HERBAL PLANTS - A BOON FOR HEPATOTOXICITY

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ABSTRACT

Liver diseases have become one of the major causes of morbidity and mortality all over the world. From among, drug-induced liver injury is one of the most common causative factors that possess a major clinical and regulatory challenge. Herbal plants have been used traditionally by herbalist worldwide for the prevention and treatment of liver disease. Herbal medicines have recently attracted much attention as alternative medicines useful for treating or preventing lifestyle related disorders and relatively very little knowledge is available about their mode of action. There has been a growing interest in the analysis of plant products which has stimulated intense research on their potential health benefits. Allopathic drugs cause toxicity to the liver by elevating the levels of various biomarkers present in the liver. At present, no single allopathic drug is available in the market for liver damage. Only Liv.52 and silymarin are herbal medicine for this purpose, so herbal drugs have a strong potential in the treatment of liver diseases. The herbal market, in the recent times, is growing day by day and is accepted at the global level. The present review focused on different herbal plants that have been tested for hepatoprotective activity in different animal models.

Keywords: Hepatoprotective activity, Liver, Hepatotoxicity, Serum enzymes, Silymarin, Liv.52, Herbal plants.

INTRODUCTION

The liver is the vital organ of metabolism and excretion. Liver plays a major role in detoxification and is generally the major site for intense metabolism [1]. Hepatotoxicity is a damage or injury to the liver which is caused by various drugs, chemicals, and other agents [2]. The extent of liver damage or injury depends on degree of exposure, mild liver damage cause dysfunction but severe liver damage result in liver failure [3]. Toxicity of chemicals majorly affects all kinds of plants and animals. Excess of any kind of compounds will be harmful to life. The manifestations of drug-induced hepatotoxicity are highly variable, ranging from an asymptomatic elevation of liver enzymes to fulminant hepatic failure. Paracetamol (PCM) also known as acetaminophen, taken in overdose can cause severe hepatotoxicity and nephrotoxicity [4]. PCM is activated and converted by cytochrome P450 enzymes to toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI) that causes oxidative stress [5,6]. Liver damage is associated with cellular necrosis, increase in tissue lipid peroxidation and depletion in the tissue glutathione (GSH) levels. In addition, serum levels of many biochemical markers like serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), triglycerides, cholesterol, bilirubin, alkaline phosphatase (ALP) are elevated.

In spite of tremendous advances in modern medicine, there are hardly any reliable drugs that protect the liver from damage and help in regeneration of hepatic cell. Herbal drugs play a major role in the treatment of hepatic disorders. A number of medicinal plants and their formulations are widely used for the treatment of these disorders. Many active plant extracts are frequently utilized to treat a wide variety of clinical diseases including liver disease. Therefore, searching for effective and safe drugs for liver disorders are continues to be an area of interest.

HEPATOTOXICITY INDUCING AGENT

Several chemicals have been known to induce hepatotoxicity: Carbon tetrachloride (CCl4), galactosamine, lipopolysaccharide, thioacetamide, antitubercular drugs, PCM, arsenic, etc., are used to induce experimental hepatotoxicity in laboratory animals. Liver injury due to PCM in rats has been widely and successfully used by many investigators. PCM is a widely used analgesic and an antipyretic drug which produces acute liver damage in high doses. PCM is metabolized by cytochrome P450 in endoplasmic reticulum and mitochondria with the formation of a toxic metabolite NAPQI, a reactive oxidative free radical, which initiates lipid peroxidation [7].

PCM administration also causes necrosis of the centrilobular hepatocytes characterized by nuclear pyknosis and eosinophilic cytoplasm followed by the large excessive hepatic lesion. The covalent binding of NAPQI to sulphhydryl groups of protein results in lipid peroxidative degradation of GSH level and thereby produces cell necrosis in the liver.

MECHANISM OF HEPATOTOXICITY

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 are 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 overdose 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. microcysts) and herbal remedies can also induce hepatotoxicity (e.g. Lycopodium serratum and Ephedra equisetina).

The unique property of liver to metabolize substances and its close relationship with the gastrointestinal tract, make it 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 two pathways-direct hepatotoxicity and adverse immune reactions. In most instances, the hepatic injury is initiated by the bioactivation 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 [8].
In addition, these reactive metabolites may induce disruption of ionic gradients and intracellular calcium stores, resulting in mitochondrial dysfunction and loss of energy production. Its dysfunction releases an excessive amount of oxidants which in turn injures hepatic cells. Activation of some enzymes in the cytochrome P450 system such as CYP2E1 also leads to oxidative stress [Fig. 1]. Injury to hepatocyte and bile duct cells lead to accumulation of bile acid inside the liver. This promotes further liver damage. This impairment of cellular function can culminate in cell death and possible liver failure [9].

PCM (acetaminophen) is an analgesic and antipyretic drug that is known to be safe at recommended doses [10]. However, it produces acute liver damage at higher doses. Hepatotoxicity of acetaminophen has been attributed to the formation of NAPQI a toxic metabolite that causes GSH depletion and oxidative stress [11].

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, natural killer (NK) cells, and NKT cells. These cells contribute to the progression of liver injury by producing proinflammatory mediators and secreting chemokines for further recruitment of inflammatory cells to the liver. It has been demonstrated that various inflammatory cytokines, such as tumor necrosis factor-α, interferon-γ, and interleukin (IL)-1β, produced during hepatic injury are involved in promoting tissue damage [12]. 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 [13]. 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

Plant drugs are known to play a vital role in the management of liver diseases. There are numerous plants and polyherbal formulations claimed to have hepatoprotective activities. Some plants which have hepatoprotective activity are turmeric, garlic, Solanum nigrum, etc. [14].

CASSIA OCCIDENTALIS

*C. occidentalis* commonly known as Kasondi, belongs to the family Caesalpiniaceae, is a common weed found throughout India and is employed in indigenous and folk medicine for a variety of purposes [15]. In Unani literature, “Kasondi” has been reported to be used as an antidote of poison, blood purifier, expectorant, anti-inflammatory agent and a remedy for the treatment of liver diseases. It is also an important ingredient of several polyherbal formulations marketed for liver diseases. The hepatoprotective effect of aqueous-ethanolic extract (50%, v/v) of leaves of Kasondi was studied on rat liver damage induced by PCM and ethyl alcohol by monitoring serum transaminase [aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT)], alp, serum cholesterol, serum total lipids and histopathological alterations. The extract of leaves of the plant produced significant hepatoprotection [16].

GLYCYRRHIZA GLABRA

*G. glabra* is commonly known as licorice and belongs to the family Leguminosae. It contains triterpene, saponin, known as glycyrrhizin, which has potential hepatoprotective activity. It belongs to a group of compounds known as sulfated polysaccharides. Several studies carried out by many researchers have shown glycyrrhizin to be for anti-viral, and it has potential for therapeutic use in liver disease [17]. Experimental hepatitis and cirrhosis studies on rats found that it can promote the regeneration of liver cells and at the same time inhibit fibrosis. Glycyrrhizin can alleviate histological disorder due to inflammation and restore liver structure and function from the damage due to CCl₄ [18]. The effects including lowering the SGPT, reducing the degeneration and necrosis and recovering the glycogen and RNA of liver cells. Effects of glycyrrhizin have been studied on free radical generation and lipid peroxidation in primary cultured rat hepatocytes. Favorable results have been reported in children suffering from cytomegalovirus after treating with glycyrrhizin.

MUSA PARADISIACA

*M. paradisiaca* is commonly known as banana and belongs to the family Musaceae. It is cultivated in tropical and semi-tropical countries. *M. paradisiaca* root is used as a tonic for congestion of the liver and to prevent scurry, anemia, veneral disease. The leaves are used in inflammation of eye, healing wounds and ulcers. The stems are used for ulcer, jaundice, nervous disorder, hysteria, diarrhoea, dysentery, antidote for opium poisoning, asthma, hair loss, treatment of piles [19]. The hepatoprotective activity of stem of *M. paradisiaca* was studied against CCl₄ and PCM induced hepatotoxicity in albino rats. Administration of hepatotoxins (CCl₄, and PCM) showed significant biochemical and histological deteriorations in the liver of experimental animals. Pretreatment with alcoholic extract (500 mg/kg), more significantly and to a lesser extent the alcoholic extract (250 mg/kg) and aqueous extract (500 mg/kg), reduced the elevated levels of the serum enzymes like SGOT, SGPT, ALP and bilirubin levels and alcoholic and aqueous extracts reversed the hepatic damage towards the normal, which further evidenced the hepatoprotective activity of stem of *M. paradisiaca* [20].

OCIMUM SANCUTUM

*O. sanctum* a common medicinal plant has a wide range of therapeutic potentials. Tulsi’s extracts are used in ayurvedic remedies for common colds, headaches, stomach disorders, inflammation, heart disease, various forms of poisoning, and malaria. Different parts of this plant have been reported to exhibit several medicinal properties. Pharmacological properties like anabolic, hypotensive, cardiac depressant, smooth muscle relaxant, anti-fertility and anti-stress activity of this plant have been reported by several workers. *O. sanctum* has been reported to possess anti-hepatotoxicity, and two triterpenes from the leaves have been shown to possess hepatoprotective effect against CCl₄ induced damage in rats. Effect of *O. sanctum* leaf extract was studied on PCM induced hepatic damage in rats. *O. sanctum* was found to protect the rats from the hepatotoxic action of PCM as evidenced by a significant reduction in the elevated serum enzyme levels. Histopathological studies showed marked reduction in fatty degeneration in animals receiving *O. sanctum* along with PCM as compared to the control group [22].

CASSIA FISTULA

*C. fistula* is commonly known as analtas, it belongs to the family Fabaceae. Hepatoprotective activity of the n-heptane extract of *C. fistula*
leaves was investigated by inducing hepatotoxicity with PCM in rats. The extract at a dose of 400 mg/kg body wt. exhibited orally, significant protective effect by lowering the serum levels of transaminases (SGOT and SGPT), bilirubin and ALP. The effects produced were comparable to that of a standard hepatoprotective agent silymarin [23].

**ALIUM SATIVUM**

*A. sativum* commonly known as garlic and belongs to the family Liliaceae. The hepatoprotective effects of *A. sativum* (garlic) were studied by on experimental rats exposed to lead for 1-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 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 [24].

**LAUNEA INTYBACEA**

*L. intybacea* is one such medicinal plant used in the treatment of liver disorders in folk medicine. The hepatoprotective activity of *L. intybacea* plant powder ethyl acetate extract was studied against liver disorders induced by PCM in wistar albino rats. The extract of plant powder was administered orally to the animals. Various biochemical parameters were studied to evaluate the hepatoprotective activity of ethyl acetate extract. Serum bilirubin, serum alkaline phosphate, SGOT and SGPT and liver homogenate superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), lipid peroxidation, glutathione-reduced and glutathione-transferase (GST) were determined to assess the effect of the various extract the PCM induced liver disorders. The study revealed that ethyl acetate extract significantly reduced serum bilirubin, SGOT, SGPT and SALT levels and liver homogenates LPO, SOD, CAT GPX, GST and GSH levels. The findings suggest that the plant *L. intybacea* possesses potential hepatoprotective activity [25].

**AZADIRACHTA INDICA**

The hepatoprotective activity of *A. indica* against PCM induced hepatic damage in rats by studies on antioxidant enzymes, (GPX, GST, SOD and CAT have been found to be of great importance in the assessment of liver damage. Administration of *A. indica* leaf extract significantly enhanced the hepatic level of glutathione-dependent enzymes like GPX from 11.2±1.0 U/g protein to 18.6±1.2 U/g protein and SOD from 40.2±2.7 U/g protein to 60.4±3.8 U/g protein and CAT activity from 52.4±2.7 U/g protein to 71.3 ± 3.7 U/g protein. The results suggest that the hepatoprotective effect exerted by neem may possibly be due to its ability to exert antioxidative effect via augmenting the level of hepatic antioxidant enzymes [26].

**CURCUMA LONGA**

*C. longa* or turmeric is a member of Zingiberaceae family which is the yellow pigment of turmeric. The hepatoprotective activity of the ethanol extract of *C. longa* was studied against PCM-induced liver damage in rats. At the dose of 600 mg/kg, PCM induced liver damage in rats as manifested by statistically significant increase in ALT and AST and ALP [27]. Pre-treatment of rats with the ethanolic extract of *C. longa* prior to PCM; dosing statistically lowered the three serum liver enzyme activities. In those animals, which received the plant extract were found to be 156.7±23.5 IU/L (ALT), 112.4±35.2 IU/L (AST) and 135.5±38.9 IU/L (ALP). These values are significantly lower (p<0.05) than the values of the toxic control group and were similar (p>0.05) to the control values [28].

**TRIGONELLA FOENUM-GRAECUM**

Fenugreek (*T. foenum-graecum* [TFG]) is an annual Mediterranean and Asiatic herb with aromatic seeds. It grows to two feet in height with brownish seeds contained in sickle-shaped pods. It is used worldwide as a culinary spice as well as a medicinal herb to soothe the stomach and help maintain blood sugar levels. The seeds are rich in protein and contain about 50% fiber and 25% soothing mucilage. The hepatoprotective activity of methanol extract of seeds of TFG was studied against CCl₄ induced toxicity in wistar albino rats. Seeds of TFG were collected, and subjected to continuous cold maceration in a macerator, for 72 hrs with solvents like petroleum ether (60-80) and methanol separately. Hepatic injury in rats was induced separately by administration of an equal mixture of CCl₄ and olive oil (50% v/v, 1.25 ml/kg, i.p.). Liver damaged was monitored by raised biochemical marker enzymes (SGOT, SGPT, and ALP). CCl₄ was administered twice a week, on every 1st and 4th day of all 14 days. The extract at the dose of 250 mg/kg b.wt. was evaluated by inducing hepatotoxicity with CCl₄ and using silymarin (100 mg/kg) as the reference standard. Biochemical parameters, such as SGOT, SGPT, and serum bilirubin level, were analyzed. A section of the liver was subjected to histopathological studies. Based on the above studies, it is reported that the methanol extract of TFG possess significant hepatoprotection against CCl₄ induced hepatotoxicity in albino rats [29].

**PHYLANTHUS POLYPHYLLUS**

Methanolic extract of *P. polyphyllus* was evaluated for hepatoprotective and antioxidant activities in rats. *P. polyphyllus* belongs to the family Euphorbiaceae. The plant extract (200 and 300 mg/kg, p.o.) showed a remarkable hepatoprotective and antioxidant activity against acetaminophen-induced hepatotoxicity as judged from the serum marker enzymes and antioxidant levels in liver tissues. The activity of the extract at a dose of 300 mg/kg was comparable to the standard drug, silymarin (50 mg/kg, p.o.). Histopathological changes of the liver sample were compared with respective control (Table 1).
CONCLUSION
The World Health Organization has estimated more than 80% of the world’s population in developing countries depends primarily on herbal medicines for their basic healthcare needs. In recent years, ethnobotanical and traditional uses of natural compounds, especially those of plant origin, have received much attention as they are well known for their efficacy and are generally believed to be safe for human use. Several investigators have shown that plant extract containing flavonoids are responsible for hepatoprotective potential in various experimental animal models. Thus, it can be interpreted that the hepatoprotective effect may be due to the presence of flavonoids. In this review article, an attempt has been made to compile the reported hepatoprotective plants. These plants may be useful to the health professionals, scientists and scholars working in the field of pharmacology and therapeutics to develop evidence-based alternative medicine to cure different kinds of liver diseases in man and animals.

REFERENCES