ABSTRACT
The liver is a major organ of the human body and the present rate of liver diseases are increased with a faster rate. In this article the plants which contain hepatoprotective constituents are studied. The plants that have numerous activities in the liver, which mentioned in traditional books are with modern methods. Herbal medicines are in great demand in the developed as well as developing countries for primary health care because of their wide biological and medicinal activities, higher safety margins and lesser costs. In this review the herbal plants that are scientifically proved the ability towards liver diseases are discussed.

KEYWORDS: Hepatoprotective, Herbal medicines, herbal plants.

INTRODUCTION
The liver plays a central role in transforming and clearing chemicals and is consequently susceptible to the toxicity induced from these agents. Chemicals that cause liver injury is termed hepatotoxins, and more than 900 drugs have been implicated in causing liver injury and it is the most common reason for a drug to be withdrawn from the market. Chemicals often cause subclinical injury to the liver, which may be manifest by abnormal liver enzyme tests. Certain medicinal agents when taken in overdoses and sometimes even when introduced within therapeutic ranges may injure the organ. Other chemical agents such as those used in laboratories and industries, natural chemicals (e.g. microcystins) and herbal remedies can also induce hepatotoxicity.

The unique property of the liver to metabolize substances and its close relationship with the gastrointestinal tract, it is highly susceptible to injury from drugs and other substances. Approximately 75% of blood reaching the liver arrives directly from gastrointestinal organs.
and then spleen through portal veins which bring drugs and xenobiotics in concentrated form. Numerous mechanisms may be cited to be responsible for either inducing hepatic injury or worsening the damage process. Although the exact mechanism of hepatic injury remains largely unknown, it appears to involve 2 pathways—direct hepatotoxicity and adverse immune reactions. In most instances, hepatic injury is initiated by the deactivation of drugs to chemically reactive metabolites, which have the ability to interact with cellular macromolecules such as proteins, lipids, and nucleic acids, leading to protein dysfunction, lipid peroxidation, DNA damage, and oxidative stress.

Additionally, these reactive metabolites may induce disruption of ion gradients and intracellular calcium stores, resulting in mitochondrial dysfunction and loss of energy Production. Its dysfunction releases excessive amount of oxidants which in turn injures hepatic cells. Activation of some enzymes in the cytochrome P-450 system such as CYP2E1 also leads to oxidative stress. Injury to hepatocyte and bile duct cells lead to accumulation of bile acid in the liver. This promotes further liver damage. This impairment of cellular function can culminate in cell death and possible liver failure.\[1\] Hepatic cellular dysfunction and death also have the ability to initiate immunological reactions, including both innate and adaptive immune responses. Stress and damage to hepatocytes result in the release of signals that stimulate activation of other cells, particularly those of the innate immune system, including Kupffer cells (KC), natural killer (NK) cells, and NKT cells. These cells contribute to the progression of liver injury by producing proinflammatory mediators and secreting chemokines to further recruit inflammatory cells to the liver. It has been demonstrated that various inflammatory cytokines, such as tumor necrosis factor (TNF) -α, interferon (IFN) -γ, and interleukin (IL) -1β, produced during hepatic injury are involved in promoting tissue damage.\[2\] However, innate immune cells are also the main source of IL-10, IL-6, and certain prostaglandins, all of which have been shown to play a hepatoprotective role. \[3\] Thus, it is the delicate balance of inflammatory and hepatoprotective mediators produced after activation of the innate immune system that determines an individual’s susceptibility and adaptation to hepatic injury.

**HEPATO-PROTECTIVE PLANTS**

In the last half a decade exploitation of herbal products in hepatic diseases immensely augmented. Hepatoprotectives that have been tested in hepatotoxicity models and provide an insight to the use of various plants against liver disorders have been scheduled below.
**Andrographis paniculata (Acanthaceae)**

Andrographolide is an active constituent extracted and isolated from *Andrographis paniculata*. *Ex vivo*, the compound illustrates a considerable dose dependent protective activity against paracetamol-induced toxicity in isolated rat hepatocytes upon administration of andrographolide. Tryptan blue exclusion and oxygen uptake tests clearly indicate an augmented percent viability of the hepatocytes. The bioactive constitution also antagonizes toxic effects of CCl4 and acetaminophen on certain enzymes (GOT, GPT and alkaline phosphatase) in serum as well as in isolated hepatic cells. [4] Evaluated the hepatoprotective efficacy of AP-extract against CCl4 and acetaminophen-induced toxicities on HepG2 cell lines. The results clearly depicted APextract to exert a choleric effect that reduces the cholestasis and diminishes retention as well as increase the excretion of toxic xenobiotics from the liver. Further, it also stimulated the immune system to fight against inflammation, is mediated by the release of cytokine from immunomodulators.

**Azadirachta indica (Meliaceae)**

The hepatoprotective activity of *Azadirachta indica* against paracetamol induced hepatic damage in rats by studies on antioxidant enzymes, (Glutathione peroxidase (GPX), glutathione-Stransferase (GST), superoxide dismutase (SOD) and catalase (CAT) have been found to be of great importance in the assessment of liver damage. Administration of A. The indicia leaf extract significantly enhanced the hepatic level of glutathione dependent enzymes like GPX from, 2 \pm 1.0 U/g protein to 18.8 \pm 1.2 U/g protein and superoxide dismutase from 40.2 \pm 2.7 U/g protein to 60.4 \pm 3.8 U/g protein and catalase activity from 52.4 \pm 2.7 U/g protein to 71.3 \pm 3.7 U/g protein. The results suggest that the hepatoprotective effect exerted by Neem may possibly be due to its ability to exert an antioxidative effect via augmenting the level of hepatic antioxidant enzymes.[5]

**Allium sativum (Liliaceae)**

The hepatoprotective effects of *Allium sativum* (Garlic) were studied by on experimental rats exposed to lead for one week. Administration of lead significantly increased (p < 0.05) plasma ALT and ALP activities in the rats. Specifically, the activities of ALT and ALP were increased by 29.1% and 69.2% respectively when compared to the control. The treatment with A. sativum produced a significant decrease (p < 0.05) on the activities of plasma ALT and ALP by 25.4% and 56.8%, respectively. Results depicted that administration of lead in
rats caused some level of liver or hepatic damage in the animals and that post-lead treatment with A. sativum exerted some hepatoprotective effects.\textsuperscript{[6]}

Boerhavia diffusa (Nyctaginaceae)
The roots of Boerhavia diffusa are used by a large number of tribes in India for the treatment of various hepatic disorders and for internal inflammation. Clinical data have also reported effectiveness of Boerhavia diffusa in cases of edema and ascites resulting from early cirrhosis of the liver and chronic peritonitis. The effect of 50\% ethanolic extract of roots of Boerhaavia diffusa on country made liquor induced hepatotoxicity was studied by in albino rats.\textsuperscript{[7]} Punarnava contains alkaloids named as punarnavine and punarnavoside which shows antifibrinolytic activity, but the hepatoprotective activity has been attributed to ursolic acid. Keppler and coworkers demonstrated that Ursolic acid isolated from the leaves showed a dose dependent (5-20 mg/kg) hepatoprotective activity (21 -100\%) in rats against thioacetamid, galactosamine and carbon tetrachloride induced hepatotoxicity in rats. These hepatotoxins decreased the viability of hepatocytes as assessed by trypan blue exclusion and the rate of oxygen uptake tests and decreased the volume of bile as well as the level of its contents. Pretreatment with ursolic acid increased the viability of rat hepatocytes significantly.\textsuperscript{[8]}

Camellia sinensis (Theaceae)
The leaves of Camellia sinensis are thermogenic, appetite, digestive, carminative, diuretic, and useful in cardiodynia, hemorrhoids, inflammation and abdominal disorders. It has been previously reported that the leaves have used to treat the cancer of duodenum, lung, liver and mammary gland. Catechins in combination with antioxidants vitamin E are hypothesized to offer a hepatoprotective defense against enzymes such as superoxide, dismutase and catalase. A number of cytokines (flavanols) especially epigallocatechin gallate, epigallocatechin, epicatechin gallate and epicatechin, which have been identified as active components responsible for antioxidant property, and also have the ability to stabilize cell membranes.\textsuperscript{[9]}

Capparis spinosa (Capparidaceae)
The plant also exerts a considerable hepatoprotective effect. Administration of ethanolic extract with CCl4 induced hepatotoxicity resulted serum ALT and AST were increased (191.80 and 239.40 U/ml, respectively), whereas these values showed 114.00 and 143.20 U/ml in normal saline group, respectively. Moreover, serum ALT and
AST in the groups treated with 100, 200 and 400 mg/kg of root bark extracts decreased significantly (p<0.05) in a dose dependent manner toward normalization.\textsuperscript{[10]}

\textbf{Cassia Tora (Leguminosae)}

\textit{Cassia Tora} is used for medicinal purposes all over the world. \textit{Cassia alata}, \textit{C. Fistula} and \textit{C. tora} are the important species recommended for primary health care to treat ringworm and skin diseases. The isolated compounds rubrofusaruin, cassisoid were found to have hepatoprotective activity against galactosamine damage, which was higher than that of silybin.\textsuperscript{[11]}

\textbf{Cichorium intybus (Asteraceae)}

\textit{Cichorium intybus} commonly known as Chicory is an indigenous perennial herb, well reputed ancient Indian medicine as a liver tonic. Accordingly, it has been used as Ayurvedic medicine for gall and liver disturbances and it forms an important component of several liver preparations in India. In preclinical studies the alcoholic extract of the \textit{Cichorium intybus} was found to be effective against chlorpromazine induced hepatic damage in adult albino rats. In a study performed by using an ethanolic extract of \textit{Cichorium intybus} in a dose of 300 mg/kg showed significant increase in circulating leukocytes and relative weights of the liver, as compared with alcohol alone which provides the evidence for liver protective effects of the herb.\textsuperscript{[12]}

\textbf{Curcuma longa (Zingiberaceae)}

The hepatoprotective activity of the ethanol extract of \textit{Curcuma longa} was studied against paracetamol-induced liver damage in rats. At the dose of 600 mg/kg, paracetamol induced liver damage in rats as manifested by the statistically significant increase in ALT and AST and ALP.\textsuperscript{[13]}

\textbf{Ginkgo biloba (Ginkgoaceae)}

The \textit{Ginkgo biloba} (GB) tree, also known as maidenhair tree is the only individual delegate of once flourishing botanical division, so called Ginkgophytes. GB exhibits a variety of interesting pharmacological properties such as oxygen free radical scavenging activity, cyclonucleotide phosphodiesterase inhibition, membrane stabilizing effect, increase in blood fluidity and improvement in cognitive function. Among the various mechanisms involved, the antioxidant property is claimed to be one of the mechanisms of hepatoprotective effect.\textsuperscript{[14]}
**Glycyrrhiza glabra (Leguminosae)**

Glycyrrhizin, a water-soluble pentacyclic triterpene derivative of β-amyrin type (oleanane), has been widely used as an antidote, demulcent and as a folk medicine. After oral administration or i.v. injection, it has been shown to be hydrolyzed by the glucuronidase in intestinal bacteria to its active principle aglycone, 18β-glycyrrhetinic acid, and absorbed into the blood. Both glycyrrhizin and 18β-glycyrrhetinic acid have been shown to possess several beneficial pharmacological activities. In addition, glycyrrhizin and 18β-glycyrrhetinic acid have been shown to protect against a number of hepatotoxicants such as CCl4 and D-galactosamine. Carbon tetrachloride-induced hepatotoxicity was also prevented, as indicated by a liver histopathologic study. The effects of 18β-glycyrrhetinic acid on the cytochrome P450 2E1, the major isozyme involved in carbon tetrachloride bioactivation, were also investigated.[15]

**Ocimum sanctum (Labiateae)**

*Ocimum sanctum*, popularly known as Tulsi is a holy plant common in most Indian households. Ancient Hindu literature is abundant with the medicinal actions of Tulsi. *Ocimum sanctum* is known to possess antiinflammatory, antimicrobial and antidiabetic activity. The leaves have been shown to exert a hepatoprotective effect in the models of predictable hepatotoxicity like paracetamol and carbon tetrachloride induced liver damage in rats.[16]

**Phyllanthus niruri (Euphorbiaceae)**

The decoction of the plant has historically been used in jaundice. In a preliminary study, carriers of hepatitis B virus were treated with a preparation of the plant Phyllanthus niruri for 30 days. 59% treated patients had lost hepatitis B surface antigen when tested 15-20 days after the end of the treatment. In no case has the surface antigen returned. Phyllanthus niruri is a component of marketed hepatoprotective combination, Liv-52.

In a study phyllanthin, hypophyllanthin and tricotanol were isolated from a 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 a hepatoprotective effect against CCl4 induced HepG2 cell damage in rabbits. Pre-treated with extract of *Phyllanthus niruri*, reduced paracetamol-induced acute liver damage in rats.[17]
Picrorhiza kurroa (Scrophulariaceae)

Picrorhiza kurroa is a renowned herb in the Ayurvedic system of medicine and has traditionally been used to treat disorders of the liver, upper respiratory tract, reduce fevers, treat dyspepsia, chronic diarrhea, and scorpion sting. Kutkin, the active principal of Picrorhiza kurroa is comprised of kutkoside and iridoid glycosides like picrosides I, II, and III. The hepatoprotective action of Picrorhiza kurroa may be attributed to its ability to inhibit the generation of oxygen anions and to scavenge free radicals. Picrorhiza’s antioxidant effect has been shown to be similar to that of superoxide dismutase, metal-ion chelators, and xanthine oxidase inhibitors. Animal studies indicate that Picrorhiza’s constituents exhibit a strong anticholestatic activity against a variety of liver-toxic substances, appearing to be even more potent than silymarin.[18]

Rheum emodi (Polygonaceae)

Roots of Rhubarb can be used as a strong laxative. The plant has an astringent effect on the mucous membranes of the mouth and the nasal cavity. Hepatoprotective effects of Rheum emodi roots and their aqueous and methanolic extracts were studied against liver damage induced by paracetamol in albino rats.[19]

Silybum marianum (Asteraceae)

Silymarin, a flavonolignan extracted and isolated from the seeds of ‘milk thistle’ has been extensively used from ancient times because of its tremendous hepatoprotective action. It is a mixture of three flavonolignans silybin, silidianin, and silychristine with silybin being most active. Silymarin has been used medicinally to treat liver disorders, including acute or chronic viral hepatitis, toxin drug-induced hepatitis, cirrhosis and alcoholic liver diseases. Its mechanism of action includes inhibition of hepatotoxin binding to receptor sites on the hepatocyte membrane, the reduction of glutathione oxidation to enhance the level of hepatocytes in the liver. Silymarin is effective in the treatment of both acute and chronic hepatitis.[20]

Taraxacum officinale (Asteraceae)

Taraxacum officinale has been used in traditional medicament for gastrointestinal and hepatic diseases. The plant is also valued as laxative and diuretic. Recently researches highlighted hepatoprotective property of dandelion to be an ingredient of liver and gall bladder preparations.[21]
**Tephrosia purpurea (Fabaceae)**

*Tephrosia purpurea*, forms one of the most effective ingredients of formulations available in Indian market for liver ailments. In the traditional Indian medicine, it was renowned for its effectiveness in bilious febrile attacks, obstruction of the liver and spleen apart. Especially it has shown good results in cirrhosis and viral hepatitis in clinical trials in humans. Dried ethanolic extract of *Tephrosia purpurea* was studied for its efficacy using both acute (D-galactosamine) and chronic models CCl4 of experimentally induced hepatotoxicity. *Tephrosia purpurea* also leads to increase in hepatic regeneration, which again contributes to its hepatoprotective efficacy.\(^{[22]}\)

**Tinospora cordifolia (Menispermaceae)**

*Tinospora cordifolia*, is one of the most valuable medicinal herbs of Ayurveda. According to the Ayurvedic lexicons *Tinospora cordifolia* is referred to as 'Amrita'. The term 'Amrita' attributes to this drug in recognition of its ability to impart youthfulness, vitality and longevity to its supporter. In modern medicine the plant is well known for its hepatoprotective, adaptogenic and immunomodulatory activities.\(^{[23]}\)

**Vitis vinifera (Vitaceae)**

The hepatoprotective effect of ethanolic extract and its four different fractions (CHCl3, EtOAc, now, and remaining water fraction) of *Vitis vinifera* leaves was investigated against CCl4- induced acute hepatotoxicity in rats. The ethanolic extract was fractionated through successive solvent-solvent extractions and the n-BuOH fraction was possessed tend to remarkable antioxidant and hepatoprotective activities.\(^{[24]}\)

**Wedelia calendulacea (Asteraceae)**

The historic use of *Wedelia calendulacea* as liver tonic is scientifically confirmed. Preclinical Studies demonstrated its protective action in paracetamol induced liver damage by increasing serum enzyme levels. In vivo alcoholic extract of whole plant exhibited protective activity against CCl4- induced liver injury. The extract also augmented the bile flow in rats, suggesting a stimulation of liver secretory capacity.\(^{[25]}\)

**Zingiber officinale (Zingiberaceae)**

Gingerol, the pungent factor in ginger, inhibited phospholipid peroxidation induced by the FeCl3 ascorbate system. Hepatoprotective activity of an aqueous ethanol extract of *Zingiber*
*Officinalis* was evaluated against single dose of acetaminophen induced (3 g/kg, p.o.) acute hepatotoxicity in rat.[26]

**CONCLUSION**

Modern society has innate knowledge about the herbal treatment of liver disease from many cultures. Research into plants traditionally used in the treatment of liver disease has significantly advanced in the past 15 years, and much of what has been discovered supports traditional knowledge. There continues to be a need for safe, effective treatments of liver disease. An assortment of botanical medicines such as Milk thistle, Turmeric, Green tea, Licorice, Tinospora cordifolia, Andographis paniculata and Picrorhiza, is the best-researched plants for the treatment of liver disease, with many human therapeutic trials available to the practicing physician to assess their potential effectiveness. Much research is yet to be done, but these plants appear to have a place in the treatment of liver poisoning, viral hepatitis, and cirrhosis of the liver.

There is no doubt that certain herbal products contain chemically defined components that can protect the liver from oxidative injury, promote virus elimination, block fibrogenesis, or inhibit tumor growth. Although additive effects may be lost, the active molecules must be isolated and tested in suitable culture and animal experiments and finally in randomized, placebo-controlled studies to enable rational clinical use of the agents. Biologically active molecules derived from herbal extracts can serve as suitable primary compounds for effective and targeted hepatotropic drugs.

**REFERENCES**


