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HEPATOPROTECTIVE DRUGS A STUDY ON THEIR PHYTOCHEMISTRY AND PHARMACOLOGY

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ABSTRACT: Plants are the major sources of hepatoprotective drugs and formulations, and this is the reason that their phytoconstituents are in great demand commercially. These drugs act prophylactically for the wellbeing of the liver as well as can cure an ailing liver. The liver is the largest solid organ and gland present in the human body. While it plays a major role in various metabolic reactions of the body, it can get damaged due to various reasons. The reasons can be consumption of excessive alcohol, jaundice, an overdose of allopathic drugs like Paracetamol *etc*. Lot of scientists have worked to find out the chemical constituents present in the hepatoprotective herbs and their actions on the liver. All the studies carried out by the team of scientists have been compiled in this article; therefore, the present review highlights all the important hepatoprotective herbs, their reported major constituents, and their effect on the liver. The herbs which are included in this article are *Silybum marianum* (Milk Thistle), *Allium sativum* (Garlic), *Glycyrrhiza glabra* (Liquorice), *Picrorrhiza kuroa* (Kutki) and *Schisandra chinensis* (Wu Wei Zi).

INTRODUCTION: Liver being a principal organ of the human body, helps in metabolism and excretion. A person's entire blood supply passes through the liver several times a day. The liver is responsible for detoxifying the body from poisonous substances by transforming them into their less harmful metabolites and then removing them from the body. Any kind of damage to the liver can make it sluggish in its functioning, the symptoms of which are fatigue, general malaise, digestive problems, blood sugar regulation dis-orders (hypoglycemia), high cholesterol, psoriasis, allergies, chemical sensitivities and cons-tipation. Extreme cases of liver problems are jaundice, hepatitis, and cirrhosis. In many cases, viral infection, known as viral hepatitis, can occur, which causes inflammation of the liver.

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Hepatitis can be caused by drugs, viruses, bacteria, mushrooms, parasites like Amoeba, Giardiasis *etc*. The most common hepatitis viruses affecting the liver are Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, and Hepatitis E. Next to Hepatitis is Cirrhosis, which is a chronic, diffusive degenerative liver disease in which the liver tissue starts degenerating. Severe cirrhosis leads to ammonia toxicity, hepatic coma, GIT hemorrhage and kidney failure. The most common cause of Cirrhosis is believed to be alcohol abuse. The liver, during the process of metabolism of alcohol, suffers serious damage. Alcohol destroys liver cells and also makes the liver cells lose their ability to regenerate. Hepatoprotective herbs play a vital role in improving liver functions.

These drugs can be given as prophylactic or as a cure to liver damage, whether it is due to excessive intake of alcohol or due to the side effects of long-term treatment from medicines. Silymarin, a flavonolignan mixture extracted from the Silybum marianum (milk thistle) is the most effective herb for hepatic diseases. Other drugs with hepato-protective potential are *Allium sativum* (garlic),

Glycyrrhiza glabra (liquorice), *Picrorrhiza kurroa* (kutkin), *Schisandra chinensis* (Wu Wei ZI, Chinese magnolia vine), *Curcuma longa* (turmeric), *etc*. These drugs in common follow the following mechanism of actions:

Phase I: Inhibition of specific cytochrome P_{450} enzymes by some herbs like Brassica.

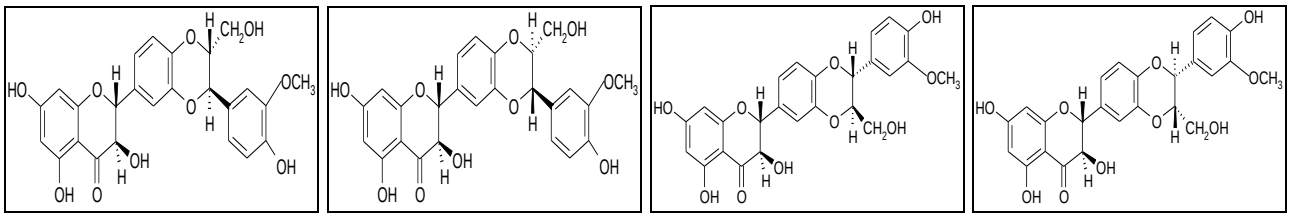
Phase II pathways are commonly affected by:

- Increase in glutathione (GSH) levels
- Glucuronidation
- Antioxidant anti-lipid peroxidation activities (*Silybum marianum*)

1. Review of Hepatoprotective Drugs:

2.1. *Silybum marianum*: It is used in cases of liver diseases like cirrhosis, jaundice hepatitis and, gallbladder disease, and is claimed to protect the liver against poisons. Siylimarin is a hepato-protective and antioxidant (radical scavenging agent) drug; thus, it stabilizes and protects the membrane lipids of the hepatocytes (liver cells). Silicristin inhibits the enzymes peroxidase and lipoxygenase [1]. Nam *et al.,* performed complete separation, isolation, and structural characterization of four diastereoisomeric flavonolignans of silymarin, silybin A (1) and silybin B (2) and isosilybin A (3) and isosilybin B (4).

The isolation was done from the seeds of milk thistle (*Silybum marianum*) using a preparative reversed-phase HPLC method. All the structures were confirmed using 2D NMR and CD spectroscopy [2].



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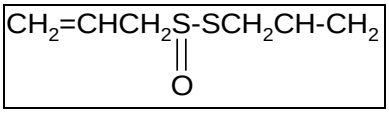
Fraschini *et al.,* found that Silymarin and Silybinin inhibited the absorption of toxins, such as phalloidin or α-amanitin, preventing them from binding to the cell surface and inhibiting membrane transport systems. These constituents exert their action by acting as free radical scavengers and interrupting the lipid peroxidation processes involved in the hepatic injury produced by toxic agents [3].

Madani *et al.,* studied the protective effects of polyphenolic extracts of *Silybum marianum* on thioacetamide-induced hepatotoxicity in rats. A significant decrease in the activity of aminotransferases, alkaline phosphatase, and bilirubin were observed in the groups treated with extracts and thioacetamide compared with the group that was treated only with thioacetamide. These findings suggested the hepatoprotective effect of *Silybum marianum* extracts on liver cells due to the presence of flavonoids and their antioxidant effects [4]. Flora *et al.,* found that Silymarin and its active constituent, silybin, work as antioxidants. It scavenges free radicals and inhibits lipid peroxidation. The study also revealed that Silymarin protects the liver against genomic injury, increases hepatocyte protein synthesis, decreases the activity of tumour promoters and stabilizes mast cells, chelate iron, and slow calcium metabolism [5]. Zdeněk *et al.,* studied the cytoprotective effects upon primary human hepatocytes of silymarin extract and its main flavonolignans following exposure to the cytotoxic actions of model toxins.

The conditions for the hepatocyte intoxication were optimized for allyl alcohol, carbon tetrachloride, d-galactosamine, and paracetamol. All main flavonolignans of silymarin tested displayed concentration dependant cytoprotection against the toxic effects of allyl alcohol and carbon tetrachloride. The best protection was achieved by silydianin and silychristin and to a lesser degree by silymarin, while silybin and isosilybin were less effective [6]. Hamid *et al.,* found that Silymarin benefits liver function in people infected with the hepatitis C virus. This study indicated that in patients with CHC (Chronic Hepatitis C) performing silymarin (650 mg/day) for 6 months, improved serum HCV-RNA titer, serum aminotransferases (ALT, AST), hepatic fibrosis, and patient's quality of life [7].

2.2 *Allium sativum*: Block E was the first who compiled the chemical analysis of garlic. Earlier, garlic's activity was attributed to garlic oil that contains sulfur and, an American chemist named the strong-smelling liquid "allicin".



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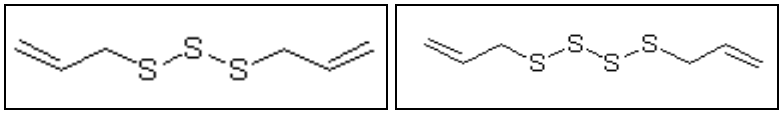
The sulfur compound alliin (S-allyl-l-cysteine sulfoxide) produces allicin (diallyl thiosulfinate) *via* the enzyme allinase when the bulb is crushed or ground. Other sulfur compounds, peptides, steroids, terpenoids, flavonoids, and phenols have increasingly been identified as possible active ingredients as allicin gets metabolized [8]. Yang *et al.,* isolated eight compounds from the aqueous ethanolic extract of garlic.

The compounds isolated were oxidant active compounds derived from garlic; bis-2-propenyl trisulfide (6), bis propenyltetrasulfide (7), bis-2-propenyl pentasulfide (8), bis-2-propenyl-thiosulfonate (9), trans-sulfuric acid allyl ester 3-allylsulfanyl-allyl ester (10), 2-propene-1-sulfino-thioic acid S-methyl ester (11), 2-propene-1-sulfinothioic acid S-(E)-1-propenyl ester (12), trans-sulfurous acid allyl ester 3-allylsulfanyl-allyl ester (13) [9].



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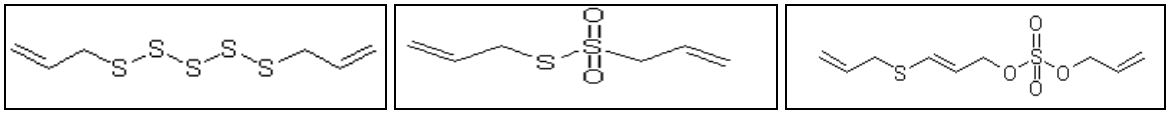

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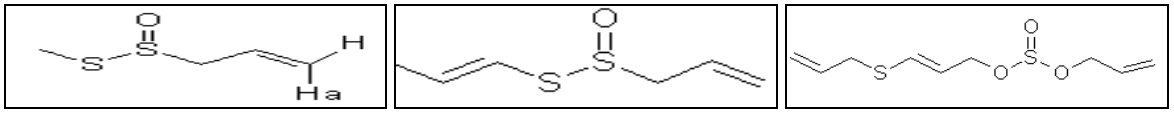


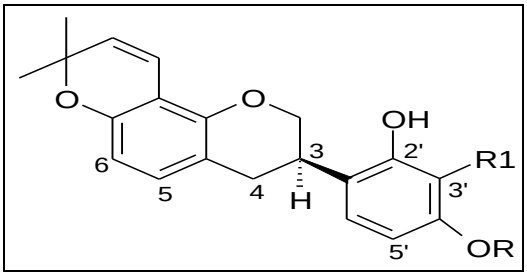
11 **12** **13**

Ajayi *et al.,* worked on the Hepatoprotective effects of *Allium sativum* and vitamin C in lead-exposed wistar rats. The experimental rats were exposed to lead (Pb) for one week. Garlic and vitamin C produced a significant reduction in the levels of ALT, ALP and PCV while the level of AST increased significantly. The level of Hb increased significantly in rats treated with garlic and reduced significantly in rats treated with Vitamin C. Above study, therefore suggested that garlic and vitamin C have some hepatoprotective and haematological effects [10].

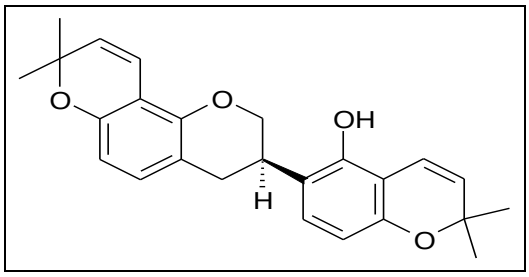
Nasim *et al.,* studied the effect of the garlic as hepatoprotective drug against the Antituberculosis drug (isoniazid) induced hepato-toxicity in experimental animal model. They found the drug to be effective since several enzymes of the cytochrome P450 were inhibited, thus decreasing the production of toxic metabolic intermediates [11]. Sankaran *et al.,* demonstrated the curative effect of Garlic on alcoholic liver disease patients. Oral supplementation of 2 small-sized raw garlic cloves (1 clove = 1.2 g) to alcoholic patients for 45 days significantly lowered the activities of liver marker enzymes, decreased the levels of lipid peroxidation, and enhanced the antioxidant status to near normal. Thus, the study suggested that raw garlic offers protection against oxidative stress and antioxidant activities in alcoholic liver disease patients [12].

2.3 *Glycyrrhiza glabra* (Liquorice): Jacob *et al.,* analyzed the antioxidative properties of compounds obtained from the roots of plant *Glycyrrhiza glabra* (licorice) toward LDL oxidation. Seven constituents, with antioxidant capacity, were isolated from *Glycyrrhiza glabra.* The isolated compounds were identified as the isoflavans; Hispaglabridin A (14), 4′-O-Methyl-glabridin (15), Glabridin (16), and Hispaglabridin B (17), the two chalcones, isoprenylchalcone derivative (18) and Iso-liquiritigenin (19) and the isoflavone, Formononetin (20).

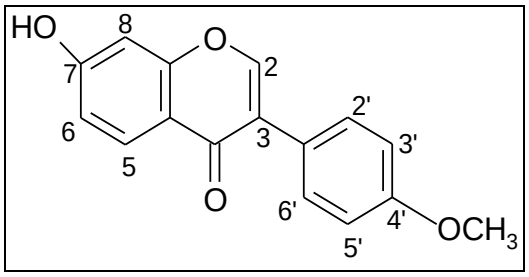
The antioxidative capacities of the isolated compounds (1–7) were tested against *β*-carotene destruction and LDL oxidation. The results suggested that all the constituents were very potent antioxidants towards LDL oxidation, with Glabridin being the most abundant and potent antioxidant [13].



R=H, R1= CH2CH=C(CH3)2 (14) R=CH3,



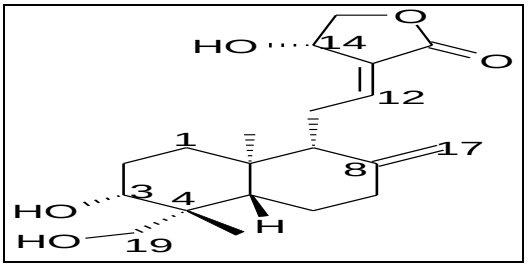
R1=H (15) R=R1=H (16) R1=R2= CH¬2CH=C(CH3)2 (18)



R1=R2= H (19)

Rajesh *et al.*, studied that the increased lipid peroxide formation in the tissues of CCl_4-treated rats was significantly inhibited by G. glabra. The observed decreased antioxidant enzyme activities of SOD, CAT, GSH-Px, GST and antioxidant concentration of glutathione were nearly normalized by *G. glabra* treatment. Thus, it was concluded that *Glycyrrhiza glabra* is a potential antioxidant and attenuates the hepatotoxic effect of CCl_4 [14]. Tajua *et al.,* evaluated the hepatoprotective and antioxidant effects of *Glycyrrhiza glabra* extract on the paracetamol (PCM) induced rat hepatocytes damage *in-vivo*. The effects were compared with a known hepatoprotective agent, Silymarin. Treatment with hydro-ethanolic extract of *G. glabra* root (200 mg/kg, bw. p.o,) brought back the altered levels of biochemical markers like AST, ALT, ALP, bilirubin, cholesterol, HDL to the near normal levels in the dose dependent manner. It was concluded that the aqueous extract of *G. glabra* root possessed commendable hepato-protective activity [15]. Kanimozhi *et al.,* studied changes in lipid peroxidation, antioxidants, and liver marker enzyme in the serum of 1, 4 DCB treated rats. The rats were given 300 mg/kg of DCB then treated with *Glycyrrhiza glabra* Linn.leaf extract. The level of malondialdehyde (MDA), an end product of lipid peroxidation, markedly increased in the 1, 4 DCB treated rats. After treating with *Glycyrrhiza glabra* extract, its level returned to its original level. Thus, it could be concluded in the above study that *G.glabra* possesses antioxidant and liver-protective effects like the standard drug, silymarin [16].

2.4 *Andrographis Paniculata*: Gorter isolated Andrographolide, a bitter principle which is a bicyclic diterpenoid lactone in pure form from Andrographis paniculata plant that possesses hepatoprotective action [17].



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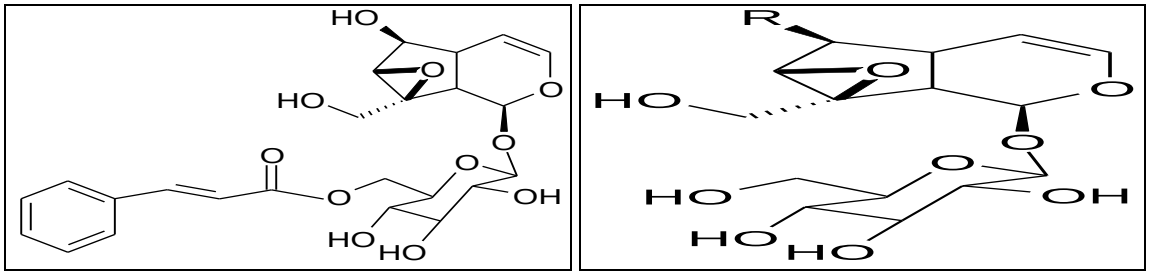
Handa *et al.,* observed the Antihepatotoxic activity of andrographolide on CCl_4-intoxicated rats.CCl_4-induced increase in the biochemical parameters like ST, SAP, SB, HT was inhibited by Andro-grapholide. The results suggested that andro-grapholide is the major active antihepatotoxic principle present in *A. Paniculata* [18]. Neha *et al.*, performed a study on the hepatoprotective effect of aqueous extract of Andrographis paniculata. The

liver damaged with hexachlorocyclohexane (BHC) was treated with Andrographis paniculata. Hepato-protective activity was monitored by estimating serum ALT & AST and other parameters like alkaline phosphatase, Glutamyl transpeptidase, glutathione and lipid peroxidase. It was found that AP inhibited BHC induced liver toxicity in Swiss male mice, which was assessed by the biochemical values. Thus, it could be concluded that aqueous extract of *Andrographis paniculata* has significant hepatoprotective activity [19]. The hepatoprotective activity of methanolic extracts of Andrographis paniculata was evaluated by Sutha *et al.* against paracetamol-induced (500 mg/kg) hepatic damage in mice. Histological analysis of the liver and the liver protein content indicated that the crude extracts of *Andrographis paniculata* exhibited a significant protective effect in the liver morphology of the paracetamol-induced hepatotoxicity in mice. There was also a significant decrease in the liver protein content of the hepatotoxic mice after the treatments indicating hepatoprotective effects of *Andrographis paniculata* [20].

2.5 *Picrorhiza kuroa*: Extensive work on the chemistry of *P. kurroa* has been initiated at RRL Jammu. The following six compounds have been isolated and recognized as Picroside I (22), Picroside II (23), Picroside IV (24), Apocynin (25), and Androcynin (26) [21].



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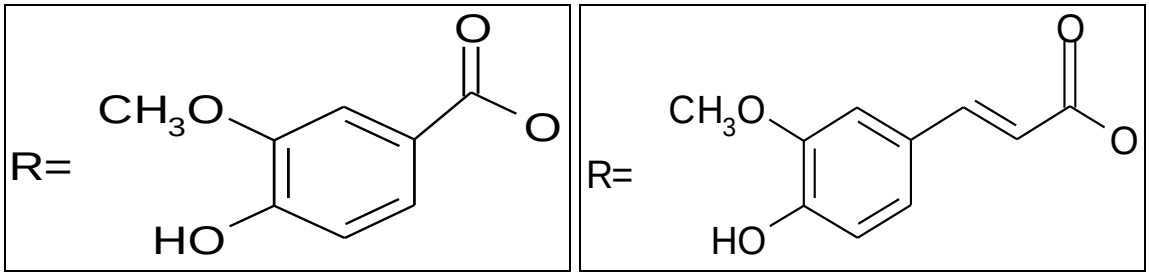

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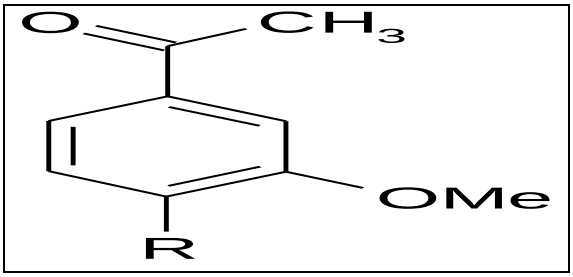
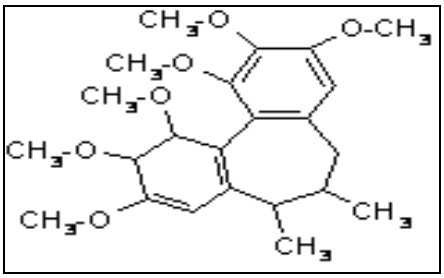


R=OH; (25) R=GLUCOSE; (26)

Visen et al., observed that Picroliv, the standardized active principle from the plant *Picrorhiza kurroa* showed significant curative activity *in-vitro* in primary cultured rat hepatocytes against toxicity induced by thioacetamide (200 microg/mL), galactosamine (400 micro g/mL), and carbon tetrachloride (3 micro l/mL). The activity was assessed by determining the change in hepatocyte viability and rate of oxygen uptake and other biochemical parameters (GOT, GPT, and AP). The results of this study showed that the *in-vitro* system could be used as an alternative for in vivo assessment of hepatoprotective activity of new drugs [22]. Sangeeta *et al.*, studied the antioxidant properties of *P. kurroa*. The drug was evaluated *in-vitro* using different radical scavenging assays.

A liver slice culture system was used to test the antioxidant activity of this extract, and ethanol was used as a hepatotoxin to generate oxidative stress. The results demonstrated that aqueous extract of *P. kurroa* possessed high antioxidant activity, as different radical scavenging assays effectively suppressed the deleterious effects of ethanol. The addition of *P. kurroa* aqueous extract along with ethanol restored the activities of antioxidant enzymes and significantly reduced lipid peroxidation [23]. Aakanksha *et al.*, evaluated the hepatoprotective effects of the methanolic extracts of *Picrorhiza kurroa* and *Andrographis paniculata* and their combined formulation on paracetamol induced liver damage on albino rats. The degree of protection was measured by using biochemical parameters like serum glutamate oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), Alkaline Phosphatase, (ALP) bilirubin and protein, lipid peroxidation, and superoxide dismutase. The methanolic extract of *P. kurroa* and *A. paniculata* and their combined form showed a significant dose-dependent (250,500 mg/kg bw.) protective effect against paracetamol-induced hepatotoxicity in albino rats. The degree of protection was maximum with a low dose of combined methanolic extract. From this study, it could be concluded that the methanolic extract of *P. kurroa* and *A. paniculata* were not only an effective hepatoprotective agent but also possessed significant antioxidant activity [24]. Vaidya *et al.*, studied *Picrorhiza kurroa* (Pk) in experimental and clinical situations. When the galactosamine-induced liver injury was conducted in rats, results showed a significant reduction in liver lipid content, GOT, and GPT. In a randomized, double-blind placebo-controlled trial in patients diagnosed to have acute viral hepatitis (HBs Ag negative), Pk root powder 375 mg three times a day was given for 2 weeks (n = 15), or a matching placebo (n = 18) was given. The difference in values of bilirubin, SGOT, and SGPT was significant between placebo and Pk groups. Thus, the present study showed an efficacy of Pk in viral hepatitis, hepatoprotection in an animal model, and an approach for standardizing extracts based on picroside content [25].

***Schisandra chinensis*:** Schisandrins from Schisandra fruit extract are lignans majorly composed of Schizandrin A (27), Schizandrin B (28), Schizandrol A (29), Gomisin A (30), Schisantherin A (31) [26].



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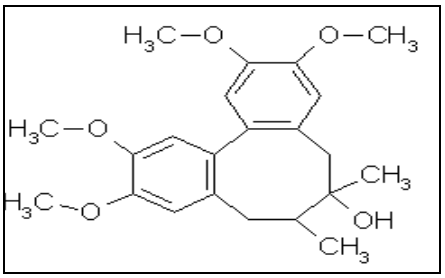

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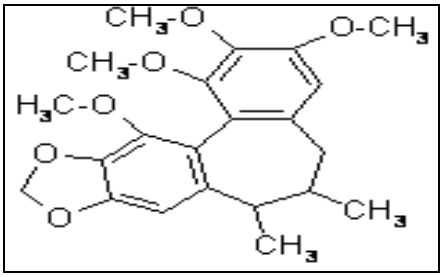

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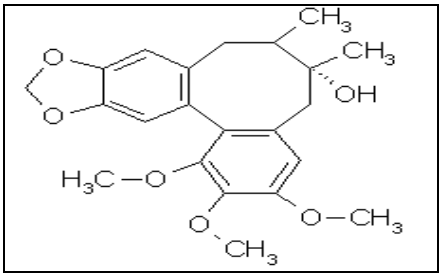

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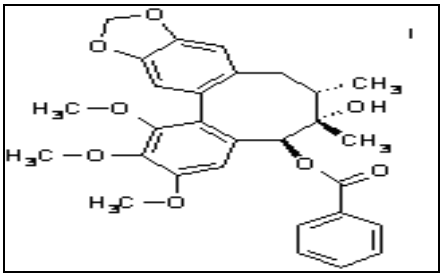

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Ip *et al.*, worked on the differences in chemical structures of constituents of *Schisandra chinensis*. They found that the presence of methylenedioxy group in Schisandrin B and C significantly increased the hepatoprotective effect [27]. Ip *et al.* demonstrated the Hepatoprotective effects of *Schisandra chinensis*. It was concluded in the above study that this drug inhibited the binding of CCl_4 metabolites to liver microsomal lipids and thus preventing CCl_4-induced lipid peroxidation.

The same study compared Schisandrin B and Butylated Hydroxytoluene (BHT), a synthetic phenolic anti-oxidant [28]. Upton *et al.,* demonstrated that pretreatment with Schisandrin B could enhance the hepatic gluta-thione antioxidant system in mice. Oral administration of 1.6 g/kg of a lignan-enriched extract was given for two days prior to CCl_4 intoxication; pretreatment with Schisandrin B resulted in 100% increase in glutathione reductase activity, 26% increase in hepatic glucose-6-phosphate activity, and a 16% increase in liver glutathione levels. Researchers established a dose-dependent range for Schisandrin B between 0.2-3.2 g/kg that established the hepatoprotective activity of this drug [29]. Mak *et al.,* compared Schisandr in B with alpha-tocopherol on lipid peroxidation. Mice were pretreated with 0.3 m mol/kg or 3 m mol/kg of Schisandrin B or 3 mmol/kg of α-tocopherol and compared to a control group.

Hepatocellular damage was assessed by measuring ALT levels. Researchers concluded that Schisandr in B inhibits lipid peroxidation while producing no pro-oxidant activity and this contributes to its hepatoprotective action [30]. Zhou *et al.,* evaluated the potential activity of Schisandra on phase one drug metabolism.

The final aqueous extract of Schisandra seeds was given to rats (dose of lignan fraction equal to 160 mg/kg) 24 h before CCl_4 and dosed 30 min and 6 h again prior to each CCl_4 dose. A single dose of antipyrine at 80 mg/kg was given to the rats with damaged livers, and levels of liver enzyme serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), and cytochrome P450 were measured.

Researchers found that CCl_4 substantially increased the elimination half-life of antipyrine from 2.59± 1.04/h to 11.25±3.91/ h and decreased its clearance from 65.94 to 10.84 ml/h compared to the control.

Pretreatment with Schisandra substantially improved antipyrine elimination half time to 3.30 ± 0.52/ h for 30 min group and 3.58 ± 1.05 / h for 6 hr group and clearance time to 49.06 ± 21.75 ml/h and 21.10 ± 10.42 ml/ h respectively.

Furthermore, normalization of SGPT, SGOT, and P_{450} levels were observed with the pretreatment of Schisandra. It was concluded that *Schisandra lignans* show a strong hepatoprotective effect on Phase one oxidative metabolism [31].

2. Human Studies: Chang *et al.,* reviewed human studies performed in China and reported that more than 5000 cases of different types of hepatitis had been treated with Schisandra preparations resulting in a short-term effect of lowering serum glutamic-pyruvic transaminase (SGPT). The onset of action for Schisandra was about twenty days and SGPT was normalized in 75% of treated cases. Elevated levels of SGPT were found in eighty-six cases of hepatitis due to drug toxicity, and levels of SGPT were normalized in eighty-three cases after 1-4 weeks of treatment with Schisandra. The references used are hospital records from the 1970's. In continuation of the above, Chang et al. reviewed that studies on one hundred and eighty-nine patients with chronic viral hepatitis B and elevated SGPT levels have been reported.

Seventy-three patients of the one hundred and seven patients (68%) given Schisandra had normal SGPT levels within four weeks, whereas only thirty-six patients of the eighty-two patients (44%) in the control group had normal SGPT levels within eight weeks.

It is important to note that SGPT levels tend to rise again in 46-69% of patients after discontinuing the use of Schisandra within three months especially in chronic persistent hepatitis, but repeated use of Schisandra normalized SGPT levels. In view of these clinical studies, an anti-hepatotoxic drug (DDB) derived from Schisandrin C was developed and is used with success in China for chronic viral and drug-induced hepatitis. These studies represent the limited amount of data available on the hepatoprotective effect of Schisandra in human studies [32].

CONCLUSION: All of the above-mentioned drugs have the potential to prevent and treat liver diseases. *Silybum marianum* (Milk Thistle) is the most favored drug for liver ailments, and a lot of research work has been done on it. Its active constituent, Silymarin, is responsible for its hepatoprotective activity. It's a mixture of flavonolignans, consisting of silibinin, isosilibinin, silicristin, and silidianin, the most active drug after Milk Thistle is Picrorrhizakuroa. It consists of

Picrosides, which contribute to its hepatoprotective activity. According to our traditional books, Picrorrhiza is the most effective herb for the liver.

To confirm this fact, some more research is desirable on this herb. Other herbs like Garlic and Andrographis also seem to have a lot of future scopes.

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CONFLICTS OF INTEREST: Nil

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