Hepatoprotective Drugs from Plants

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Liver is a vital organ in the body, any change in its physiology leads to other secondary complications like liver abscesses, liver cirrhosis, hepatitis and liver cancer. No effective measures are available for the treatment of liver diseases in modern medicine. Moreover, hepatotoxicity is a common condition associated with various drugs used in modern medicine. In such a situation, man always looks towards nature as a source of medicine, since herbal drugs, used in the Indian System of Medicine are claimed to be effective and safe in such ailments. The systematic and scientific investigation of these plants justifies their use as hepatoprotective drugs.

Introduction

Liver is a vital organ in the body which secretes bile and is a site of great metabolic functions. Its physiology can be affected by various environmental factors: chemicals, drugs, alcohol, contaminated food, toxins, malnutrition as well as some hereditary factors. Such changes in physiology lead to other secondary physiological complications. Disorders of liver can be classified as:

a) Liver abscess — manifested by temperature elevation, sweat and chills, liver enlarged, painful, tender and bulging.
b) Liver cirrhosis — generalised pathology of liver with disturbed normal architecture of the lobes due to infiltration of fibrous tissue and nodule formation.
c) Hepatitis — inflammation of liver caused by viral or bacterial infections and chemical or physical agents.
d) Liver cancer.

No effective measures are available for the treatment of liver diseases in modern medicine. In such a situation, man always looks towards nature as a source of medicine since herbal drugs, used in the Indian System of Medicine, are claimed to be effective and safe in such ailments. Scientists have studied various prospectives of plant remedies for liver disorders. In seventies, *Vinca rosea* was investigated for the liver protecting activity. In eighties, attention was focused on *Panax ginseng.* Now, Neem tree, apart from its other activities, is also under investigation for the hepatoprotective activity. Indian Council of Medical Research, New Delhi, had adopted liver diseases as one among its six thrust areas for multidisciplinary study. Under this programme, screening of active ingredients from *Picrorrhiza kurroa* and *Phyllanthus niruri* have shown marked protection against jaundice due to viral hepatitis. *Phyllanthus urinaria,* allied species of *Phyllanthus* which is devoid of phyllanthin shows greater activity as compared to *Phyllanthus niruri* (60%). The *Phyllanthus* genus of plants is known to the common man as Bhuiamala or Bhuiamlaki which is considered to be most effective for liver disorders. The leaf, stem and root extract of *Phyllanthus debilis* are as effective as the whole plant extract in treatment of carbon tetrachloride induced liver dysfunction. Thus use of aerial parts of *Phyllanthus debilis* by folk healers is justified by these results. Extracts of milkthistle fruit is under investigation for the treatment of alcoholic hepatitis. According to Indian Society of Gastroenterology, *Glycyrrhiza glabra* prevents multiplication of viruses inside the liver.

Hepatotoxic Models

There are many hepatotoxic models used for the biological evaluation of hepatoprotective activity. It has also been known that biochemical and physiological functions of liver are altered when the animal is exposed to a variety of hepatotoxic chemicals like carbon tetrachloride, galactosamine, thioacetamide, heavy metals or drugs such as paracetamol. Based on this, several models are available and various plants are tested for their hepatoprotective activity, if any. Various parameters studied for the activity are SGPT, SGOT, total proteins, albumin, bilirubin, cholesterol, phospholipids, triglycerides, alkaline phosphatase, acid phosphatase, cytochrome P-450, and glucose-6-phosphate, etc.

Herbal Medicines

The subject of hepatoprotective herbal medicines is very wide. According to one survey, nearly forty polyherbal commercial preparations are available. Some of the recently tested herbal drugs which show promising hepatoprotective activity are Dextrina, Jigrine and Icterene[1]. Dextrina increased hepatic glutathione levels by inhibiting lipid peroxidation in rats. Jigrine progressively reduced alcohol, carbon tetrachloride and paracetamol induced increase in serum transaminase, bilirubin and lipid peroxides in liver. Clinical and histochemical observations of Jigrine and Icterene revealed better tolerance, weight gain, increased appetite and elevated levels of hemoglobin in hepatitis induced rats.

Picrolive, a standardised fraction of *Picrorrhiza kurroa* roots, containing about 60% of a mixture of picroside I and kutkoside in the ratio of 1:1.5, provides significant protection against most of the biochemical alterations in liver produced by carbon tetrachloride[2]. Ayurvedic medicines like Kalmegh, Kumari asav, Argyovardini, Kumarkalp[3] and Kamilari[4] showed protection against carbon tetrachloride induced hepatic necrosis. Kalmegh, *Andrographis paniculata* showed excellent hepatoprotective action by stimulating glucose metabolism. Kamilari consists of extracts of *Thespesia populnea* flowers, *Elettaria cardamom, Zingiber officinalis, Glycyrrhiza officinalis, Piper longum* and honey. Kolaviron, a mixture of *Garcinia kola* biflavonides prevents thioacetamide induced liver toxicity. Hepatogard protects ethanol induced liver damage by reversing the rise in liver transaminases. Incidence of severe hepatotoxicity, caused by some antitubercular drugs like isoniazid, pyrazinamide, para-aminosalicylic acid thiacetazone and rifampicin, were shown to be effectively managed by Stimulive[5], an indigenous compound formulation. The methanol extract of crude composite drugs made from *Aurantium nobilis* and *Polygonum aviculare* are effective in hepatic toxicity caused by alpha napthyl isothiocynate. The increased bilirubin level by alpha napthyl isothiocynate is suppressed by the drug by release of some intrahepatic enzymes. The composite drug from plants *Berberis asiatica, Solanum nigrum* and *Achyranthes aspera* minimizes the lesions of hepatotoxicity induced by paracetamol poisoning.

Euphorbia microphylla is suggested to be efficaciously able to afford protection against liver intoxication by carbon tetrachloride[6]. *Ocimum sanctum* has been reported to possess antihepatotoxicity and two triterpenes from the leaves have shown to possess hepatoprotective effect against carbon tetrachloride induced liver damage in rats[7]. Recently, Central Institute of Medicinal and Aromatic Plants (CIMAP) has developed a hepatoprotective drug from *Lantana camara* (seeds). The triterpenoid, oleanolic acid, a phytochemical present in the plant may be responsible for its activity. *Curculigo orchiodes* Gaertn. and *Fumaria indica,* the constituents of several traditional drug formulations, show hepatoprotective activity against various hepatotoxicants, such as, carbon tetrachloride, paracetamol and rifampicin. *Apium graveolens* and *Hygrophila auriculata* show marked hepatoprotective activity against paracetamol induced hepatotoxicity. These are extensively employed in indigenous medicines for the treatment of liver ailments and are ingredients of polyherbal formulations marketed in India for liver diseases.

The fumaric acid and diethyl fumarate, isolated by the fractional solubilisation and column chromatography from *Tridax procumbens,* were found to possess antihepatotoxic activity against carbon tetrachloride and D-glactosamine induced hepatoxicity in rats. Administration of the alcoholic extracts of leaves and bark of *Delonix elata* orally in dose of 100 mg/kg followed by carbon tetrachloride after 30 minutes administration, prevented the rise of bilirubin, ALKP, SGOT and SGPT levels. Results of histopathological studies also show significant recovery. The hepatoprotective nature of the flavone isolated from *Pentanema indicum* was tried against thioacetamide induced hepatotoxicity on mice. The drug treated

nimals showed significant protection as evident from he fall in lipid peroxides and enhanced glutathione ontent.

Ficus racemosa syn. *Ficus glomerata* Roxb. Moraceae) is a well known plant in Indian folklore nedicine. The petroleum ether extract showed ignificant protective effect by lowering the serum evels of transaminase, bilirubin and alkaline phosphatase levels in carbon tetrachloride induced hepatotoxicity. The effect produced was comparable to that of standard hepatoprotective agents. Alcohol and light petroleum extracts of *Coccinia indica* (Cucurbitaceae) were screened for antihepatotoxic activity against carbon tetrachloride induced hepatotoxicity. Both extracts showed marked hepatoprotective activity. *Murraya koenigii* extracts were able to decrease the liver damage induced by paracetamol both by decreasing the serum level and normalising the liver cytology. The hot extract of *Murraya koenigii* also increased glutathione levels, decreased lipid peroxidation and protein degradation which were increased by paracetamol administration.

The biochemical estimation from serum had shown that rutin isolated from *Ruta graveolens* (Rutaceae) had significantly decreased the SGOT, SGPT, alkaline phosphatase, total and direct bilirubin and lipid peroxidation as compared to that of carbon tetrachloride induced hepatotoxicity. Rutin showed a marked hepatoprotective activity. The powder and different extracts of the fruits of *Moringa pterygosperma* Gaertn., traditionally used in the treatment of ascites, rheumatism, liver and spleen diseases were screened for their hepatoprotective activities in albino rats. The aqueous extracts showed significant hepatoprotective activity against carbon tetrachloride and paracetamol induced hepatic damage, whereas the methanolic extract was found more effective against rifampicin induced toxicity on the liver[8].

The ethanol extract of *Polygala elongata* and magniferin were screened for their antihepatotoxic activity using carbon tetrachloride intoxicated rats as the model of liver injury. The activity was monitored using biochemical and histopathological parameters. Both fractions tested exhibited significant reversal of the carbon tetrachloride elevated serum enzyme levels with normalisation of the liver cytology. The study justifies the use of *Polygala elongata* as a hepatoprotective in the indigenous system of medicine.

Cassia fistula Linn. (Leguminosae) is widely cultivated throughout India as an ornamental plant. This plant has been used in the treatment of various ailments including hepatoprotective, dating back to Sushruta samhita and Charak samhita. The protective effect of *Cassia fistula* leaf extract was confirmed by histopathological examination of liver sections of leaf extract treated group of rats. The extract showed significant protective effect by lowering levels of SGOT, SGPT, bilirubin and alkaline phosphatase. The extract at a dose of 400 mg/kg showed significant hepato-protective activity which was comparable to the standard hepatoprotective agent Neutrosec containing methionine, choline and vitamins.

The grape seed oil is obtained from grape seed after the wine pressing. It has a very high level of antioxidant, vitamin E. The antioxidant property is claimed to be due to the mechanism of hepatoprotective activity. There was a significant increase in the serum enzyme levels after paracetamol induced liver damage in male albino rats which was reversed with grape seed oil. The liver damage produced by paracetamol was also reversed with grape seed oil[9]. Extracts from the leaves of *Ginkgo biloba* reversed the increase in the serum enzyme levels and significant decrease in total proteins and albumin levels after carbon tetrachloride. There was a significant increase in malondialdehyde levels and decrease in glutathione levels which were reversed with *Ginkgo biloba*. These extracts were comparable to silymarin[10]. A study of the hepatoprotective activity of *Tinospora cordifolia* on kupffer cell function using carbon clearance test as a parameter showed significant improvement in kupffer cell function and a trend towards normalisation. *Tinospora cordifolia* appears to improve surgical outcome in patients with malignant obstructive jaundice by strengthening the host defence. The Ayurvedic use of the plant in liver ailments appears justified although the active principle is yet to be isolated and identified[11]. The plant *Feronia elephantum*, Correa (Rutaceae) has been mentioned in the Ayurvedic literature as a hepatoprotective. The hepatoprotective effect of aqueous extract was confirmed by histopathological examination in carbon tetrachloride induced rats.

The proprietary herbal formulation, containing a mixture of *Azima tetracantha, Allium cepa, Foeniculum vulgare* and *Glycyrrhiza glabra* advocated as hepatoprotective was investigated. In experimental

carbon tetrachloride induced liver damage in rats, post-treatment with this formulation provided hepatoprotection against most of the biochemical alterations produced by carbon tetrachloride and also reversed the altered. The degree of hepatoprotection was maximum at 3 days regimen at 360 mg/kg dose. The hepatoprotective activity was compared with the marketed formulations Liv 52 and Hepatogard. LIVP-7, a polyherbal formulation composed of various hepatoprotective herbal extracts and each 450 mg capsule contains the standardised extracts of *Andrographis paniculata,* 75 mg; *Picrorrhiza kurroa,* 75 gm; *Eclipta alba,* 75 mg; *Boerhaavia diffusa,* 45 mg; *Azadirachta indica,* 30 mg; *Swertia chirata,* 30 mg; *Solanum nigrum,* 37.5 mg; *Terminalia arjuna,* 15 mg; *Aphanamixis rohituka,* 15 mg; *Terminalia chebula,* 30 mg, and *Fumaria indica,* 22.5 mg. LIVP-7 provided significant protection against alcohol/carbon tetrachloride induced liver damages in rats. LIVP-7 has also been reported to provide protection against carbon tetrachloride induced damage in isolated rat hepatocytes. The formulation was reported to be nontoxic following long term administration in rats[12].

The different extracts of *Wrightia tinctoria* Roxb. R.Br. (Apocynaceae) leaves were tested for its hepatoprotective activity against carbon tetrachloride induced hepatotoxicity in albino rats. Petroleum ether and ethanolic extracts have shown significant hepatoprotective activity. The alcoholic extract of *Trianthema portulacastrum* has shown decrease in enzyme activity of both SGPT and SGOT, and as the inducer of the microsomal enzymes. Thus hepatoprotective action of this drug is likely to be due to its ability to induce microsomal enzymes thereby accelerating the excretion of carbon tetrachloride, or could be due to the inhibition of lipid peroxidation induced by carbon tetrachloride. Further the alcoholic extract has shown equal degree of activity as compared to silymarin used as a standard[13].

Conclusion

The world has tremendous potential in plant based drugs, the systematic and scientific investigations and validation of therapeutic efficacy of various plants will likely to give such leads in the future for wide range of disease conditions. Since India is one of the largest reservoir of herbs and medicinal plants, there is great potential to develop new drugs from plants. There are some diseases like osteoporosis, asthma, memory loss, and immune system disorders for which no effective drugs are available in modern system of medicine. Remedies for these are claimed by Traditional System of Medicine. These claims and clues are needed to be justifiably presented and developed to provide relief worldwide and to give firm footing to traditional systems of medicines employing herbal drugs.

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