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A review of evidence based hepatoprotective selected medicinal plants used in Bangladeshi traditional medicine

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Abstract
Liver toxicity is a prime concern for patients as well as physicians, scientists and drug development agencies. However researchers have revealed several mechanisms and also the effecting factors that might be used in diagnosis of liver diseases. The aim of the present study was to evaluate the evidence based hepatoprotective selected medicinal plants used in Bangladeshi traditional medicine. Medication has its own limitations with regard to their effectiveness, side effects and cost, plant derived compounds are an effective alternative for the treatment of liver diseases. Available traditional medicinal survey illustrates that herbal drug containing different phytoconstituents can have hepatoprotective property which may be due to the individual or combined effects of these phytoconstituents. The exact phytochemical compounds responsible for the hepatoprotective property need to be isolated and further investigation. Several pharmaceutical companies and regulatory agencies have lager amount of pre and post clinical trial data which demonstrates the value of medicinal plants and their role in the cure of liver disorders and it was proved clinically for their safety and efficacy.

Keywords: Hepatoprotective, Medicinal plants & Hepatic toxicity

1. Introduction
Liver is the largest gland and one of the vital organs of the body. It is located in the upper and right side of the abdominal cavity immediately beneath diaphragm. Metabolism of carbohydrates, proteins, lipids and vitamins and many of hormones is carried out in liver. The bile secreted by the liver, has among other things, plays an important role in digestion. It excretes cholesterol, bile pigments, heavy metals, toxins, bacteria. Liver also involved in removal of toxic property of harmful agent, it is called as detoxification [1]. Hepatic damage is associated with distortion of these metabolic functions. About 20,000 deaths found every year due to liver disorders [2]. Liver diseases may reduce hepatic blood flow, causes hepato cellular damage and dysfunction, reduce the production of albumin and raise the bilirubin levels, due to excessive exposure to hazardous chemicals, sometimes leading to hepatic damage and cause jaundice, cirrhosis and fatty liver. Production of reactive species depletion, lipid peroxidation, plasma membrane damage etc.., culminating into severe hepatic injury [3]. Herbal drugs have gained importance and popularity in recent years because of their safety, efficacy and cost effectiveness. Several Bangladeshi medicinal plants have been extensively used in the Bangladeshi traditional system of medicine for the management of liver disorder. The use of natural remedies for the treatment of liver diseases has a long history and medicinal plants and their derivatives are still used all over the world in one form or the other for this purpose. Scientific evaluation of plants has often shown that active principles in these are responsible for therapeutic success. A large number of medicinal plants have been tested and found to contain active principles with curative properties against a variety of diseases. Liver protective plants contain a variety of chemical constituents like phenols, Coumarins, Lignans, essential oil, monoterpenes, carotinoids, glycosides, flavonoids, organic acids, lipids, alkaloids and xanthenes. Therefore a large number of plants and formulations have been claimed to have hepatoprotective activity so the development of plant based hepatoprotective drugs has been

given importance in the global market. This review article has been presented to enumerate some plants that have hepatoprotective properties such as *Solanum nigrum, Andrographis paniculata, Berberis aristata, Rosa damascena, Tinospora cordifolia, Phyllanthus niruri, Foeniculum vulgare, Rubia cordifolia, Mimosa pudica, Phyllanthus emblica, Phyllanthus emblica, Nyctanthes arbortritis, Ficus hispida, Aegle marmelos, Capparis spinosa, Cassia fistula, Azadirachta indica etc.*

Solanum nigrum

In Ayurveda, the drug is known as kakamachi. Aromatic water extracted from the drug is widely prescribed by herbal vendors for liver disorders. Although clinical documentation is scare as far as hepatoprotective activity is concerned, but some traditional practitioners have reported favorable results with powdered extract of the plant [3].

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 CCl4intoxicated 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 [4].

Berberis aristata

Berberis aristata being an important medicinal plant is used extensively for treating variety of ailments like infection of eyes, skin diseases, jaundice and rheumatism [5]. The major alkaloid of this plant is reported to be berberin which possess anti-oxidant property The roots of Berberis aristata possess more effective hepatoprotective activity against CCl_4 intoxication in rats because of its antioxidant bearing capacity. Acute CCl_4 administration increased serum and liver lipid peroxides significantly. Berberine treatment could reduce these elevated levels. Pathological analysis showed degeneration and necrosis after CCl_4 administration. Berberine treatment could minimize these effects to a certain extent.

Rosa damascena

The hepatoprotective activity of the alcoholic extract of Rosa damascena was studied against paracetamol induced acute hepatotoxicity in rats. Liver damage was assessed by estimating serum enzyme activities of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and histopathology of liver tissue. Pre- and post-treatment with ethanolic extracts showed a dose-dependent reduction of paracetamol induced elevated serum levels of enzyme activity. The mechanism underlying the protective effects was assayed in vitro and the R. damascena extracts displayed dose dependent free radical activity using DPPH (IC 50 = 162.525 µg/ml) and TBA method. The hepatoprotective action was confirmed by histopathological observation. The ethanolic extracts reversed paracetamol induced liver injury. These results suggest that the hepatoprotective effects of *R. damascena* extracts are related to its antioxidative activity [6].

Tinospora cordifolia

Tinospora cordifolia (Willd.) Miers., known as Guduchi, Amrita is one of the most valuable medicinal herbs of Ayurveda. The term 'Amrita' is attributed to this herb in recognition of its ability to impart youthfulness, vitality and longevity to its patron. In modern medicine, it is well known for its hepatoprotective, adaptogenic, immunomodulatory activities and anti-fibrolytic activity. The active principle Tinosporin corrects immunosuppression associated with deranged hepatic function [7]. Kupffer cells are major determinants of outcome of liver injury. The effect of *Tinospora cordifolia* was evaluated on Kupffer cell function, using carbon clearance test as a parameter. Antihepatotoxic activity of *Tinospora cordifolia* was studied in albino rats intoxicated with Carbon tetrachloride (CCl_4). Liver function was assessed based on morphological, biochemical (SGPT, SGOT, Serum alkaline phosphatase, Serum bilirubin) and functional (Pentobarbitone sleep time) tests. A study conducted by Nagarkatti *et al*., (1994) on *Tinospora cordifolia* Indicates that it had decreased fibrosis in rats, induced by CCl_4 and significantly improved the suppressed Kupffer cell function in another rat model of chronic liver damage induced by heterologous serum. This raises the possibility that anti-fibrotic effect of *Tinospora cordifolia* is mediated through activation of kupffer cells [8].

Phyllanthus niruri

Phyllanthus niruri Linn. is a medicinal herb used in connection with secondary hepatitis and other ailments, in Ayurvedic medicine for over 2000 years. It is a proved antiviral drug in Hepatitis-B in human subjects. In the preliminary study, carriers of Hepatitis-B virus were treated with a preparation of the plant 200 mg for 30 days. 22 of the 37(59%) treated patients had lost Hepatitis-B surface antigen, when tested 15– 20days after the end of the treatment, compared with only 1 out of 23 (4%) placebo treated controls. It has exhibited an inhibition of DNA polymerase on Hepatitis–B virus which is responsible for the replication of virus [9]. In a study, phyllanthin, hypophyllanthin and tricotanol were isolated from petroleum ether extract of *Phyllanthus niruri* shows significant results on rat hepatocytes. Preclinical studies demonstrate that an extract of the *Phyllanthus niruri* plant inhibits endogenous DNA polymerase of hepatitis B virus and binds to the surface antigen of Hepatitis B virus. Extracts of *Phyllanthus niruri* have been shown to exert hepatoprotective effect against CCl_4 induced HepG2 cell damage in rabbits. Pre-treatment with extract of *Phyllanthus niruri* Linn., reduced paracetamol-induced acute liver damage in rats as monitored by estimating the SGOT. In the in vitro-study, it decreased the release of AST and ALT in rat primary cultured hepatocytes being treated with ethanol [10].

Foeniculum vulgare

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 colour. 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. 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 bilirubin [11].

Rubia cordifolia

Rubiadin isolated from *Rubia cordifolia* Linn, (Rubiaceae) at a dose of 50, 100 and 200 mg/kg was administered orally once daily for 14 days in rats. The substantially elevated serum enzymatic activities of serum GOT, GPT, ALP and GGT; decreased activities of glutathione S transferase and glutathione reductase were restored towards normalization in dose dependent manner which were induce by CCl_4 treatment in rats. It also significantly prevents the elevation of hepatic MDA formation and depletion of reduced GSH content in the liver [12].

Mimosa pudica

Mimosa pudica is used to treat dysentery with blood mucus, piles, urinary calculi, internal bleeding, fissures, skin wound, and ulcers and most importantly in treating menorrhagia. Mimosa pudica is effective as antiasthmatic, aphrodisiac, hepatoprotective, antimicrobial, diuretic, analgesic, anxiolytic and antidepressant [13-14]. Leaf extract of *Mimosa pudica* showed a considerable hepatoprotection by ameliorating oxidative stress and liver damage in alcohol fed mice. The ethanol extract of Mimosa pudica Linn possess significant hepatoprotective activity against $CC1_4$ induced liver damage in rats [15-16]. Phytoconstituents such as flavonoids, glycosides, alkaloids present in the methanolic extract of this plant is considered responsible for the significant hepatoprotective activity [17].

Phyllanthus emblica

This plant possesses several pharmacological properties due to the presence of phytochemicals such as tannins, flavonoids, terpenoids and alkaloids [18]. This plant is used for anti-inflammatory, anti-oxidant and anti-pyretic treatments and also used for treating scurvy, cancer and heart diseases [19-20]. The efficacy of this plant in preventing paracetamol and CCl_4 induced hepatotoxicity in rats has been examined [21-22]. There is evidence for the use of P.emblica fruits as a chondroprotective agent in osteoarthritis therapy [22].

Nyctanthes arbortritis

The plant is reported to possess antimicrobial activity, antihistaminic activity, CNS activities (hypotonic, tranquilizing, anesthetics), analgesic, anti-inflammatory, antipyretic, antiulcer, antiparasite, antidepressant, antiviral and immunodulatory activities. Study reveals that this plant leaves possess hepatoprotective activity against CCl_4 induced liver damage in rats [23-25].

Ficus hispida

This plant is known to possess a vital role in the management of liver diseases. Paste of the whole plant is mixed with salt is taken to cure jaundice [26]. It is reported that 50% ethanolic extract of *Ficus hispida* confer hepatoprotective effect against CCl_4 induced liver damage in rats [27]. Oral dose of plant extract exhibited a significant hepatoprotective effect. It contains different phytochemicals and is recently reported to possess antineoplastic, cardioprotective, neuroprotective and antiinflammatory effects [28].

Aegle marmelos

Aegle marmelos leaves 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 hepatoprotective effect. Similar findings were also reported by other workers [29].

Capparis spinosa

Capparis spinosa (CS) is a plant belonging to the family of Capparidaceae. According to ethnopharmacological data collected in the southeastern region of Morocco, CS is alleged to possess a hypoglycaemic effect, which has been experimentally demonstrated [30-32]. Furthermore, it has been reported that some species of the genus Capparis possess molluscicidal activity [33], chonroprotective effect [34] and in vitro antitumour effect [35]. Protective action of C. spinosa ethanolic root bark extract was evaluated in this study in an animal model of hepatotoxicity, which was induced by carbon tetrachloride. Healthy male mice 30-35 g body weight, 6-8 week old) were divided into 7 groups. Group 1 was normal control group; Group 2, the hepatotoxic group was given CCl_4; Group 3 was administered olive oil (vehicle); Groups 4-6 received different doses of ethanolic root bark extract (100, 200 & 400 mg/kg) with CCl4; Group 7 was administered overdose of the extract (800 mg/kg). The parameters studied were alanine transaminase and aspartate transaminase activities and duration of sleep. The hepatoprotective activity was also supported by histopathological studies of liver tissue. Results of the biochemical studies of blood samples of CCl_4 treated animals showed significant increase in the levels of serum enzyme activities, reflecting the liver injury caused by CCl_4. whereas blood samples from the animals treated with ethanolic root bark extracts showed significant decrease in the levels of serum markers, indicating the protection of hepatic cells. The results revealed that ethanolic root bark extract of C. spinosa could afford significant dose-dependent protection against CCl_4 induced hepatocellular injury [36].

Clitoria ternatea

Clitoria ternatea (Family- Liguminoceae, previously known as Papillioneceae), a perennial twining herb, Various parts of C. ternatea have been reported to have tranquilizing property, anti-inflammatory, analgesic, antipyretic, and immunomodulatory activities [37]. The flavonol glycoside present in roots is reported to have antibacterial activity [38]. Considering the high economical and pharmacological importance of secondary metabolites of this plant, industries are deeply interested in utilizing this plant in tissue culture technology. C. ternatea has been reported to have hepatoprotective [39], antihyperlipidemic [40] and immunoinhibitory activities. The organic solvent extracts of C. ternatea could be used as antimicrobial agents for the control of infectious diseases.

The hepatoprotective activity of C. ternatea against experimentally induced liver injury was evaluated. The hepatoprotective effect against paracetamol-induced liver toxicity in mice with the methanolic extract of C. ternatea leaf was measured by monitoring the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and billirubin along with histopathological analysis. The results of

the paracetamol-induced liver toxicity experiments showed that mice treated with the ME of C. ternatea leaf (200 mg/kg) showed a significant decrease in ALT, AST, and bilirubin levels, which were more elevated in the paracetamol group ($p < 0.01$). C.ternatea leaf extract therapy also showed protective effects against histopathological alterations. Histological studies supported the biochemical findings and a maximum improvement in the histoarchitecture was seen. The hepatoprotective effect of C. ternatea leaf extract was confirmed against the hepatotoxicant, paracetamol [41].

Azadirachta indica

Effect of *Azadirachta 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 metabolites [42].

Cassia fistula

It is very common Bangladeshi plant which is known as Bhandor lathi. It is reported to possess various pharmacological activities like antifungal, antioxidant, antimicrobial, antiinflammatory, anti tumour, hepatoprotective and hypoglycemic. Studies reveal the presence of various phytochemical constituents. It is used in the treatment of hematemesis, intestinal disorders, leucoderma, diabetics and as antipyretic, analgesic and laxative [43-44] and also effective against constipation. Ethanolic leaf extract of *C. fistula* followed by CCl_4 treatment reversed back lipid peroxidation and the activities of catalase and glutathione reductase in the liver tissue towards normalcy [45]. CCl_4-induced liver damage in rats can also be ameliorated by treatment of aqueous extracts of leaves and bark of C.fistula [46]. Methanolic extract of Cassia fistula seeds showed hepatoprotective activity and aqueous extract of seeds exhibited moderate hepatoprotective activity in rats [47]. N heptane extract of *Cassia fistula* leaves produced comparable hepatoprotective effects to that of standard hepatoprotective agents on paracetamol induced hepatoxicity in rats [48-49].

Conclusions

Liver cell injury caused by various toxic chemicals such as anti-biotic, chemotherapeutic agents, carbon tetrachloride (CCl_4), thioacetamide etc., excessive alcohol consumption and microbes is well-studied. The available synthetic drugs to treat liver injury in this condition also cause further damage to the liver. Hence, medicinal plants 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 so the maintenance of a healthy liver is essential for the overall well-being of an individual. Liver injury induced by toxins is more common nowadays. Herbal remedies are focused in the pharmaceutical industry to evolve a safe route for liver disorders. Therefore, hepatoprotective natural medicinal plants *Solanum nigrum, Andrographis paniculata, Berberis aristata, Rosa damascena, Tinospora cordifolia, Phyllanthus niruri, Foeniculum vulgare, Rubia cordifolia, Mimosa pudica, Phyllanthus emblica, Phyllanthus emblica, Nyctanthes arbortritis, Ficus hispida, Aegle marmelos, Capparis spinosa, Cassia fistula, Azadirachta indica etc.* is reviewed. The present review is aimed at compiling data on promising phytochemical from medicinal plants that have been tested in hepatotoxicity models using modern scientific system.

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