



A REVIEW OF HEPATOPROTECTIVE NATURAL PRODUCTS

Fasalu Rahiman O.M^{*}, Rupesh Kumar M, Tamizh Mani T, Mohamed Niyas k

Dept. of Pharmacology, Bharathi College of pharmacy, Bharathinagara, Mandya, Karnataka, India – 571422

*Corresponding author's E-mail: fasaluom@gmail.com

Accepted on: 25-02-2011; Finalized on: 28-04-2011.

ABSTRACT

The maintenance of a healthy liver is essential for the overall well being of an individual. Because liver is a vital organ which can't replace and were it plays a major role in metabolism and excretion of xenobiotics from the body. Liver injury or liver dysfunction is a major health problem that challenges not only health care professionals but also the pharmaceutical industry and drug regulatory agencies. Liver cell injury caused by various toxic chemicals such as certain antibiotic, chemotherapeutic agents, paracetamol, carbon tetrachloride, thioacetamide etc., excessive alcohol consumption and microbes are well studied. The available synthetic drugs to treat liver disorders in this condition also cause further damage to the liver. Hence, Herbal drugs have become increasingly popular and their use is wide spread. Herbal medicines have been used in the treatment of liver diseases for a long time. A number of herbal preparations are available in the market. The present review is aimed at compiling data on promising phytochemicals from medicinal plants that have been tested in hepatotoxicity models using modern scientific system.

Keywords: Liver, liver disease, hepatotoxicity, hepatoprotective activity, natural products.

INTRODUCTION

The liver plays an astonishing array of vital functions in the maintenance, performance and regulating homeostasis of the body. It is involved with almost all the biochemical pathways to growth, fight against disease, nutrient supply, energy provision and reproduction¹. And it functions as a centre of metabolism of nutrients such as carbohydrates, proteins and lipids and excretion of waste metabolites. The bile secreted by the liver has, among other things, plays an important role in digestion. Therefore, maintenance of a healthy liver is essential for the overall well being of an individual.

Liver cell injury caused by various toxicants such as certain chemotherapeutic agents, carbon tetrachloride, thioacetamide, chronic alcohol consumption and microbes are common. Enhanced lipid per oxidation during metabolism of ethanol may result in development of hepatitis leading to cirrhosis.

Since time immemorial, mankind has made the use of plants in the treatment of various ailments. Herbal drugs have gained importance and popularity in recent years because of their safety, efficacy and cost effectiveness. The Indian Traditional Medicine like Ayurveda, Siddha and Unani are predominantly based on the use of plant materials. The association of medical plants with other plants in their habitat also influences their medicinal values in some cases. One of the important and well-documented uses of plant-products is their use as hepatoprotective agents. Hence, there is an ever increasing need for safe hepatoprotective agent². In spite of tremendous strides in modern medicine, there are hardly any drugs that stimulate liver function, offer protection to the liver from damage or help regeneration of hepatic cell.³ many formulations containing herbal extracts are sold in the Indian market for liver disorders.

But management of liver disorders by a simple and precise herbal drug is still an intriguing problem. Several Indian medicinal plants have been extensively used in the Indian traditional system of medicine for the management of liver disorder. Some of these plants have already been reported to posse's strong antioxidant activity^{4, 5, 6}.

HEPATOPROTECTIVE NATURAL PRODUCTS

Herbal-based therapeutics for liver disorders has been in use in India for a long time and has been popularized world over by leading pharmaceuticals. Despite the significant popularity of several herbal medicines in general, and for liver diseases in particular, they are still unacceptable treatment modalities for liver diseases. Hence development of plant based hepato protective drugs has been given importance in the global market. A large number of plants and formulations have been claimed to have hepatoprotective activity. Nearly 160 phytoconstituents from 101 plants have been claimed to possess liver protecting activity. In India, more than 87 plants are used in 33 patented and proprietary multi ingredient plant formulations⁷. In spite of the tremendous advances made, no significant and safe hepatoprotective agents are available in modern therapeutics. Therefore, due importance has been given globally to develop plant-based hepatoprotective drugs effective against a variety of liver disorders. The present review is aimed at compiling data based on reported works on promising phytochemicals from medicinal plants that have been tested in hepatotoxicity models. Hence the present review is aimed at collecting and compiling data based on reported works on promising phytochemicals from medicinal plants that have been tested in hepatotoxicity models. The hepato protective activities of *Solanum nigrum*, *Curcuma longa*, *Phyllanthus emblica*, *Foeniculum*



vulgare, *Swertia Chirata*, *Picrorhiza kurroa*, *Azadirachta indica*, *Andrographis paniculata*, *Flacourtia indica*, *Wedelia calendulacea*, *Aegle marmelos* and *Prostechea michuacana* is reviewed.

Solanum nigrum

The effects of *Solanum nigrum* extract (SNE) was evaluated on thioacetamide (TAA) induced liver fibrosis in mice. Mice in the three TAA groups were treated daily with distilled water and SNE (0.2 or 1.0 g/kg) via gastrogavage throughout the experimental period. SNE reduced the hepatic hydroxyproline and α -smooth muscle actin protein levels in TAA-treated mice. SNE inhibited TAA-induced collagen (α 1) (I), transforming growth factor- β 1 (TGF- β 1) and mRNA levels in the liver. Histological examination also confirmed that SNE reduced the degree of fibrosis caused by TAA treatment. Oral administration of SNE significantly reduces TAA-induced hepatic fibrosis in mice, probably through the reduction of TGF- β 1 secretion⁸.

In other study, the protective effects of aqueous extract of SN (ASNE) against liver damage were evaluated in CCl₄-induced chronic hepatotoxicity in rats. The results showed that the treatment of ASNE significantly lowered the CCl₄-induced serum levels of hepatic enzyme markers, superoxide and hydroxyl radicals. Liver histopathology showed that ASNE reduced the incidence of liver lesions including hepatic cells cloudy swelling, lymphocytes infiltration, hepatic necrosis, and fibrous connective tissue proliferation induced by CCl₄ in rats. Therefore, the results of this study suggest that ASNE could protect liver against the CCl₄-induced oxidative damage in rats, and this hepatoprotective effect might be contributed to its modulation on detoxification enzymes and its antioxidant and free radical scavenger effects (Lin *et al.*, 2008). The presence of plant extracts of *Solanum nigrum* and *Cichorium intybus* in the reaction mixture containing calf thymus DNA and free radical generating system protect DNA against oxidative damage to its deoxyribose sugar moiety. The effect was dependent on the concentration of plant extracts. However, the effect of *Cichorium intybus* was much pronounced as compared to the effect of *Solanum nigrum*. These studies suggested that the observed hepatoprotective effect of these crude plant extracts may be due to their ability to suppress the oxidative degradation of DNA in the tissue debris⁹. Since these herbs are commonly known as hepatoprotective agents and have shown their efficacy in protecting against CCl₄-induced hepatic injury¹⁰, it may be proposed that their efficacy may be attributed to their free radical scavenging ability.

Curcuma longa

Curcuma longa or turmeric is a member of Zingiberaceae family which is a perennial herb with short and thick rhizomes. Turmeric has been used extensively in traditional Chinese medicine and Ayurvedic medical system¹¹. *Curcuma longa* contains approximately 2% volatile oil, composed mainly of a- and b-turmerone,

monoterpenes (Leung and Foster 1996), 5% curcuminoids, mainly curcumin¹², minerals, carotene and vitamin C¹¹. The active constituent of *Curcuma longa* is Curcumin, which is the yellow pigment of turmeric. The hepatoprotective activity of the ethanol extract of *Curcuma longa* was investigated against paracetamol-induced liver damage in rats. At the dose of 600 mg/kg, paracetamol induced liver damage in rats as manifested by statistically significant increase in serum alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) and alkaline phosphatase (ALP). Pretreatment of rats with the ethanolic extract of *Curcuma longa* (100 mg/kg) prior to paracetamol dosing at 600 mg/kg statistically lowered the three serum liver enzyme activities. Moreover, treatment of rats with only the ethanolic extract of *Curcuma longa* (100 mg/kg) had no effects on the liver enzymes. This current result suggests that ethanolic extract of *Curcuma longa* has potent hepatoprotective effect against paracetamol-induced liver damage in rats¹³.

Phyllanthus emblica

Ethanol extract of *Phyllanthus emblica* Linn. (Euphorbiaceae) (PE) induced rat hepatic injury. PE (0.5 and 1 mg/ml) increased cell viability of rat primary cultured hepatocytes being treated with ethanol (96 μ l/m) by increasing % MTT and decreasing the release of transaminase. Pretreatment of rats with PE at oral dose of 25, 50 and 75 mg/kg or SL (silymarin, a reference hepatoprotective agent) at 5 mg/kg, 4 h before ethanol lowered the ethanol induced levels of AST, ALT and IL-1 β . The 75 mg/kg PE dose gave the best result similar to SL. Treatment of rats with PE (75 mg/kg/day) or SL (5 mg/kg/day) for 7 days after 21 days with ethanol (4 g/kg/day, p.o.) enhanced liver cell recovery by bringing the levels of AST, ALT, IL-1 β back tonormal¹⁴.

Foeniculum vulgare

Fennel (*Foeniculum vulgare* Mill. family Umbelliferae) is an annual, biennial or perennial aromatic herb, depending on the variety, which has been known since antiquity in Europe and Asia Minor. The leaves, stalks and seeds (fruits) of the plant are edible. *Foeniculum vulgare* is an aromatic herb whose fruits are oblong, ellipsoid or cylindrical, straight or slightly curved and greenish or yellowish brown in colour¹⁵. Volatile components of fennel seed extracts by chromatographic analysis include transanethole, fenchone, methylchavicol, limonene, α -pinene, camphene, β -pinene, β -myrcene, α -phellandrene, 3-carene, camphor, and cisanethole^{16, 17}. Hepatoprotective activity of *Foeniculum vulgare* (fennel) essential oil was studied using a carbon tetrachloride-induced liver fibrosis model in rats. The hepatotoxicity produced by chronic carbon tetrachloride administration was found to be inhibited by *Foeniculum vulgare* essential oil with evidence of decreased levels of serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and bilirubin¹⁸.



Swertia Chirata

Simultaneous treatments with *S. Chirata* (Gentianaceae). (in different doses, viz, 20, 50, and 100 mg/kg body wt daily) and (CCI4) cause improvement at both biochemical and histopathological parameters compared to that of (CCI4) treatment alone but it was most effective when *S. chirata* was administered in a moderate dose (50 mg/kg body wt)^{19,20}.

Picrorhiza kurroa

Administration of picroliv, a standardized fraction of alcoholic extract of *Picrorhiza kurroa* (Scrophulariaceae) (3-12 mg/kg/day for two weeks) simultaneously with *P. berghei* infection showed significant protection against hepatic damage in *Mastomys natalensis*. The increased levels of serum glutamate oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT), alkaline phosphatase, lipoprotein-X (LP-X) and bilirubin in the infected animals were marked reduced by different doses of picroliv. In the liver, picroliv decreased the levels of lipid peroxides and hydroperoxides and facilitated the recovery of superoxide dismutase and glycogen^{21, 22}.

Azadirachta indica

Effect of *A. indica* leaf (*meliaceae*) extract on serum enzyme levels (glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, acid phosphatase and alkaline phosphatase) elevated by paracetamol in rats was studied with a view to observe any possible hepatoprotective effect of this plant. It is stipulated that the extract treated group was protected from hepatic cell damage caused by paracetamol induction. The findings were further confirmed by histopathological study of liver. The antihepatotoxic action of picroliv seems likely due to an alteration in the biotransformation of the toxic substances resulting in decreased formation of reactive metabolites²³.

Andrographis paniculata

Antihepatotoxic activity of the *Andrographis paniculata* (acanthaceae) methanolic extract (equivalent to 100 mg/kg of andrographolide) and 761.33 mg/kg ip, of the andrographolide free methanolic extract (equivalent to 861.33 mg/kg of the methanolic extract) of the plant, using CCI4-intoxicated rats. Biochemical parameters like serum transaminases--GOT and GPT, serum alkaline phosphatase, serum bilirubin and hepatic triglycerides were estimated to assess the liver function. The results suggest that andrographolide is the major active antihepatotoxic principle present in *A. paniculata*²⁴.

Flacourtia indica

The extracts of the aerial parts of *Flacourtia indica* (Burm. f.) Merr., were evaluated for hepatoprotective properties. In paracetamol-induced hepatic necrosis in rat models, all extracts were found to reduce serum aspartate transaminase (AST), serum alanine transaminase (ALT) and serum alkaline phosphatase (ALP). The most significant reduction of the serum level of AST and ALT

were exhibited by petroleum ether and ethyl acetate extracts at a single oral dose of 1.5g/kg of body weight with a reduction of 29.0% AST & 24.0% ALT level by petroleum ether extract, and 10.57% AST & 6.7% ALT level by ethyl acetate extract compared to paracetamol (3 g/kg of body weight) treated animals. Histopathological examination also showed good recovery of paracetamol-induced necrosis by petroleum ether and ethyl acetate extracts. On the other hand, the methanol extract did not show any remarkable effect on paracetamol-induced hepatic necrosis. The hepatoprotective effects exhibited by petroleum ether and ethyl acetate extract might be mediated through the inhibition of microsomal drug metabolizing enzymes²⁵. But, in this study the dose they have used is too high and it is not successful or rationale for human dose.

Wedelia calendulacea

The hepatoprotective activity of ethanolic extract of *Wedelia calendulacea* L. (Family: Asteraceae) was studied against CCI4-induced acute hepatotoxicity in rats. The treatment with ethanolic extract of *Wedelia calendulacea* showed a dose-dependent reduction in CCI4 induced elevated serum enzyme activities with parallel increase in total proteins and bilirubin, indicating the extract could enhance the return of normal functional status of the liver comparable to normal rats. The weight of the organs such as liver, heart, lung, spleen and kidney in CCI4-induced hepatic damaged animals that received ethanolic extract of *Wedelia calendulacea* showed an increase over CCI4-treated control group²⁶.

Prostechea michuacana

Methanol, hexane and chloroform extracts of *Prostechea michuacana* (PM) were studied against CCI4-induced hepatic injury in albino rats. Pretreatment with methanolic extract reduced biochemical markers of hepatic injury levels demonstrated dose-dependent reduction in the *in vivo* peroxidation induced by CCI4. Likewise, pretreatment with extracts of PM on paracetamol-induced hepatotoxicity and the possible mechanism involved in this protection were also investigated in rats after administering the extracts of PM at 200, 400 and 600mg/kg. The degree of protection was measured by monitoring the blood biochemical profiles. The methanolic extract of orchid produced significant hepatoprotective effect as reflected by reduction in the increased activity of serum enzymes, and bilirubin. These results suggested that methanolic extract of PM could protect paracetamol-induced lipid peroxidation thereby eliminating the deleterious effects of toxic metabolites of paracetamol. This hepato-protective activity was comparable with silymarin. Hexane and chloroform extracts did not show any apparent effect. The findings indicated that the methanolic extract of PM can be a potential source of natural hepatoprotective agent²⁷.



Aegle marmelos

Aegle marmelos leaves (*Bael*, family of Rutaceae) which is also called as *Bilva* in ancient Sanskrit, was used as herbal drug in the Indian System of medicine. The hepatoprotective effect of *Aegle marmelos* in alcohol-induced liver injury was evaluated rats using essential marker biochemical parameters. The results indicated that, the *Bael* leaves have excellent hepato-protective effect. Similar findings were also reported by other workers²⁸.

DISCUSSION

Popularity of herbal remedies is increasing globally and at least one quarter of patients with liver diseases use ethno botanicals. This approach will help exploring the real therapeutic value of these natural pharmacotherapeutic agents and standardized the dosage regimen on evidence based findings to become more than a fashionable trend. Many herbals are on the market to support health, relieve symptoms and cure diseases. However, most of these products lack scientific pharmacological validation. In experimental hepatotoxicity models in laboratory or higher animals, several herbals exerted hepato-protective/curative effects that warrants their clinical testing. Due to lack of scientific-based pharmacological data, most of the herbal formulations cannot be recommended for the treatment of liver diseases²⁹.

CONCLUSION

In this review article, effort has been taken to collect and compile the details regarding a few hepato protective natural products, which will be useful to the society to venture in to a field of alternative systems of medicine. A more thorough review on various herbal products available in India and abroad as a hepato protectant is in near future.

REFERENCES

1. Ward FM, Daly MJ, Hepatic Disease, Clinical Pharmacy and Therapeutics, Churchill Livingstone, New York, 1999, 195-212.
2. Agarwal SS. Development of hepatoprotective formulations from plant sources, *Pharmacology and Therapeutics in the New Millennium*, New Delhi, 2001, 357-358.
3. Chaterjee TK., Medicinal Plants with Hepatoprotective Properties, Herbal Options, Books & Allied (P) Ltd., Calcutta, 2000, 155.
4. Achuthan CR, Babu BH, Padikkala J, Antioxidant and Hepatoprotective effects of *Rosa damascene*, *Pharmaceut. Biol.*, 41, 2003, 357-361.
5. Aniya Y, Miyagi A, Nakandakari, Kamiya N, Imaizumi N, Ichiba T, Free radical scavenging action of the medicinal herb *Limonium wrightii* from the Okinawa islands, *Phytomedicine*, 9, 2002, 239-244.
6. Gupta AK, Chitme H, Dass SK, Misra N, Antioxidant activity of *Chamomile recutita* capitula methanolic extracts against CCl₄-induced liver injury in rats *Journal of Pharmacology and Toxicology*, 1, 2006b, 101- 107.
7. Handa SS, Sharma A, Chakraborti KK, Natural products and plants as liver protecting drugs, *Fitoterapia*, 57(5), 1986, 307-352.
8. Hui-Mei L, Hsien-Chun T, Chau-Jong W, Jin-Jin L, Chia-Wen L, Fen-Pi C, Hepatoprotective effects of *Solanum nigrum* Linn extract against CCl₄-induced oxidative damage in rats, *Chemico Biological Interactions*, 171, 2008, 283–293.
9. Sultana S, Perwaiz S, Iqbal M, Athar M, Crude extracts of hepatoprotective plants, *Solanum nigrum* and *Ci-chorium intybus* inhibit free radical-mediated DNA damage, *J. Ethnopharmacol.*, 45, 1995, 189-192.
10. Karandikar SM, Joglekar GV, Chitale GK, Balwani JH, Protection by indigenous drugs against hepatotoxic effect of carbon tetrachloride, a long term study, *Ac-ta Pharmacologia et Toxicologia (Copenhagen)*, 20, 1963, 274.
11. Kapoor LD, CRC Handbook of Ayurvedic Medicinal Plants, Boca Raton, CRC Press, 1990, 149-150
12. Budavari S, The Merck Index: An Encyclopedia of Chemicals, Drugs and Biological, 12th Edition, New York Merck & Co. Inc., Whitehouse Station, 1996, 1674.
13. Somchit MN, Sulaiman MR, Noratunlina R, Ahmad Z, Hepatoprotective effects of *Curcuma longa* rhizomes in paracetamol-induced liver damage in rats, *Proceedings of the Regional Symposium on Environment and Natural Resources*, 1, 2002, 698-702.
14. Pramyothin P, Samosorn P, Pongshompoo S, Chaichantipyuth C, The protective effects of *Phyllanthus emblica* Linn. Extract on ethanol induced rat hepatic injury, *J. Ethnopharmacol.*, 107(3), 2006, 361-64.
15. Warriar PK, Nambiar VPK, Ramankutty C, *Foeniculum vulgare*, *Indian Medical Plants*, 3, 5, Chennai , 1996, 492.
16. Simándi B, Deák A, Rónyani E, Yanxiang G, Veress T, Lemberkovic É, Then M, Sass-Kiss Á, Vámos- Falusi Z, Supercritical carbon dioxide extraction and fractionation of Fennel oil, *J Agric Food Chem*, 47, 1999, 1635-40.
17. Özcan M, Akgül A, Baser KHC, Özok T, Tabanca N, Essential oil composition of sea fennel (*Crithmum maritimum*) from Turkey, *Nahrung/Food*, 45(5), 2001, 353-6.
18. Hanefi Özbek, Serdar Ugras, Irfan Bayram, Ismail Uygan, Ender Erdogan, Abdurrahman Öztürk1, Zübeyir Huyut1, Hepatoprotective effect of *Foeniculum vulgare* essential oil: A carbon-tetrachloride induced liver fibrosis model in rats, *J. Lab. Anim. Sci.*, 1, 3, 2004.
19. Karan M, Vasisht K, Handa SS, Antihepatotoxic activity of *Swertia chirata* on paracetamol and galactosamine induced hepatotoxicity in rats, *Phytotherapy Research*, 13(2), 1999, 95-01.
20. Mukherjee S, Sur A, Maiti BR, Hepatoprotective effect of *Swertia chirata* on rat, *Indian J Exp Biol.*, 35(4), 1997, 384-8.



21. Chander R, Dwivedi Y, Rastogi R, Sharma SK, Garg NK, Kapoor NK, Dhawan BN, Evaluation of hepatoprotective activity of picroliv from *Picrorhiza kurroa* in *Mastomys natalensis* infected with *Plasmodium berghei*, I J Medicinal Res., 92, 1990, 34-7.
22. Ansari RA, Tripathi SC, Patnaik GK, Dhawan BN, Antihepatotoxic properties of picroliv: an active fraction from rhizomes of *Picrorhiza kurroa*, J Ethnopharmacol., 34(1), 1991, 61-8.
23. Chattopadhyay RR, Sarkar SK, Ganguly S, Banerjee RN, Basu TK, Mukherjee A, Hepatoprotective activity of *Azadirachta indica* leaves on paracetamol induced hepatic damage in rats, Indian J Exp Biol., 30(8), 1992, 738-40.
24. Handa SS, Sharma A, Hepatoprotective activity of andrographolide from *Andrographis paniculata* against carbontetrachloride, Indian J Med Res., 92, 1990, 276-83.
25. Marina Nazneen, Md. Abdul Mazid, Joydev K Kundu, Sitiesh C Bachar, Farida Begum, Bidyut K Datta, Protective effects of *Flacourtia indica* aerial parts extracts against paracetamol-induced hepatotoxicity in rats, journal of taibah university for science, 2,2009, 1-6.
26. Murugaian P, Ramamurthy V, Karmegam N, Hepatoprotective activity of *Wedelia calendulacea* L. against acute hepatotoxicity in rats, Res J Agri & Biol Sci., 4(6), 2008, 685-687.
27. Rosa MP, Gutiérrez, Rosario VS, Hepatoprotective and inhibition of oxidative stress of *Prostechea michucana*, Rec Nat Prod, 3(1), 2009, 46-51.
28. Vinodhini singanan, Malairajan singanan, Hazeena begum, Hepatoprotective effect of bael leaves (*aegle marmelos*) in alcohol induced liver injury in albino rats, international journal of science & technology, 2, 2007, 83-92
29. Stickel F, Schuppan D, Herbal medicine in the treatment of liver diseases, Digestive and Liver Disease, 39, 2007, 293–304.

About Corresponding Author: Mr. Fasalurrahman o.m

Mr. Fasalurrahman o.m graduated from Rajiv Gandhi University of health sciences, Bangalore, Karnataka, India and doing post graduation from the same university. At post graduation level taken specialization in pharmacology, and doing master thesis in "hepatoprotective activity".