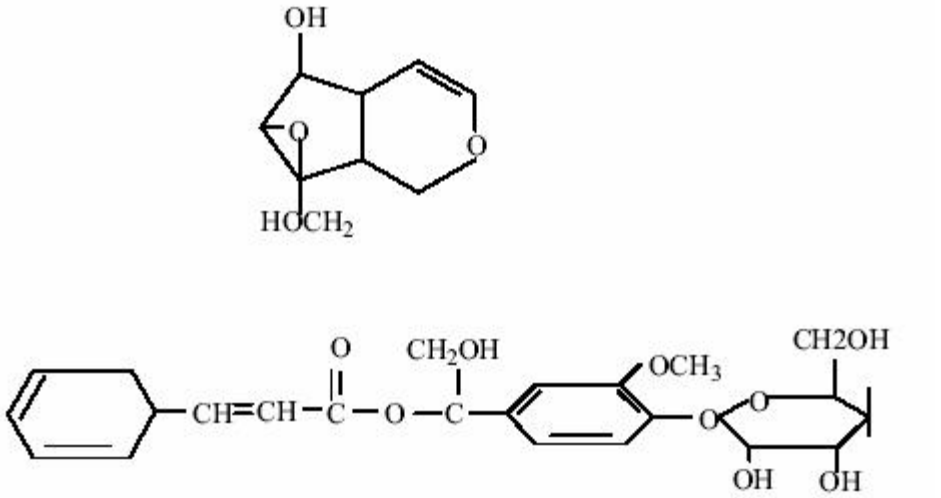
Picrorhiza kurroa is a distinguished medicinal herb of Ayurveda. It has been described under the group of bitter drugs. It is an established herbal remedy for variety of disease ranging from indigestion to hepatitis. Modern clinical studies have confirmed the efficacy and safety of *Picrorhiza kurroa* for the treatment of liver disease. The roots and rhizomes are used in medicinally important parts. Powder, decoction, infusion, confection, and alcoholic extract of the drug are prescribed in Ayurveda and Homeopathy.

The chemistry of *Picrorhiza kurroa* is complex. The active constituent is known kutkin, a mixture of kutkoside and picroside.



Structure of Kutkins (Kutkosides and Picrosides).

Picrosides are iridoid glycosides and have been further divided into picrosides I, II, and III. Other constituents are apocynin, andorsin, and cucurbitacin glycosides. Pharmacologically, Kutkin (Picrosides and kutkosides) has hepatoproptective activity. Apocynin is a potent NADPH oxidase inhibitor and has anti-oxidant and anti-inflammatory activity.

Some herbalists have described *Picrorhiza kurroa* as liver herb. Today we have estimated active constituents of the drug, which may be responsible for the hepatoprotective activity of the drug. Most of the studies have shown *Picrorhiza kurroa* extract (standardized to kutkin content) has potential hepatoprotective activity as compared to placebo.

Kutkin from *Picrorhiza kurroa* has shown significant curative activity in vitro in primary cultured rat hepatocytes against toxicity induced by thioacetamide, galactosamine, and carbon tetrachloride. Liver injury was induced in 16 mice by thrice-a-week injection of carbon tetrachloride for nine weeks. Eight of them were given daily feeding of *Picrorhiza kurroa* extract (12 mg/Kg) 10 days prior to carbon tetrachloride injection. Control mice (n = 6) were injected with olive oil for the same period. Serum markers of liver injury and histology of liver tissues were studied. Hepatic glutathione, total thiol, glucose 6-phosphate dehydrogenase, catalase, lipid peroxidation and plasma membrane-bound Na+/K+ ATPase were also determined. The extract of *Picrorhiza kurroa* appears to offer significant protection against liver damage by carbon tetrachloride. In another study, the active constituent of *Picrorhiza kurroa* showed a dose dependent hepatoprotective activity against oxytetracycline induced hepatic damage in rats.

Phyllanthus niruri **Linn (Bhumyamla)**

Phyllanthus niruri is well-known Ayurvedic pant used for its beneficial effect in liver diseases. It is folk remedy for asthma, bronchitis, anemia, jaundice and tuberculosis. Whole plant is used in medicine. It contains lignans (phyllanthin and hyophyllanthin). Syamasundar, Singh, Thakur, Huasin, Kiso and Hikino (1985) studied the Hepatoprotective constituents of *Phyllanthus niruri*. They isolated phyllanthin, hypophyllanthin and tricontanal from hexane extract of

Phyllanthus niruri. All the three constituents demonstrated hepatoprotecvtive activity. Phyllanthin and hypophyllanthin were active against carbon tetrachloride and galactosamine induced hepatotoxicity whereas tricontanal was active only against galactosamine induced hepatotoxicity.

***Taraxacum officinale* Wigg.**

Taraxacum officinale is commonly known as dandelion, loin's teeth and fairy clock. In Ayurveda, the plant is known as dugdhpheni as it abounds in milky juice. The root of the medicinal plant is reputed remedy for liver and gall bladder diseases in various systems of alternative medicine. The medicinal plant contains rich amount of bitter principles including taraxacin, taraxacerin and lactupicrin. It also contains triterpenoids (taraxasterol and taraxerol), flavonoids and tetrahydrodetin B.

Animal research has given indication that Taraxacum officinale has no effect on bile flow. According to European Scientific Cooperation of Phytotherapy T. officinale has demonstrated cholretic effect in dogs and rats. However human trials indicating definite use of the drug in liver diseases are missing.

***Cichorium intybus* Linn**

Cichorium intybus, member of family Compositae and leaves of the plants are used as salad. It contains bitter principles (Cichorin, lactucin and intybin). In addition it contains inulin. Kalanatri and Rastmanesh from Ahwaz University of Medical Science, Iran studied the hepatoprotective potential of crude extract of *Cichorium intybus*. The extract was administered at doses of 25mg/kg, 50mg/kg, 75 mg/kg, 100 mg/kg, 125 mg/kg and 150 mg/kg orally to the mice. The extract demonstrated hepatoprotective effect at a dose of 75mg/kg and carbon tetrachloride elevated liver enzymes were significantly reduced as compared to control group. The drug also showed liver tissue regenerating capacity.

***Tephrosia purpurea* Pers**

Tephrosia purpurea is commonly known as Wild Indigo. In Ayurveda, it is known as Sharpunkha, as the tip of the leaves are pointed. In Ayurveda, the drug is especially indicated in the treatment of enlarged spleen but animal research has demonstrated *Tephrosia purpurea* to be hepatoprotective. Root and alkali preparation (Sharpunkha-kshara) are used in medicine. It contains bioflavonoids including rutin, rotenoid and tephrosin. Ramamurthy and Srinivisan (1993) studied the hepatoprotective effect of *Tephrosia purpurea* against galactosamine and carbon tetrachloride induced liver damage in experimental animals. Powder of aerial parts was administered orally at a dose of 500 mg/kg. *Tephrosia purpurea* inhibited the rise of SGOT, SGPT and bilirubin. The drug also demonstrated liver tissue regenerating capacity as evident by histopatahological changes. Thus the authors concluded the drug to be effective in acute and chronic hepatotoxicity and the action may be due to membrane stabilizing effect on liver cells.

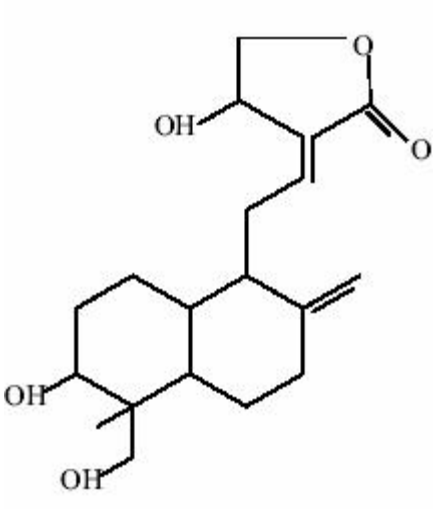
***Solanum nigrum* Linn**

In Ayurveda the plant is known as Kakamachi. *Solanum nigrum* is a small herb growing in waste and shady places. Whole plant and berries are used in medicine. The fruit contains four glyco-alklaoids including Solamargine, solasonine or solanine and solanigrine. Solamargine and solasonine are present in leaves also. Sultana, Perwaiz, Iqbal and Athar (1995) demonstrated the antioxidant activity of crude extract of *Solanum nigrum* and *Cichorium intybus*. The drugs inhibited the free radical mediated DNA damage. According to Authors, free radical scavenging activity of *Solanum nigrum* and *Cichorium intybus* may account for there hepatoprotective activity.

Raju, Anbuganpathi, Gokulakrishan, Rajkapoor, Jayakar and Manian (2003) studied the hepatoprotective effect of ethnaolic extract of *Solanum nigrum* against carbon tetrachloride induced hepatotoxicity. They evaluated the effect by studying biochemical and histopatalogical parameters. According to authors the extract demonstrated significant hepatoprotective effect.

***Andrographis paniculata* Nees**

Andrographis paniculata is well known medicinal plant for its usefulness in liver diseases. In Ayurveda it is known as Bhunimba or Kalmegha. It is used as bitter tonic and febrifuge. Because of bitter taste it is popularly known king of bitters. It contains diterpene lactones (Andrographolide, neoandrographolide and kalmeghin).



Structure of Andrographolide

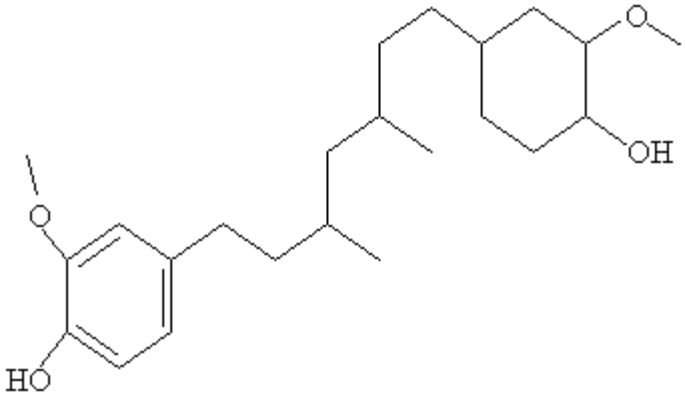
Shukla, Visen, Patnaik and Dhawan (1992) studied the cholretic activity of Andrograpaholide. The diterpene lactone produced dose dependent chloretic effect evidenced by increase in bile flow, bile salt and bile acids in animal models. The cholretic effect of *Andrographis paniculata* was found to be better than silymarin. According to Trivedi and Rawal (2001), alcoholic extract of *Andrographis paniculata* demonstrated significant hepatoprotective activity against carbon tetrachloride induced hepatotoxicity. The fact was further supported at morphological, biochemical and functional parameters.

***Boerhaavia diffusa* Linn.**

In Ayurveda it is known as Punarnava and commonly known as spreading hogweed. It is found throughout India. In India the roots of the plant find application in Ayurvedic prescriptions for liver and gall bladder dieses. However its specific use in Ayurveda is as diuretic. It contains an alkaloid punarnavine. Chandan, Sharma and Anand (1991) reported hepatoprotective activity of alcoholic extract of B. diffusa against carbon tetrachloride induced hepatotoxicity in animal models. The extract demonstrated significant cholretic activity. Rawat, Mehrotra, Tripathi and Shome (1997) studied the hepatoprotective activity of roots and aqueous extract in thioacetamide intoxicated rats. The aqueous extract demonstrated significant hepatoprotective activity as compared to root powder.

***Curcuma longa* Linn.**

Curcuma longa commonly known as turmeric is another plant which has got scientists attention as novel hepatoprotective agent. Dried rhizomes are used in medicine. It is cultivated throughout India. In Ayurveda, paste of the drug is applied over the right hypochondriac region for the treatment of enlarged liver. Above all the use of drug in the treatment of jaundice is mentioned. It contains yellow coloured coloring matter called curcumin.

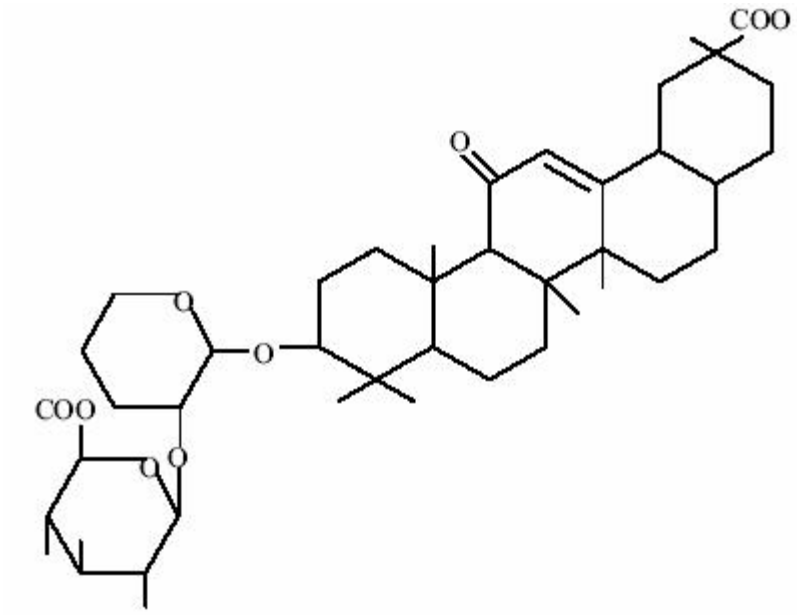


Structure of Curcumin

Curcuminoids have shown to be antioxidant and anti-inflammatory activities. Hepatoprotective activity can be ascribed to antioxidant activity.

***Glychyrrhiza glabra* Linn.**

Glychyrrhiza glabra is popularly known as licorice. In Ayurveda, it is known as Yastimadhu which signifies sweet taste of the drug. The roots are used in medicine. It contains glycosides including glychyrrhizin, glycyramarin, isoliquiritin and isoliquiritin. Glychyrrhizin is the sweet principle of licorice and is fifty times sweeter than sugar. Other components include asparagine, resin and estrogen steroid. Glychyrrhizin is anti viral, anti-inflammatory and anti-allergic. Recent work in Japan has thrown light on hepatoprotective activity of licorice. Glycyrrhizin has demonstrated hepatoprotective activity in animal models against carbon tetrachloride induced toxicity. It reduces alanine transaminase and aspartate transaminase values in serum. The exact mode of action is not clear but it has been proposed that glycyrrhizin has inhibitory effect on immune mediated cytotoxicity against hepatocytes and on nuclear factor (NF)-kappa B, which activates genes encoding inflammatory cytokines in the liver.

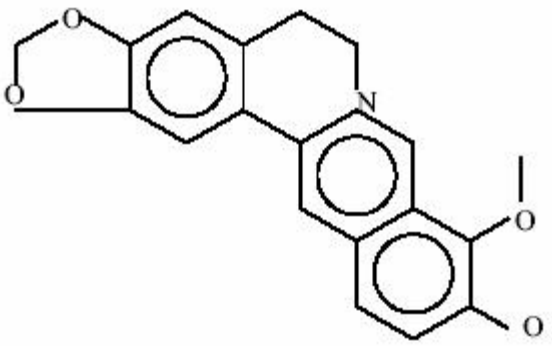


Structure of Glychyrrhizin

***Berberis aristata* DC**

Berberis aristata, commonly known as Indian Barberry is important medicinal plant of Ayurveda and Western herbal

medicine. In Ayurveda it is known as Daruharidra. Rasaut is semisolid watery extract obtained from *Berberis aristata*. The plant is used as hepatic stimulant and chalogouge. Chemically it contains alkaloids (berberine, berbamine and oxycanthine), tannins, gum and resin.



Structure of Berberine

***Sida rhombifolia* Linn**

Sida rhombifolia (Atibala) is one of the five plants described under 'Bala' drug of Ayurveda. It is commonly known as Alkali Traditionally it used as antirheumatic, astringent and demulcent. It is reported to contain an alkaloid (ephedrine) and mucilage.
Rao and Mishra (1997) studied the hepatoprotective and anti-inflammatory activity of various parts and aqueous extract of *Sida rhombifolia*. The animals were rendered hepatotoxic by treatment with carbon tetrachloride, paracetamol and rifampicin. Inflammation was induced by carrageenan. The aerial parts and there aqueous extract demonstrated significant hepatoprotective activity whereas methanolic extract of aerial parts demonstrated significant anti-inflammatory activity. It was concluded that hepatoprotevtive activity of the drug can de due to free radical scavenging activity.

***Swertia chirata* Ham.**

Swertia chirata is known as *Kiratatikta* in Ayurveda. The infusion was once a time a popular remedy for convalescence from a severe illness. It is also used in the treatment of loss of appetite. Whole plant is used in medicine. It contains bitter glycosides including amarogentin and gentiopicrin and xanthones. Mukherjee, Sur and Maiti (1997) reported hepatoprotective activity of *Swertia chirata* in rats.

***Emblica officinalis* Gaertn**

Emblica officinalis, commonly known as Indian Gooseberry or Emblic myrobalan. It is important ingredient of *Triphala*, famous Ayurvedic remedy for constipation. Fruits are used in medicine. *Emblica officinalis* is considered to the best source of Ascorbic acid (vitamin C). In addition, it contains gallic acid, tannic acid, albumin and calcium. The bark contains leukodelphinidin and procyanidin. The fruit contains alkaloids phyllantidine and phyllanthine. Aqueous extract of *Emblica officinalis* has significant antioxidant and hepatoprotective activity. The extract was found to be potent inhibitor of lipid peroxide formation of scavenger of hydroxyl and super oxide radicals.

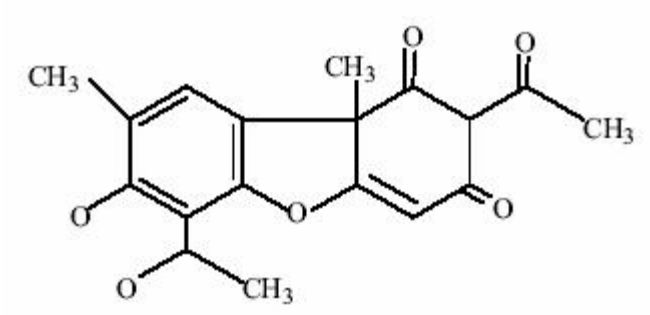
Spirulina platensis

Spirulina is a blue green alga growing in fresh water. *Spirulina* is widely prescribed in anemia. It has curative effect on inflammatory disease of liver and pancreas. It contains vitamins A, C, E and B-complex, ß-carotene and polyunsaturated fatty acids. Vadiraja, Gaikwad and Madyastha (1998) studied the effect of C-phycocyanin on carbon

tetrachloride and R-(+) - pulegone induced liver damage. Intraperitoneal administration of single dose of phycocyanin in a dose of 200mg/kg one to three hours prior to carbon tetrachloride and R-(+) - pulegone, demonstrated significant hepatoprotective activity.

Eucalyptus terelicomis

Ursolic acid isolated from leaves of *Eucalyptus terelicomis* demonstrated hepatoprotective effect against thiacetamide, galactosamine and carbon tetrachloride in rats. Pretreatment with ursolic acid increased the viability of liver cells. In large doses, ursolic acid demonstrated choleretic effect. Further the authors concluded that hepatoprotective activity of ursolic acid was comparable to silymarin.



Structure of Ursolic acid

***Tecoma undulata* G.Don**

In Ayurveda it is used in the treatment of enlarged spleen, hence the name *plihaghana* (*pliha* = spleen). It is also prescribed in liver diseases. *Rohitkarishta* is formulation based on the plant.

***Achyranthes aspera* Linn**

Achyranthes aspera is small herb which grows all over India. In Ayurveda, it is also known as *Apamarga*. In English it is known as Prickly chaff flower. In traditional medicine, it is popular remedy for bronchitis and asthma. Decoction of the herb is said to be diuretic. Whole herb and alkali prepared from the herb (*Apamargakshara*) are used in enlarged liver.

Conclusion: From the work cited in the article it can be concluded that herbals/ botanicals have usefulness in the treatment of diseases like hepatitis, jaundice, and loss of appetite. Animal research has thrown light on possible hepatoprotective mechanism of herbals. Ayurvedic drugs have promising profile as far as drug development from natural source is concerned. One can expect herbal drugs to acts as lead compound for development of economical, effective and non toxic hepatoprotective agents.

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