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A REVIEW ON HEPATOPROTECTIVE PLANTS AND COMPOUNDS

[1]Harsha Motwani, [1]Harshida Gadhavi, [1*]Hitesh A. Solanki, [1]Saumya K. Patel and [2]Rakesh M. Rawal

[1]Department of Botany, Bioinformatics and Climate Change Impacts Management,
[2]Department of Life Science, School of Sciences,Gujarat University, Ahmedabad, Gujarat
Email id: husolanki@yahoo.com

ABSTRACT

The liver is one of the most significant organs in the body, executing a fundamental role in the regulation of diverse processes, among which the metabolism, secretion, storage, and detoxification of endogenous and exogenous substances are noticeable. Due to these functions, hepatic diseases have become threat to public health, and they remain as major worldwide issue. 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 many herbs or their extracts for treatment of various ailments has been documented in Ayurvedic medical system. The immense potential of medicinal plants used in traditional systems has been well recognized and documented in recent years. Numerous plants and polyherbal formulations are used for the treatment of liver diseases. Phytotherapeutic approach to modern drug development can provide many invaluable drugs from traditional medicinal plants. Search for pure phytochemicals as drugs is time consuming and expensive. This review article is going to enumerate some plants with hepatoprotective properties and it is going to provide a robust insight into the phytochemistry, medicinal uses and pharmacology of a few hepatoprotective plants and their compounds. Nonetheless, further study on the phytochemistry and mechanism of action of the pure compounds are necessary to fully understand the phytochemical profile and the complex pharmacological effects of this plant.

Keywords: *Hepato protective plants, Andrographis Paniculata, Aerva lanata, Andrographolide.*

INTRODUCTION

Liver being one of the largest glandular organ in human body, and having more functions than anyother organ, plays a key role in maintaining complete homeostasis of human body. Beside metabolism and producing bile, liver fabricates prothrombin and fibrinogen, both blood-clotting factors, and heparin, a muco-polysaccharide sulfuric acid ester that helps keeps blood from clottingwithin the circulatory system [1, 3]. Hepatotoxicity due to drugs appears to be one of the major cause for liver damage and mortality due to same. Since decades, tribal communities are known touse their traditional knowledge to cure multiple diseases by using plants and herbs as source of drug and this process is experienced over hundreds of years, which says that the medicinal plants have been in the focus as lifesaving drugs right from the beginning of the human civilization. Recent research postulates that plant derived drugs are relatively non-toxic, safe and even free fromserious side effects. Till date a large number of medicinal plants have been tested and found to contain active constituents with curative properties against a variety of diseases[2, 4]. A number of liver-protective plants containing a variety of chemical constituents like phenols, coumarins, lignans, essential oil, monoterpenes, carotinoids, glycosides, flavanoids, organic acids, lipids, alkaloids and xanthenes have been reported in literature. Drug-induced liver injury encompasses a spectrum of diseases ranging from mild biochemical abnormalities to acute liver failure; for instance hepatotoxicity caused by the first-line anti-tuberculous drugs isoniazid, rifampin and pyrazinamide, which are basic for treatment of drug-sensible and drug-resistant tuberculosis. The hepatoprotective activity of *Boerhaavia diffusa* was examined in thioacetamide intoxicated rats, the results showed that an aqueous extract of roots exhibited

marked protection of a majority of serum parameters, i.e., GOT, GPT, ACP and ALP, but not GLDH and bilirubin [10]. Further, the studies also proved that the aqueous form of drug administration has more hepatoprotective activitythan the powder form. The investigation also validates the use of *B. diffusa* L. roots in hepatic ailments by the several tribes in India [10]. An alcoholic extract of whole plant *Boerhaavia diffusa* given orally exhibited hepatoprotective activity against experimentally induced carbon tetrachloride hepatotoxicity in rats and mice. The extract does not show any signs of toxicity up to an oral dose of 2 g/kg in mice. Another study analyzed the hepatoprotective potential of ethanolicextracts of two plants, A. paniculata and S. chirayita, the results indicated the potential of these two plant extracts to offer protection against the acute hepatotoxicity induced by paracetamol [7].The S. chirayita extract has been found to provide higher hepatoprotection than A. Paniculata. A literature states that oral administration of ethanolic extract of A. paniculata or S. chirayita at the doses of 100 and 200 mg/kg significantly prevented the elevation of the serum markers of hepatotoxicity. Some results also recommend that the extracts protected the membrane integrity ofthe liver cells against paracetamol induced leakage of marker enzymes into the circulation. The paracetamol induced elevation of this enzyme in the serum is lined up with high level of serum bilirubin. Administration of the ethanol extract of A. paniculata or S. chirayita decreased the ALP activity and serum bilirubin levels and stabilized biliary dysfunction and normal functional statusof the liver [7]. Treatment with ethanol extract of A. paniculata or S. chirayita significantly reversed hepatotoxicity. A recent study indicates that A. paniculata or S. chirayita maintain the cellular integrity of hepatic tissues and helped its regeneration. In another study, the ethanol (EtOH) extract from the leaves of Cnidoscolus chayamansa administered orally demonstrated a protective effect in Wistar rats against the hepatotoxicity induced by the mixture of RIF/INH (100mg/kg each) [16]. The aqueous extract of Allium sativum bulbs generates a hepatoprotective effectagainst the sub-acute liver damage induced by the mixture of INH/RIF in wistar rat. Allium sativum also protects from liver injury caused only with INH [16].

2 Hepatotoxicity Inducing Agents:

Literature reports several chemicals that have been identified to cause hepatotoxicity. In laboratoryanimals hepatotoxicity is experimentally induced by using Carbon tetrachloride (CCl4), galactosamine, d-galactosamine/lipopolysachharide (GalN/LPS), thioacetamide, antituberculardrugs, paracetamol, arsenic, cadmium, etc [2,3].

2.1 Carbon tetrachloride (CCl4):

Extracting from literature studies, liver injury due to CCl4 was first reported in in rats and has been widely exploited by many investigators. Carbon tetrachloride is metabolized by cytochrome P-450in endoplasmic reticulum and mitochondria with the formation of CCl3O-, a reactive oxidative free radical, which initiates lipid peroxidation. In a study conducted on rats administration of a single dose of CCl4 to a rat produces, a centrilobular necrosis and fatty changes. The poison reaches its maximum concentration in the liver within 3 hrs of administration. The development ofnecrosis is associated with leakage of hepatic enzymes into serum. Studies also confirm that doseof CCl4 that induces hepatotoxicity ranges from 0.1 to 3 ml/kg administered intraperitoneally [9].

2.2 Thioacetamide:

Thioacetamide interferes with the movement of RNA from the nucleus to cytoplasm which may cause membrane injury. Studies report a metabolite of thioacetamide (perhaps S-oxide) is responsible for hepatic injury. Thioacetamide reduce the number of viable hepatocytes as well as rate of oxygen consumption. It also decreases the volume of bile and its content i.e. bile salts, cholic acid and deoxycholic acid. Experimentally hepatotoxic dose of thioacetamide is reported tobe 100 mg/kg, subcutaneous [9].

2.3 Paracetamol:

Paracetamol, a widely used analgesic and antipyretic drug, is reported in literature to produce acuteliver damage in high doses. A study revealed that paracetamol administration causes necrosis of the centrilobular hepatocytes characterized by nuclear pyknosis and eosinophilic cytoplasm followed by large excessive hepatic lesion. The covalent binding of Nacetyl-P-benzoquinoneimine,an oxidative product of paracetamol to sulphydryl groups of protein, result in lipid peroxidative degradation of glutathione level and thereby, produces cell necrosis in the liver. Experimentally reported hepatotoxic dose of Paracetamol is 1 gm/kg

Post oral [9].

3 Hepatoprotective plants

Andrographis lineata
Hepatoprotective effect of *Andrographis lineata* (Acanthaceae) extracts in CCl(4)- induced liver injury have been experimentally reported in rats. Male Wistar rats with chronic liver damage, induced by subcutaneous injection of 50% v/v CCl(4) in liquid paraffin at a dose of 3 mL/kg on alternate days for a period of 4 weeks, were treated with methanol and aqueous extracts of Andrographis lineata orally at a dose of 845 mg/kg/day. This dosage proved to be hepatoprotectiveagainst ccl(4) induced liver injury. The biochemical parameters such as serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, serum bilirubin and alkaline phosphatase were estimated to assess the liver function. The activities of extracts were comparableto a standard drug [2].

Andrographis paniculata
Antihepatotoxic activity of the *Andrographis paniculata* (acanthaceae) were assessed in an experiment, methanolic extract of 100 mg/kg of andrographolide and andrographolide-free methanolic extract of the plant, using CCl4-intoxicated rats, and the results postulated this extractas hepatoprotective. 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* [2, 3].

Azadirachta indica
Effect of *A. indica* leaf *(meliaceae)* extract on serum enzyme levels elevated by paracetamol in ratswas studied with a view to observe any possible hepatoprotective effect of this plant. It is stipulatedthat the extract treated group was protected from hepatic cell damage caused by paracetamol induction. 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[2, 6].

Eclipta alba
The hepatoprotective effect of the ethanol/water (1:1) extract of *Eclipta alba* (Asteraceae) was studied at subcellular levels in rats against (CCl4) -induced hepatotoxicity. The loss of hepatic lysomal acid phosphatase and alkaline phosphatase by (CCl4) was significantly restored by *Ecliptaalba*. The study shows that hepatoprotective activity of *Eclipta alba* is by regulating the levels of hepatic microsomal drug metabolising enzymes [2, 18].

Fumaria indica
In a research *Fumaria indica* (Fumariceae) was studied for its hepatoprotective activity against carbontetrachloride, paracetamol and rifampicin-induced heptatotoxicites in albino rats. The petroleum ether extract against carbonetrachloride, total aqueous extract against paracetamol and methanolic extract against rifampicin-induced hepatotoxicities showed reduction in the elevated levels of some of the serum biochemical parameters. These findings are indicative of its potentialas a hepatoprotective agent [2,18].

Picrorhiza kurroa
It is a very common herb in the Indian traditional Ayurveda medicine. From the various literaturesurvey, it found that *Picrorhiza kurro* has used as a vital medicine for liver disorder and it used asvery significant ingredient for many Ayurvedic formulations for the treatment of liver toxicity. It was reported in several studies that *P. kurroa* possess antioxidant propertie. In an experiment, it
revealed that drug reduces the glutathione level and activates the enzyme which is helpful for antioxidant activity such as glutathione peroxidase. *Picrorhiza kurroa* extract treated rat group (antitubercular drug-induced model) for 50 mg/kg body weight for 50 days, give the significant result to normalize the elevated body serum level, which proves it as an anti-hepatotoxic agent [18,6].

Aerva lanata
In a study conducted to examine hepatoprotective effect of Aerva lanata, Petroleum ether extractable fraction of the whole plant *Aerva lanata* was evaluated for the protective effect againstliver damage induced by carbon tetra chloride (CCl4) in Sprague Dawley rats. The results demonstrated *Aerva lanata* administration significantly reversed the histopathological changes, reduced hepatic lipid peroxidation and proved to be a promising hepato protective agent against ccl4 induced liver damage [5].

Colchicum autumnale
Colchicine, the major alkaloid in *Colchicum autumnale* is reported to protect the liver of experimental animals against several hepatotoxins i.e., D-galactosamine and paracetamol by its ability to bind microtubule protein. In a research a colchicine derivative, trimethyl colchicinic acid(TMCA) tested on chronic liver damage induced by CCl4 and by bile duct ligation (BDL). So, both compounds proved to be equally potent but that TMCA could be administered at larger dosesthan colchicines without side effects and better hepatoprotective action. These results are suggestive that colchicum autumnale can be used as a promising hepato protective alternative [2
,6, 18].

4 Hepatoprotective compounds

Literature mining reveals a number of natural compounds and phytochemicals with hepato protective activity, which includes some flavanoids, Flavonols, Terpenes and Terpenoids [13].

Andrographolide
recent study showed that andrographolide attenuated concanavalin A-induced liver injury and inhibited hepatocyte apoptosis. Shukla et al. reported that the effect of andrographolide was foundto be more potent than silymarin against acetaminophen-induced reduction of the volume and contents of bile. Andrographolide was also shown to protect against ethanol-induced hepatotoxicity in mice with an equivalent efficacy of silymarin. A protective effect of a single oraldose each of the extract and of andrographolide has been studied in carbon tetrachloride- (CCl4-)induced hepatic microsomal lipid peroxidation. A study also reported the hepatoprotective effectsof the crude alcohol extract of leaves against CCl4-induced liver damage; these effects have had also been established against paracetamol-induced toxicity in an *ex vivo* rat model of isolated hepatocytes [11,17].

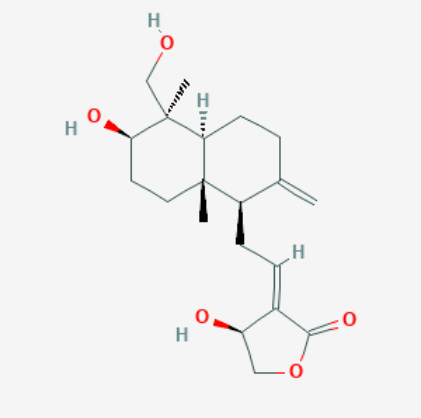

Figure 1 Andrographolide

Luteolin

Luteolin (3´, 4´, 5, 7-tetrahydroxy-flavone) is a natural flavonoid, isolated from various plants. The general appearance of luteolin is a yellow microcrystalline shape. Luteolin is now becoming very important herbal drug uses for various type of disease including the life-threatening disease cancer.From the various study, it has clarified that there is a relation between the oxidative stress and antioxidant in the liver. A study reported that when human beings are suffering from free oxygen radical, a complex defense system is activated. Here, luteolin has strong superoxide radical scavenging propertie. Thus it proves to be a promising hepato protective compound [16, 19].

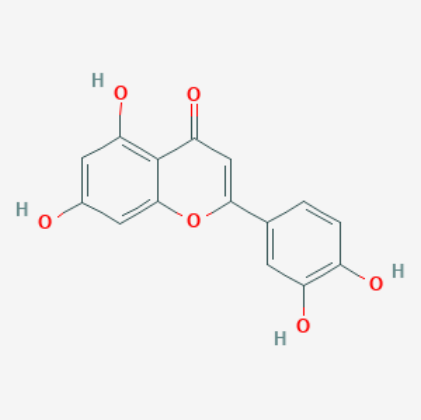

Figure 2 Luteolin

Acacetin

Acacetin is an O-methylated flavone found in *Robiniapseudo acacia.* A number of experiments confirm that acacetin is effective in the hepatic disorder of rat which was caused by carbon tetrachloride-induced. Thus due to its hepato protective activity it can be used as a promising alternative in anti hepato toxic drugs.

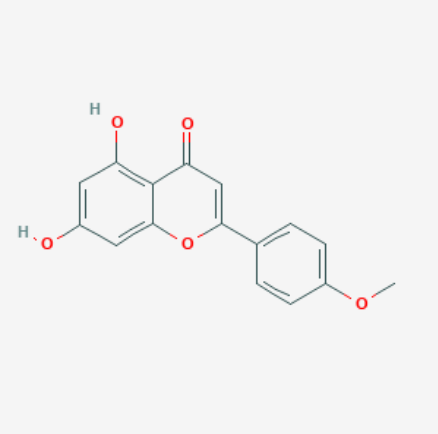

Figure 3 Acacetin

Apigenin: Apigenin (4′, 5, 7-trihydroxyflavone), obtained from many plants. It belongs to the flavones class. It is the aglycone part of the glycoside. Apigenin is the yellow crystalline solid. Various studies reported that it was found that apigenin has very good antiulcer and anti hepto toxic activities. Some findings also postulate Apigenin having hepato protective activity against anumber of hepato toxic agents [16].

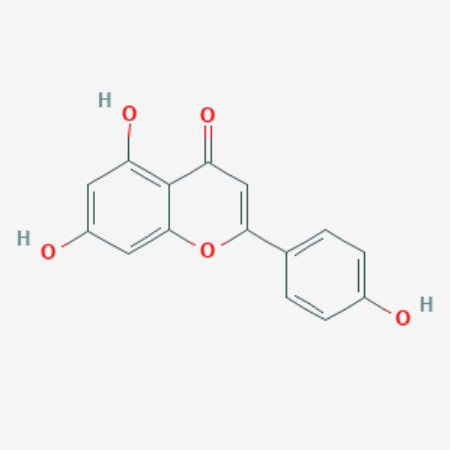

Figure 4 ApigeninSilymarin

Silymarin is the unique flavanoids complex - containing silybin, silydianin and silicristin-that is the derivative from the milk thistle plants. Now a day role of oxidative free radicals has been implicated in mediating cold-restraint stress. Antioxidant bioflavonoid silymarin has a significantrole in the acute cold- restraint stress model of gastric and hepatic ulceration. Oral treatment withsilymarin was found to be effective in the prevention of hepatic ulceration induced by cold-restraintstress, in rats. Thus it is regarded as a promising alternative for various types of liver injuries induced by multiple hepato toxic agents [19].

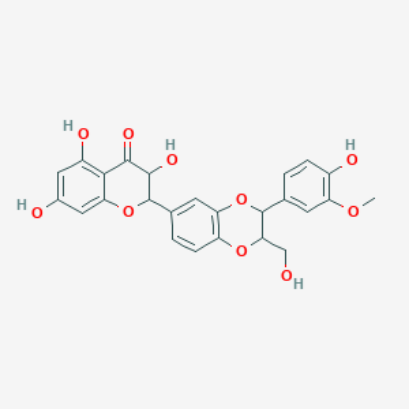

Figure 5 SilymarinKaempferol
Kaempferol is a natural flavonol found from various plants. The appearance of kaempferol is likea yellow crystalline solid. The melting point of kaemferol is 276 - 278 °C (529 - 532 °F). It is slightly soluble in water and highly soluble in hot ethanol, ethers, and DMSO. Kaempferol has a great antioxidant activity, reduce the free radical in our body and thus proves to be hepato protective compound. A number of studies reported anti hepato toxic effect of Kaempferol againstvarious hepato toxic agents [16, 19].

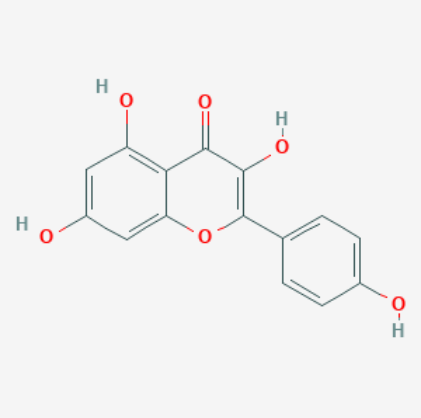

Figure 6 KaempferolSalvigenin
Salvigenin was isolation from *Dorema glabrum*. In a research salvigenin was found to possess potent free radical scavenging activity. It was also found that this moiety shows the hepatoprotective activity in acetaminophen induced liver damage in Swiss albino mice [19].

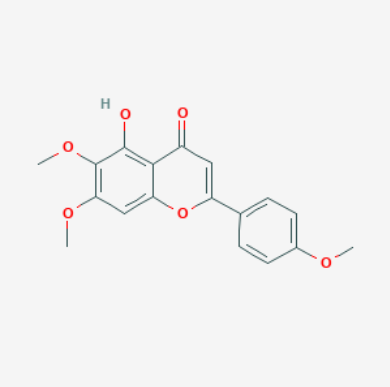

Figure 7 Salvigenin

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