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TREATMENT OF LIVER DISEASE BY HERBAL DRUGS

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ABSTRACT

It is very interesting to note that there is no drug available in the modem system of medicine for treating hepatic disorders; only certain herbal preparations are available to treat this quite vulnerable disease. Several hundred plants have been examined for use in a wide variety of liver disorders. Just handfuls have been fairly well researched. The latter category of plants include *Silybum marianum* (milk thistle), *Picrorhiza kurroa* (kutkin), The standardized aqueous extact of *Glcyrrhiza glabra* (Stronger Neo-Minophagen C) has to be administered parenterally (80 gram, daily) can normalize aspartate transaminase and alanine transaminase in over 60% of the patients. Hepatoprotective activity of *Emblica officinalis* and Chyavanaprash extracts were studied using carbon tetrachloride induced liver injury model in rats, both extracts were found to inhibit the hepatotoxicity produced by acute chronic CCl_4 adminstration has seen from the decreased levels of serum and liver lipid peroxides (LPO), glutamate-pyruvate transaminase (GPT), and alkaline phosphate (ALP).

KEYWORDS: Liver disease, Herbal drugs, Hepatoprotective activity.

1.0 INTRODUCTION

Liver disease is one of the major causes of morbidity and mortality in public, affecting humans of all ages. Viral hepatitis is caused by infection with any of at least five distinct viruses, of which the three most commonly identified are hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV) (Negi *et al.*, 2008).There were 30,000 cases of hepatitis A reported to the Centre for Disease Control (CDC) in the U.S. in 1997. The agency estimates that there were as many as 270,000 cases each year from 1980 through 2000 (Fiore *et al*., 2006).

The global prevalence of hepatitis B virus (HBV) is over 350 million people worldwide and globally around 1 million die due to consequences of this infection annually (Al-Mahtab et al 2008). In low prevalence areas such as the continental United States and Western Europe, less than 2% of the population is chronically infected (Redd et al 2007). In moderate prevalence areas, which include Eastern Europe, Russia, and Japan, where 2-7% of the population is chronically infected. In high prevalence areas such as China and South East Asia, transmission during childbirth is most common, although in other areas of high endemicity such as Africa, transmission during childhood is a significant factor (Alter 2003).

HBV is responsible for 31.25% cases of acute hepatitis 76.3% cases of chronic hepatitis (Mahtab *et al* 2007), 61.15% cases of cirrhosis of liver and 33.3% cases of hepatocellular carcinoma in Bangladesh (Afroz *et al.*, 2007). Around 130 million people in China are carriers of HBV (almost a third of the people infected with HBV worldwide); 1 million people in the country are chronically infected (Liu *et al* 2002). During a 5 year period, 10-20% of patients with chronic hepatitis developed cirrhosis, and 20–23% of the cases with compensated cirrhosis progressed to decompensate cirrhosis. 6–15% of the people with cirrhosis and chronic hepatitis progressed to hepatocellular carcinoma (HCC). 5-year survival for compensated cirrhosis is 55%, that for decompensate cirrhosis is 14%, and that for HCC is less than 5% (Si 2006). Every year, 300,000 people die from HBV-related diseases in China, including 180,000 patients with HCC. However, the incidence of hepatitis B is still increasing, from 21.9 in 100,000 people in 1990 to 53.3 in 100,000 in 2003 (Jia and Zhuang 2004).

Hepatitis C infects nearly 200 million people worldwide and 4 million in the United States. There are about 35,000 to 185,000 new cases a year in the United States. It is currently a leading cause of cirrhosis, a common cause of hepatocellular carcinoma, and as a result of these conditions it is the leading reason for liver transplantation in the United States (McGovern et al 2006; Campbell *et al* 2006; Ruiz and Molitor 2002).

In industrialized nations, low HCV seroprevalence rates have been reported (0.6% in Germany, 0.8% in Canada, 1.1% in France, and 1.8% in USA) in comparison to Asian countries (2.1% in Indonesia, 3.2% in China, and 2.4–6.5% in Pakistan). Six major genotypes of HCV have been identified. In USA and Europe, genotype 1 is most prevalent (60–70%), while genotypes 2 and 3 are less common. In Eastern countries, genotype 3 is most common in India and the Far East, genotype 4 in the Middle East, and genotype 6 in Hong Kong and Vietnam. Genotype identification is clinically important because genotypes 1 and 4 are more resistant than genotypes 2 and 3 to the current standard interferon-based therapies (Limas 2007).Prevalence is higher in some countries in Africa and Asia. Egypt has the highest seroprevalence for HCV, up to 20% in some areas (Frank et al 2000). Approximately 350,000 or 35% of patients in the USA infected with HIV are also infected with the hepatitis C virus, mainly because both viruses are blood-borne and present in similar populations. Hepatitis E was first identified in India and it has been recognized in the Middle and Far East, in northern and western Africa, the central Asian Republics of the former Soviet Union, in China and Hong Kong SAR. Epidemic and sporadic cases have been reported from southeast and central Asia, the Middle East, northern and western Africa and North America (Mexico).

20,000 cases occurred in Mandalay, Myanmar, (1976-1977), Burma (20,000 cases in 1976-1977) and China 100,000 cases between 1986 and 1988. 11,000 cases occurred in Somalia, and about 4000 cases were reported in Mexico between 1988 and 1989 (WHO 2004).

Two billion people worldwide consume alcoholic beverages and 76.3 million are estimated by the World Health Organization to have diagnosable alcohol use disorders The prevalence of alcohol liver diseases (ALD) in the US in conservatively estimated at about 2 million persons. Approximately 40% - 90% of patients with cirrhosis have a history of alcohol abuse (WHO 2004).In India, on meta-analysis, the point prevalence of hepatitis B in non tribal populations was found to be 2.1 % and this corresponded to a chronic carrier rate of 1.7 per cent. Among tribal populations the point prevalence was 19.4 % in the groups studied and this corresponded to a chronic carrier rate of 15.5 %. The National Cancer Registries maintained by the Indian Council of Medical Research (ICMR) records all deaths from cancer in well defined areas and looks at liver cancer as a proportion of deaths from all cancers. Analysis shows that HCC forms 1.6 % of all cancers in the country. Approximately 773,000 deaths in the country are due to cancer. About 11000 deaths in the country are due to HCC and of that, 5000 are due to hepatitis B (Puliyel et al 2008).

1.1 LIVER DISEASES AND AYURVEDA

The liver is known as "Yakrita" in Ayurveda. It is the largest (organ of metabolism) in the body. The basic functions of the liver are production and secretion of bile, metabolic activities related to carbohydrates, fats and proteins and filtration of the blood. The liver helps remove bacteria and other foreign particles that enter the blood from the lumen of intestine. It is also mentioned as the main site of blood formation with the help of Ranjaka pitta (fire) (one of five types of pitta (fire)). Problems related to liver are mainly due to the excess of pitta dosha (fire humors) in the body. Hepatic disorders are severe pain in ribs, right shoulder and right leg, stiffness in the right arm, discoloration of stool (whitish), nausea, yellow-blood like urine, lassitude, anorexia, jaundice, heartburns. All these can lead to liver abscess. Jaundice (Pandu Roga) is mainly due to pitta dosha (fire humor) and the symptoms are yellowish color of eyes, skin, nails, face and urine, faded skin color like that of a frog, impaired senses, burning pain in the epigastrium, indigestion, asthenia and anorexia (Singh 1998).

The various herbs used in Ayurveda are liver protective, corrective and have regenerating effect on the dead liver cells. These herbs stimulate liver regeneration, have bile purgative (pitta) effects and act as pitta-nashaka (pitta destroyer) and pitta-shamka (reduces pitta). They have been proved to have special action on viral hepatitis due to antiviral properties. Therefore, by keeping the pitta in its balanced state and due to their hepatoprotective action, all these herbs are capable of dealing with all liver problems.

There are more than 300 preparations in the Indian system of medicine for the treatment of jaundice and chronic liver diseases. There are some Ayurvedic preparations approved by the Indian medical practioner's cooperative pharmacy stores for the treatment of jaundice and chronic liver diseases i.e Bhringarajasava, Chadraprabhavati, Drakahadi rasayam, Guuchi satwan, Jambeeradipanakam, Panchatiktakwatha, Churnam, Dhathri loham, Tapyadi loham, Pipilyadi loam and Saptamiruda loham. Specific herbal formulations have been studied for the treatment of chronic liver disease, including Liv-52, Liv.42, Liver cure, Livol, B.Liv, Hepatomed, Jigrine, Tefroli, Stimuliv, Koflet, Icterine, HD-03 and AO-8 herbal formulations (Thyagarajan *et al* 2002; Kataria and Singh 1997). Liv-52, marketed in India as an Ayuvedic hepatoprotective agent, is an herbal formulation that comprises *Capparis spinosa* (capers), *Cichorium intybus* (wild chicory), *Terminalia arjuna* (arjuna), *Solanum nigrum* (black nightshade), *Achillea millefolium* (yarrow) and *Tamarix gallica* (tararisk) (Schuppan *et al* 1999). Amalkadi Ghrita is one of the Panchagavya Ayurvedic formulation containing *Emblica officinalis* (Amla), *Glycyrrhiza glabra* (liquorice), and cow's ghee (clarified butter fat) was showed hepatoprotective activity against CCl_4 induced hepatic damage in rats comparable to silymarin due to combined action of all ingredients (Achliya et al 2004).

1.11 TREATMENT FOR LIVER DISEASES BY HERBAL MEDICINES

It is very interesting to note that there is no drug available in the modem system of medicine for treating hepatic disorders; only certain herbal preparations are available to treat this quite vulnerable disease. Medicinal systems conceptualize a general imbalance of the dichotomous energies leads to the disease and they focus on medicine that balance these energies and maintain good health. In spite of the phenomenal advances in cellular, biochemical and therapeutic approaches to many diseases, liver diseases remain enigmatic today. Though liver diseases are among the important diseases affecting humans, there is a dearth of effective remedies to treat them satisfactorily. None of the available preparations are specific for liver disorders. The indigenous system of medicine in India has abundant data on drugs available for the treatment of various liver disorders. These drugs have been used for centuries and have been claimed to offer significant relief. Besides, the folklore remedies, many plant products are also commonly used to treat liver disorders throughout India.

Several hundred plants have been examined for use in a wide variety of liver disorders. Just handfuls have been fairly well researched. The latter category of plants include *Silybum marianum* (milk thistle), *Picrorhiza kurroa* (kutkin), *Curcuma longa* (turmeric), *Camellia sinensis* (green tea), *Chelidonium majus* (greater celandine), *Glcyrrhiza glabra* (liquorice) and *Allium sativum* (garlic) (Luper et al 1998).

Ocimum sanctum leaf extract was found to protect rat from hepatotoxic action of paracetamol as evidenced by significant reduction in the elevated serum enzyme levels (Chattopadhyay et al 1992).

Picrorhiza has been shown to protect liver cells from a wide variety of insults including amanita poisoning (Dwivedi et al 1992; Floersheim et al 1990), CCl_4 (Saraswat et al 1993; Santra et al 1998), galactosamine (Dwivedi et al 1993; Visen et al 1993), ethanol (Rastogi et al 1996), aflatoxin B1 (Dwivedi et al 1993), acetaminophen (Singh et al 1992), thioacetamide (Dwivedi et al 1993; Dwivedi et al 1991), oxytetracyline (Saraswat et al 1997) and monocrotaline (Dwivedi et al 1991) in both *in vitro* and *in vivo* experiments. When compared with silymarin, the hepatoprotective effect was found to be similar, or in many cases, superior to the effect of silymarin (Saraswat et al 1993; Singh et al 1992; Saraswat et al 1997).

The standardized aqueous extact of *Glcyrrhiza glabra* (Stronger Neo-Minophagen C) has to be administered parenterally (80 gram, daily) can normalize aspartate transaminase and alanine transaminase in over 60% of the patients (Yamamura et al 1997).

Hepatoprotective activity of *Emblica officinalis* and Chyavanaprash extracts were studied using carbon tetrachloride induced liver injury model in rats, both extracts were found to inhibit the hepatotoxicity produced by acute chronic CCl_4 adminstration has seen from the decreased levels of serum and liver lipid peroxides (LPO), glutamate-pyruvate transaminase (GPT) and alkaline phosphate (ALP) (Jose et al 2000).

Water extract of three herbal plants (*Hibiscus sabdariffa, Rosamarinus officinalis* and *Alvia officinalis*) that have been commonly used for treating against azathioprine-induced hepatoxicity in rats (Amin et al 2005).

In animal studies, *Phyllanthus amarus* extract reduced or eliminated woodchuck hepatitis virus in woodchucks but not duck HBV in ducks. Recent studies show that an extract of *Phyllanthus amarus* down-regulates HBV *in vitro* by inhibiting the viral polymerase, decreasing episomal HBVDNA content, and suppressing virus release through specifically inhibiting HBV enhancer I activity by complexing with the C/EBP α and ß transcription factors (Ott et al 1997).

Phyllanthus niruri Linn. has been effective against infective hepatitis (Jayaram et al 1997; Thyagarajan et al 1988) and other disorders of liver (Prakas et al 1995; Lee et al 2006). Human studies also showed its liver protective and detoxifying actions in children with hepatitis and jaundice. In India, it is used as a single drug in the treatment of jaundice in children (Dixit and Achar 1983) and British researchers showed that children treated with *Phyllanthus* extract for acute hepatitis could return the liver function to normal within 5 days. Chinese researchers also found its liver protective actions in adults affected with chronic hepatitis (Wang 2000).

The extracts of *C. longa* rhizomes exhibited protective activity against CCl_4 induced liver injury *in vivo* and *in vitro* (Kiso et al 1983).

The ethanolic extract of *Trianthema portulacastrum* L. (Aizoaceae) showed a significant dose dependent protective effect against paracetamol and thioacetamide induced hepatotoxicity in albino rats (Kumar 2004).

Phyllanthus maderaspatensis (whole plant extracts) (200 mg/kg, *n*-hexane, ethyl alcohol or water) was showed a remarkable hepatoprotective activity against acetaminophen induced hepatotoxicity (Asha 2004) while aqueous-methanolic extract of *Artemisia maritima* showed hepatoprotective against acetaminophen and CCl_4 induced hepatic damage (Janbaz et al 1995). The methanolic extract of the leaf of *Phyllanthus amarus* was showed hepatoprotective effect against ethanol-induced liver damage (Faremi et al 2008).

The protective effects of *Dunaliella salina* on liver damage was showed by CCl_4 induced hepatotoxicity in mice may be due to both the increase of antioxidant enzymes activities and inhibition of lipid peroxidation (Hsu et al 2008).

Pretreatment with *Aralia continentalis* roots prior to the administration of CCl_4 has shown significantly prevented the increased serum enzymatic activity of ALT and AST as well as the formation of hepatic malondialdehyde (Hsu et al 2008).

Bark of *Commiphora berryi* was significantly protected the liver against CCl_4-induced oxidative damage in rats, effect might be correlated with its antioxidant and free radical scavenger effects (Shankar et al 2008).

The protective effects of single dose of garlic oil was showed on acute ethanol-induced (4.8 g/kg bw) in mice. Single dose of garlic oil possessed ability to prevent acute ethanol-induced fatty liver, but may lose its capacity when used after ethanol exposure (Zenga et al 2008).

The ethanolic roots of *Hemidesmus indicus* was showed hepatoprotective effects on experimental liver damage against hepatotoxicity induced in rats by ethanol at a dosage of 5 g/kg body weight for 60 days (Saravanan and Nalini 2008).

The ethanol extract of *Bacopa monnieri* Linn. aerial parts was protect the liver cells from paracetamol-induced liver damage perhaps, by its antioxidative effect on hepatocytes, hence eliminating the deleterious effects of toxic metabolites of paracetamol (Ghosh et al 2007).

Hepatoprotective activity of aqueous ethanol extract of *Zingiber officinale* was significantly protected against single dose of acetaminophen-induced acute hepatotoxicity in rat due mediated either by preventing the decline of hepatic antioxidant status or due to its direct radical scavenging capacity (Ajith et al 2007).

The ethanol extract of *Hemidesmus indicus* roots 100 mg/ kg, for 15 days significantly prevented rifampicin and isoniazid-induced hepatotoxicity in rats (Prabakan 2000).

Hepatoprotective activity of different extracts of the stem bark of *Moringa pterygosperma* was showed hepatoprotective action against carbon tetrachloride and rifampicin-induced hepatotoxicities, while the petroleum ether extract exhibited similar activity against paracetamol-induced hepatotoxicity (Kurma 1998).

The effects of intake of carotenoid lycopene or tomato extract, a rich source of lycopene, on acute liver injury caused by the oxidant carbon tetrachloride. Feeding with tomato extract (10% tomato powder), but not with lycopene (0.25% lycopene beadlets), partially inhibited CCl_4 induced hepatic injury (Kim 2004).

The hepatotoxic activity of methanol extract of rhizomes of *Curculigo orchioides* rats was administered for 90 days (daily, orally at the dose of 70 mg per kg body weight) was protected against using carbon tetrachloride intoxicated rat liver (Venukumar et al 2002).

Hydroethanolic extract (70%) of *Calotropis procera* flowers (200 mg/kg and 400 mg/kg) was showed significantly dose dependent hepatoprotective activity against paracetamol induced hepatitis in rats (Ramachandra 2007).

The ethanol insoluble component of a water extract from *Acanthopanax koreanum* Nakai was showed protective effect against the induction of fulminant hepatitis in mice by galactosamine and lipopolysaccharide in mouse (Nan 2004).

The significant hepatoprotective activity of the aqueous extract of the roots of *Hygrophila auriculata* was showed on CCl_4 induced liver toxicity in rats (Shanmugasundaram 2006).

The protective effect of *Lygodium flexuosum* extract was showed against D-galactosamine induced in rat, comparable to that of silymarin, the standard hepatoprotective drug (Wills and Asha 2006).

Adhatoda vasica leaf showed significant hepatoprotective effect at doses of 50–100 mg/kg, p.o., on liver damage induced by D-galactosamine in rats (Bhattacharyya 2005).

Hepatoprotective activity of chloroform extract of *Polygala arvensis* at an oral dose of 200 mg/kg and 400 mg/kg exhibited a significant protection in wistar albino rats by inducing hepatic injury with D-galactosamine (Dhanabal 2006).

The seeds of *Cuscuta chinensis* Lam. ethanolic extract exhibited a significant effect prevent hepatic injuries from paracetamol induced hepatotoxicity in rats (Yen 2006).

Hepatoprotective effect of the methanolic extract of the whole plant of *Hedyotis corymbosa* produced significant hepatoprotective against paracetamol overdose induced liver damage in wistar rats and shortened hexobarbitone-induced sleeping time in mice, besides showing significant antilipid peroxidant effect *in vitro* (Sadasivan 2006).

Pretreatment of rats with different doses of *Cytisus scoparius* L. extract (250 and 500 mg/kg) significantly lowered antioxidant activity of on CCl_4 treated oxidative stress in wistar albino rats. The activity of extract at the dose of 500 mg/kg was comparable to the standard drug, silymarin (25 mg/kg) (Raja et al 2007). A list of some plants used for liver complaints are given in table no 1.4.

1.11.1 Hepatoprotective phytoconstituents from Plants

Around 170 phytoconstituents isolated from 110 plants belonging to 55 families were stated to possess liver protective activity. The active constituents elucidated to date involve a wide range of components including terpenoids, curcuminoids, lignoids, flavonoids, cyanogenetic glycosides etc (Girish, 2009).

Silymarin, derived from the seeds of *Silybum marianum* L. (Family: Asteraceae or Compositae). The active extract of *S. marianum*, known as silymarin, is a mixture of flavanolignans namely; silibinin, silydianin, and silychristine (Wagner and Seligmann 1985). Most of its hepatoprotective properties are attributed to silybin (silibinin, 60–70%) of silymarin (Chavez 2001). It showed antihepatotoxic activity against *Amanita phalloides*, ethanol, paracetamol, carbon tetrachloride induced liver injury acute viral hepatitis and alcohol related liver cirrhosis (Blumenthal 2000; Mourelle et al 1989). The mechanisms which provides silymarin's hepatoprotective effects are many and varied, and include antioxidation (Halim et al 1997, Pietrangelo et al 1995; Basaga et al 1997), anti-lipid peroxidation (Bosisio et al 1992; Basaga et al 1997; Rui 1991), enhanced detoxification (Kim et al 1994) and protection against glutathione depletion (Cabrera 1996; Campos et al 1989). Silymarin has also shown protection of liver cells from ischemic injury, radiation, iron toxicity and viral hepatitis (Pietrangelo et al 1995; Mcpartland et al 1996).

Andrographolide and neoandrographolide are obtained from *Andrographis paniculata* Nees (Family: Acanthaceae), a well known plant for liver diseases (Puri et al 1993). Andrographolide exhibited protective effects comparable to silymarin against liver damage in rats induced by carbon tetrachloride, paracetamol, galactosamine and t-butylhydroperoxide (Visen et al 1993).

Curcumin is a main component of rhizomes of ancient spice, turmeric (*Curcuma* spp. Family: Zingiberaceae). Treatment with curcumin on fibrotic rats, after hepatic damage, showed significant improvement as well as restoration of lipid profile, marker enzymes and thiobarbituric acid reactive substances to normal (Akila et al 1998).

Picroside and kutkoside are active constituents of roots and rhizomes of *Picrorrhiza kurroa* Royle (Family: Scrophulariaceae). Picroliv a combined formulation of picroside I and kutkoside has been developed as a potent hepatoprotective drug (Gupta 2001). Picroliv showed curative *in vitro* activity in primary cultured rat hepatocytes against toxicity induced by thioacetamide, galactosamine, and CCl_4 and it was also found to possess potent anti-HBsAg, anti-hepatocarcinogenesis and also dose dependent choleretic effects (Kumar and Kuttan 2000., Visen et al 1993).

Phyllanthin and hypophyllanthin are potent hepatoprotective lignans found in *Phyllanthus niruri* Linn. (Family: Euphorbiacea). Both phyllanthin and hypophyllanthin protect liver against carbon tetrachloride and galactosamine-induced cytotoxicity in primary cultured rat hepatocytes (Syamsunder et al 1985).

Glycyrrhizin is a major and active constituent of roots of *Glycyrrhiza glabra* (Family: Leguminacae). It has shown hepatoprotective activity in animal models against carbon tetrachloride induced toxicity and hepatitis (Jeong et al 2002). One of Japanese formulations of glycyrrhizin, known as stronger neominophagen C (SNMC), combined with, 0.1% cysteine, and 2% glycine has been used for the treatment of chronic liver diseases and cirrhosis (Kumada 2002).

Cliv-92 is isolated from the seeds of *Cleome viscosa* Linne (Family: Capparidaceae), mixture of three structurally similar coumarinolignoids, cleomiscosins A, B, and C. It has shown potent hepatoprotective activity against carbon tetrachloride and phalloidin induced liver damage in rats and comparable to silymarin (Takeda et al 1979; Ray and Chattopadhyay 1980).

Oleanolic acid a triterpenic aci
d found in weed *Lantana camara* Linn. (Family: Verbenaceae). Oleanolic acid has also been reported from several other plants like *Syzygium aromaticum* L., *Ocimum basilicum* L., *Salvia triloba* L., etc. It has been found to be effective at inhibiting carbon tertrachloride induced liver injury (Liu 1995).

Pretreatment with kahweol and cafestol, coffee-specific diterpenes, prior to the administration of CCl_4 showed significantly prevented the increase in the serum levels of hepatic enzyme markers and reduced oxidative stress in the liver in a dose-dependent manner (Lee et al 2007).

Ursolic acid, a common triterpenic acid found in the leaves of *Eucalytus tereticornis*, *Salvia triloba*, *Vinca minor*, *Ocimum basilicum*, etc. has been reported to possess hepatoprotective activity against carbon tetrachloride, ethanol, thioacetamide, and galactosamine damaged liver in rats (Liu 1995; Shukla et al 1992).

Berberine is an isoquinoline alkaloid obtained from the roots, rhizomes and stembark of *Berberis aristata* DC (Family: Berberidaceae). The oxidative damage induced in the hepatocytes by tert-butyl hydroperoxide (t-BHP) was inhibited by berberine probably due to its antioxidant potential. In another study, the hepatoprotection activity is also believed to stem from its inhibitory effects on the ion channels of potassium and calcium in the rat hepatocytes (Marek et al 2003).

α and β-amyrin, a triterpene mixture isolated from the trunk wood resin of folk medicinal plant, *Protium heptaphyllum* were significantly hepatoprotective against

acetaminophen-induced liver injury in mice (Oliveira et al 2005).

Caffeic and fumaric acids, isolated for the first time from the bioactive total aqueous extract *Moringa pterygosperma*, showed significant hepatoprotective activity against galactosamine and thioacetamide-induced hepatic cytotoxicities (Kurma 1998).

Pretreatment with Allicin (diallythiosulfinate) is the main biologically active component of freshly crushed garlic (Alliaceae, *Allium sativum* Linn.) was significantly showed hepatoprotective activity against D-galactosamine/lipopolysaccharide induced hepatitis rats (Vimal 2004).

The other recent leads which are reported as emerging hepatoprotective agents against various hepatotoxins have been described in table 1.5 and figure no 1.2.

1.11.2 Nutrition supplements for hepatic disorder

The strict relationship between diet and health is known since ancient time and recent studies demonstrated the relevance of many food components in modulating human health. There is increasing evidence that an alteration of the cellular redox state with production of reactive oxygen species (ROS) plays a crucial role in the various steps that initiate and regulate the progression of liver diseases independently from the type of etiologic agents. ROS are involved in the liver damages induced by alcohol, virus, alteration of lipid and carbohydrate metabolism and xenobiotics (Loguercio et al 2001).

1.11.2.1 *Phenolic compounds*

Many polyphenol rich plants have been used for centuries in folk medicine for liver dysfunctions. Studies to elucidate the chemical composition of the plant extracts have been carried out, aiming to attribute to a single or more compounds elucidating positive health effect. The potential *in vivo* antioxidant effect of individual food polyphenols or extracts has been widely investigated in cultured cells (Froemming and Brien, 1997; Al´ıa, et al 2003), animal models (Cai et al 1997; Pataki et al 2002) and humans (Duthie et al 2000; Natella et al 2001). The main studies dealing on the potential health effects of this class of compounds are summarized in table 1.6.

Quercetin, one of the most abundant flavonoids in human diet, exerts its antioxidant activity acting as a strong oxygen radical scavenger, good metal chelator, inhibit production of nitric oxide and TNF-α by lipopolysaccharide stimulated kupffer cells (Jovanovic et al 1998; Peres et al 2000). It has also been reported that quercetin scavenges superoxide in liver ischemia-reperfusion injury (Peres et al 2000; Huk et al 1998).

A study on rats demonstrated that after initiation of the cirrhogenic process, quercetin administration at a dose of 150 pmol/kg body wt/day markedly reduces liver injury (Peres et al 2000) beside its action as antioxidant, quercetin may have prooxidant effects in rats (Choi et al 2003).

Esculetin, is a coumarin derivative found in a popular food plant, *Cichorium intybus* (chicory), esculetin could be the responsible of the anti hepatitis effect (Chang et al 1994). Pretreatment of mice with esculetin 6 mg/kg reduced the death rate due to paracetamol (dose 1 mg/kg) to 40%, prevented the paracetamol-induced increase of serum enzymes (ALP, AST and ALT) and the carbon tetrachloride induced prolongation in pentobarbital sleeping time (Gilani et al 1998).

1.11.2.2 *α-Tocopherol*

The supplementation with vitamin E is the most common dietary integration in the management of liver diseases. The well known antioxidant properties as well as the depletion of liver tocopherol observed in patients with hepatitis and cholelithiasis are the main justification for this treatment (Nagita and Ando 1997; Okita et al 2003).
In vitro and some human *in vivo* studies reported that vitamin E can inhibit pro-inflammatory cytokine production and attenuate hepatic fibrosis and collagen production. It showed that vitamin E (doses from 400 to 1,200 IU/d for 4–10 months) caused major improvements in liver enzyme levels (Hill et al 1999; Pietrangelo et al 1995).

In the second one, 300 mg/day of vitamin E was given for 1 year to 12 patients with liver biopsy proven NASH and 10 patients with the clinical diagnosis of NAFLD. An improvement of some biochemical indicators such as liver enzymes was observed; but the degree of steatosis, inflammation and fibrosis remained unchanged in the patients with NASH. In this study, plasma levels of TGF-β in patients with NASH were reduced significantly by vitamin E treatment (Hasegawa et al 2001).

Vitamin E supplementation was showed to improve aminotransferase status of patients with long-term HCV and to decrease the excretion of 8-iso-prostaglandin F2α in cirrhotic patients (Sodergren et al 2000; Pratico et al 1998).

1.11.2.3 *β-Carotene and Vitamin A*

β-carotene is the most abundantly stored carotenoid in the liver (Dimitrov et al 1998; Rock and Swendseid 1992) In particular hepatic stellate cells are considered to be the major site of storage and metabolism of retinoids and carotenes (Martucci et al 2004).

The concentration of all antioxidant liposoluble vitamins, such as retinol, tocopherol, and β-carotene is reduced in both plasma and liver tissue of liver cirrhosis patients. An experimental study on rats to test the efficacy of β-carotene therapeutic potential showed the ability of this compound to decrease the severity of liver fibrosis without marked toxicity, as previously found with retinyl esters (vitamin A) (Seifert et al 1995).

Oral administration of β-carotene during CCl_4 treatment of rats exerted, biochemically, a significantly lower increase in the hydroxyproline liver content and, histopathologically, a less severe liver fibrosis as compared with the liver of rats not treated with β-carotene. Moreover β-carotene administration is able to prevent the long-term loss of retinoids from the CCl_4 injured liver. β-carotene, differently to retinolpalmitate and lycopene, was able to attenuate also liver cirrhosis induced by thioacetamide in rats (Seifert et al 1995; Wardi et al 2001). An inhibition of ROS generation by 50% was reported in freshly isolated rat hepatocyte suspensions exposed to the toxic hydrophobic bile acid glycochenodeoxycholic acid (100 or 500 μM) and treated with 100 μM β-carotene (Gumpricht et al 2004).

1.11.2.4. *Lycopene*

Epidemiological evidence suggests a possible role for lycopene-rich foods in the prevention of many type of cancers and chronic diseases (Stahl and Sies 1992; Khachik et al 2002). Lycopene administration to rats by oral route for 4 weeks incresed the activities of SOD and GSH-Px and the concentrations of MDA were decreased significantly compared with control group. This study suggested that lycopene could increase antioxidative effect and reduce lipid peroxidation in wistar rats (Pan et al 2000). Moreover treating rats with lycopene in doses of 10 or 50 mg/kg for 2 weeks led to accumulation of this carotenoid in the liver, liver microsomes, and blood plasma, increased total plasma antioxidant activity, inhibited lipid peroxidation in the liver, and decreased solubilization of lysosomal enzymes (Kravchenko et al 2003). Lycopene was also able to oppose the ethanol-induced oxidative stress and apoptosis in HepG2 cells overexpressing CYP2E1.

2. DISCUSSION AND CONCLUSION

Although the number of patients with liver diseases has been increasing steadily, the treatment outcomes are still considered poor. Herbal medicine has become a major contributor to the treatment of liver diseases. The increasing number of studies that are being undertaken on various herbal medicines show a positive sign on the future of drug development from herbs. The future of the treatment of liver diseases with herbal medicines depends on our understanding of each and every chemical constituent and their interactions with each other. Currently, a handful of herbal drugs, such as Silymarin, Glycyrrhizaglabraand Liv- 52, have been studied thoroughly. These drugs and the other drugs mentioned in the presented study, have shown the scientific community their significance and possible usage as major treatment modalities for liver diseases. Unlike the conventional drugs which are composed of known chemical constituents and are accurately quantified, herbal drugs are composed of a complex mixture of ingredients. Due to this complexity, the studies being conducted face major obstacles, with the major setback being the purifying of herbal medicines, and finding and quantifying each of their components. Currently, new techniques, such as high performance liquid chromatography, protein precipitation and microdialysis, are being used to pretreat and separate the chemical constituents. However, studying the clinical effects of individual chemical constituents separately will be of little use for many reasons, among them the neutralization of harmful chemicals in the mixture by other chemicals, and the synergistic or inhibiting effects of chemicals on each other which provides a perfect combination in vitro for therapeutic purposes. Obtaining information only on the pharmacodynamics of herbal medicine on liver diseases provides insufficient details for developing drugs with similar effects. Factors such as metabolism, absorption, distribution and intrinsic concentration of the drug need to be known accurately to determine the dosage, duration of treatment, and the safety margin of each drug. The number of patients seeking herbal therapy is growing exponentially. Thousands of years of traditional use can provide the guiding principles for the selection, preparation and application of herbal formulations. In order to be recognized as feasible substitutes for contemporary medicine, the same technical method of scientific and clinical substantiation must be practiced to demonstrate the safety and efficacy of herbal therapeutic products. The therapeutically significant molecules should be identified, isolated, purified and examined with carefully devised experiments, both experimentally and clinically, which will help the scientific community to elucidate the advantages and disadvantages of any particular herbal remedy. Currently, there are more than 1,000 herbal medicines with many active compounds which need thorough investigation to prove that they are hepatoprotective as mentioned in Chinese medicine, Ayurveda medicine, and in ancient Egyptian herbal treatment. Looking back, it is obvious that a great deal of progress has already been made; the world is looking to the future with great anticipation and great expectations. Due to its culturally accepted nature, comparatively fewer side-effects, and the compatibility with the human body, herbal medicines are now increasing in demand in primary health care, not only in the developing world, but also in developed western countries.

Table 1.4: Some of the plants reported to possess hepatoprotective activity.

Botanical Name	Family	Extract	Reference
Acacia catechu	Leguminosae	Ethyl acetate extract	Jayasekhar et al 997
Andrographis paniculata	Acanthaceae	Aqueous extract of leaves	Neha et al 2000
Aspalathus linearis	Fabaceae	Aqueous extract	Ulinca et al 2003
Apium graveolens	Apiaceae	Different extracts of seeds (Pet, Ether, Acetone Methanol)	Bahar et al 2002

Adhatoda vasica	Acanthaceae	Ethanolic extract of fresh leaves	Pandit et al 2004
Artemisia maritiama	Compositae	Aqueous and methanolic extract of whole plant	Khalid et al 1999
Aerva lanata	Amaranthaceae	Alcoholic extract of entire herb	Majmudar et al 1999
Balinite aegyptiaca	Simarubicaceae	Ethanolic extract of bark	Jaiprakash et al 2003
Ballota glandulosissima	Lamiaceae	Water extract of whole plant	Ozbek et al 2005
Bombax ceiba	Bombacaceae	Methanolic extract of leaves	Ahsana et al 2005
Boehmeria nivea	Urticaceae	Aqueous extracts of roots and leaves	Chun-Ching et al 1998
Bupleurum kaoi	Umbelliferae	Aqueous extract of roots	Ming-Hong et al 2005
Berberis tinctoria	Beriberidaceae	Methanolic extract of leaves	Kandasamy et al 2005
Beta vulgaris	Chenopodiaceae	Aquous and ethanolic extracts of fruits	Agarwal et al 2006
Cyperus rotondus	Cyperaceae	Alcoholic and Aqueous extracts of tuberous roots	Mehta at al 2004
Cassia tora	Leguminosae	Ethanolic extract o	Kumud et al 2000
Lawsonia alba	Cucurbitaceae	Different extract of the fruits	Bahar et al 2001
Nymphaea stellata	Lythraceae	Ethanolic and water extracts of bark	Bhandarkar et al 2004
Ocimum sanctum	Nymphaeaceae	Methanolic of extract flowers	Manoj et al 2004
Plumbago zeylanica	Labiateae	Ethanolic extract of dried powder of the leaves	Ubaid et al 2003
Phyllanthus maderaspaton	Plumbagoginaceae	Aqueous and alcoholic extracts of roots	Tilak et al 2004
Pleurotus ostreatus	Euphorbiaceae	n-hexane ethyl alcohol and water extract of whole plant	Asha et al 2004
Phyllanthus distichus	-	Oyster mushroom	Jayakumar et al 2006
Rosmarinus tomentosus	Euphorbiaceae	Aqueous and alcoholic extracts of fruit pulp	Jalalpure et al 2006
Swertia pseudochinensis	Labiateae	Ethanolic extract of whole plants	Galisteo 2006
Saroostemma brevistigma	Gentianaceae	Methanolic extract of whole plant	Li et al 2005
Solanum trilobatum	Ascepiadaceae	Ethyl acetate extracts of stem bark	Sethuraman 2003
Solanum nigrum	Solanaceae	-	Shahjahan et al 2004

Table 1.6: Some more hepatoprotective leads and their activity against hepatotoxins.

Lead molecule	Basic structure	Plant origin	Hepatoprotective	References
Schisandrin B	Dibenzocyclooctadiene derivative	*Schisandra chinensis*	CCl_4 and drug induced	Ip et al 1995
Kahweol and Cafestol	Diterpenes	*Coffea arabica*, *C. robustica*.	CCl_4	Lee et al 2007
Quercetin	Flavonoid	*Oenothera biennis*, *Podophyllum spp*. etc.	Ethanol	Molina et al 2003
Lupeol	Pentacyclic triterpene	*Crataeva nurvala*	aflatoxin B_1	Preetha et al 2006
Rubiadin	anthraquinone derivative	*Rubia cordifolia*	CCl_4	Rao et al 2006
Caffeic acid	Phenolic acid	*Ipomoea purga*, *Ocimum basilicum* etc.	CCl_4 and Paracetamol	Janbaz et al 2004
Bergenin	C-glucoside of 4-*O*-methyl gallic acid	*Mallotus japonicus*	CCl_4 and D-galactosamine	Kim et al 2000
Tiliroside	Flavanol glycoside	*Magnolia fargesii*	D-galactosamine induced	Matsuda et al 2002
Kolaviron	Biflavonoid	*Garcinia kola*	CCl_4	Iwu et al 1987
Thymoquinon	Benzoquinone	*Nigelle sativa*	t-butyl hydroperoxide and CCl_4	Daba et al 1998
Bupleurosides III, VI, IX, & XIII	Triterpenic saponins	*Bupleurum scorzonerifolium*	D-galactosamine	Matsude et al 1997

Emodin	Anthraquinone derivative	*Ventilago leiocarpa*	CCl_4 and D-galactosamine	Lin et al 1996
Myristicin	Phenolic derivative	*Myristica fragrans*	Lipopolysaccharide and D-galactosamine	Morita et al 2003

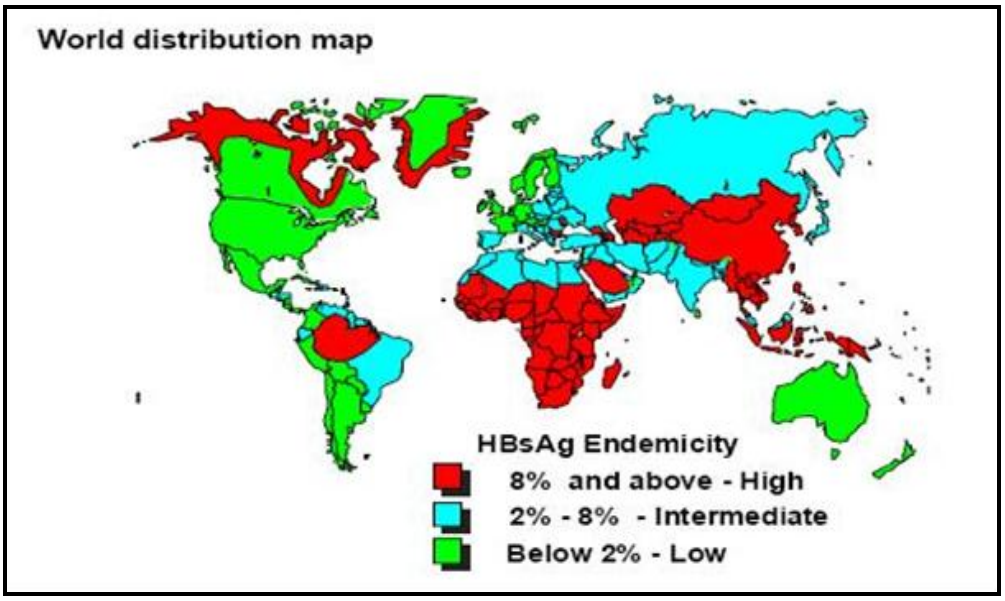

Fig. No. 1 World distribution map.

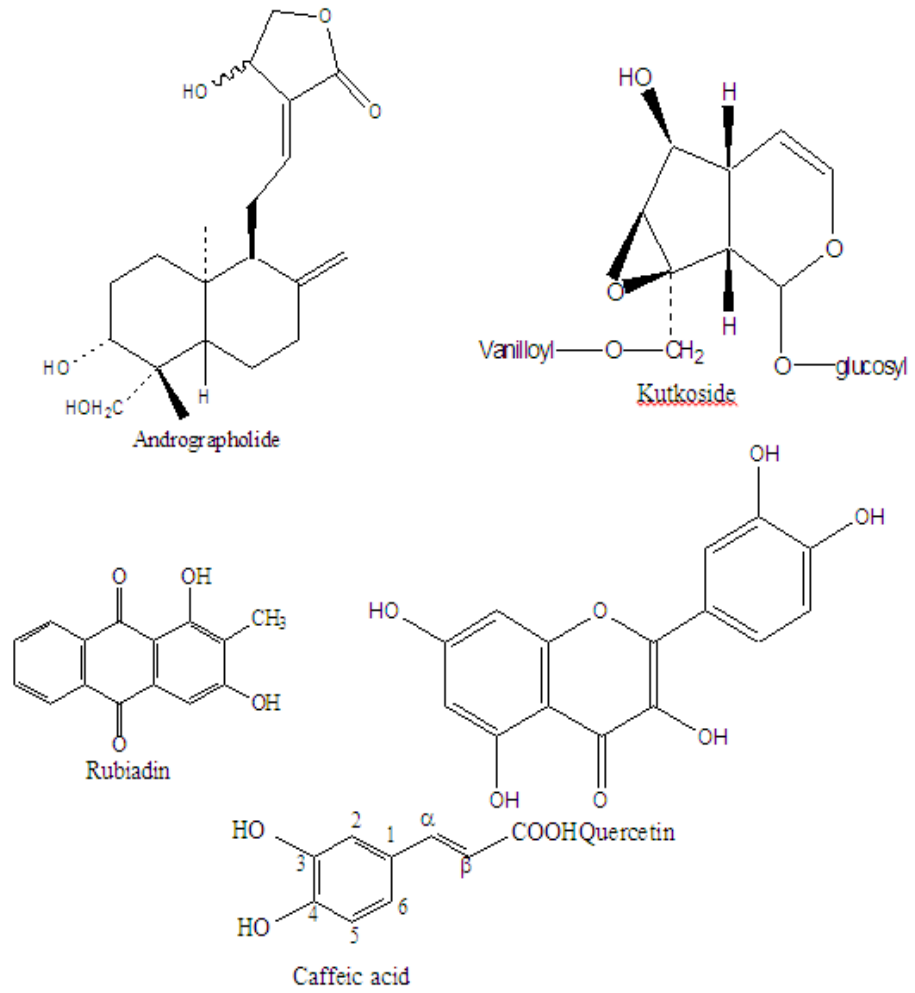

Fig. No. 1.2: Plant-derived hepatoprotective agents in clinical use

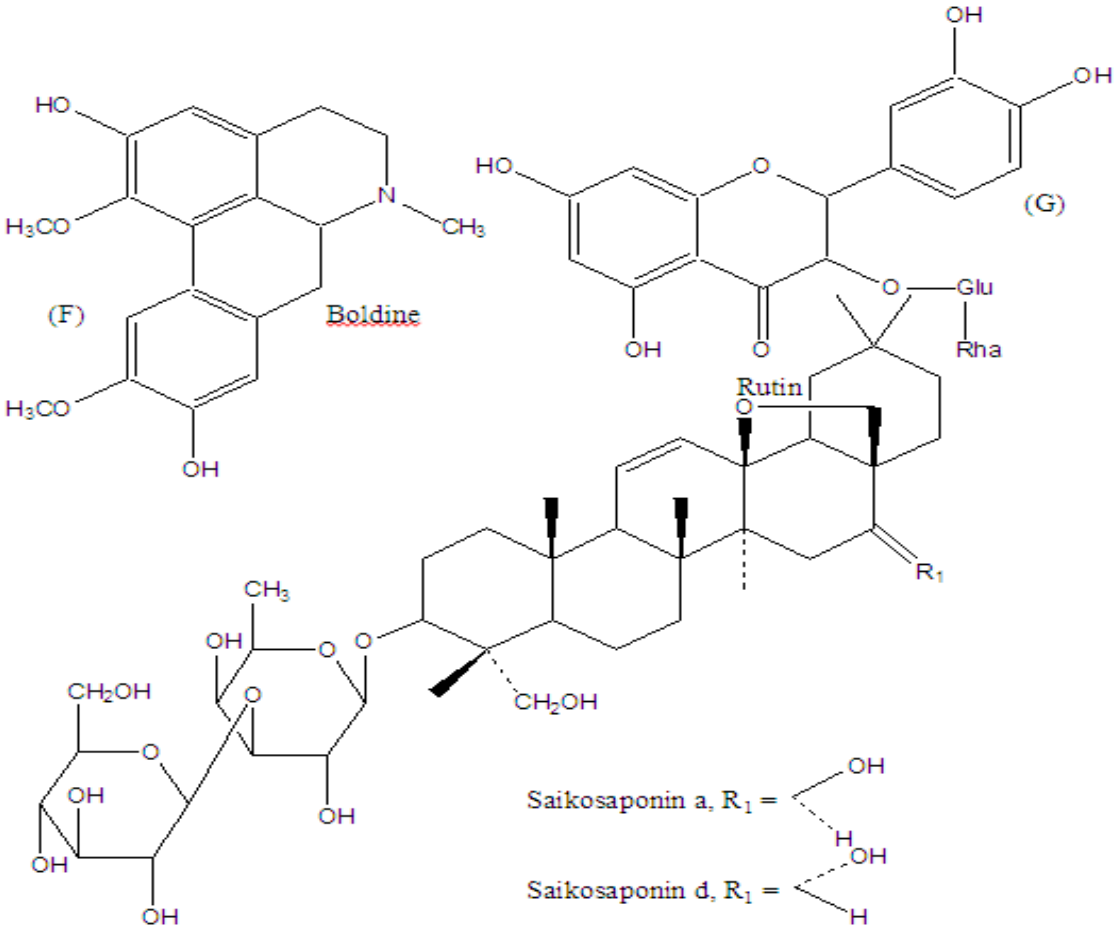

Fig No. 1.2: Plant-derived hepatoprotective agents in clinical use.

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