CHAPTER 3

REVIEW OF LITERATURE
Herbal Medicine Today

In recent times, focus on plant research has increased all over the world and a large body of evidence has been collected to show immense potential of medicinal plants used in various traditional systems. More than 13,000 plants have been studied during the last 5 year period. Integrative care for cancer patients using modern medicine and traditional Chinese medicine (TCM) is an emerging trend today. Liu et al., (2011) demonstrated that use of TCM preparations improved liver function during chemotherapy among patients with cancer receiving chemotherapy. Randomized controlled trails are warranted in order to confirm the effectiveness of various TCM preparations for protection of liver function among cancer patients receiving chemotherapy. Approximately one-third of the top-selling drugs in the world are natural products or their derivatives. Moreover, natural products are widely recognized in the pharmaceutical industry for their broad structural diversity, lesser side effects as well as their wide range of pharmacological activities (Strohl, 2000).

Although drug discovery focus has been shifted from natural products to synthetic chemicals, natural product-derived drugs still constitute a substantial percentage of recently approved drugs, 26% of the 46 FDA approved new molecular entries in 2009–2010 are natural product derived (Zhu et al., 2011). There is a renewed interest in natural products as sources for drug discovery (Li and Vederas 2009). Knowledge of the natural sources of drugs, the species of origin of the natural products approved clinical trials and pre-clinical drugs are highly useful for facilitating the search and development of new drug leads (Zhu et al, 2012). Thus the phytotherapeutic approach to modern drug development can provide many invaluable drugs from traditional medicinal plants.

Liver Diseases

Injury to liver can result in many disorders ranging from transient elevation of liver enzymes to life threatening liver cirrhosis and hepatic failure. Chronic liver cirrhosis and drug induced liver injury accounts for the ninth leading cause of death in western and developing countries (Mohamed et al., 2011; Saleem et al., 2010). Liver diseases have become a worldwide problem and are associated with significant morbidity and mortality. Liver diseases are among the most serious ailments. They may be classified as acute or chronic hepatitis (inflammatory liver diseases), hepatosis (non inflammatory diseases) and cirrhosis (degenerative disorders,
resulting in fibrosis of the liver). Liver diseases are mainly caused by toxic chemicals (certain antibiotics, chemotherapeutics, peroxidised oil, aflatoxin, carbon-tetrachloride, chlorinated hydrocarbons, etc.), excess consumption of alcohol, infections (Hepatitis B, A, C, D) and autoimmune disorders (Hari et al., 2011).

**Modern Medicine in Liver Diseases**

In severe liver damage, most of the liver cells die or turn into fibrotic state. In this case, the treatment should include in addition to the therapeutic agents, agents which can stimulate liver cell proliferation (Hari et al., 2011). There are no specific allopathic medicines used as hepatoprotective, although different research works are going on in some drugs. Limited therapeutic options, disappointing therapeutic success and serious adverse effects of modern medicine; use of herbal drugs has increased worldwide (Stickel et al., 2007). Management of liver disease is still a challenge to the modern medicine (Reddy et al., 1993). Herbal drugs are more widely used than allopathic drugs as hepatoprotectives because they are inexpensive, have better cultural acceptability, better compatibility with the human body and minimal side effects. These herbal drugs have shown the ability to maintain the normal functional status of the liver with or without fewer side effects. These are the reasons why herbal hepatoprotectives are mostly preferred by medical practitioners, as well as over- the- counter (Rana et al., 2011).

**Herbal Medicine in Liver Disease**

In the absence of reliable therapeutic hepatoprotective drugs in modern medicine, a large number of herbal preparations have become increasingly popular for the treatment of liver disorders (Chatterjee, 2000). Herbal drug usage against liver disease increased all over the World, they are believed to be harmless and free from serious adverse reactions and easily available (Girish et al., 2009). The traditional or ethnomedicinal plants have well proven its therapeutic property as well as lesser side effects with compared to modern drugs. The efficacy of the traditional and new herbal drugs should be tested by standard experimental methods such as *in vitro* and *in vivo* studies to validate the therapeutic potential claimed (Girish et al., 2009). But still, the screening of plants for antihepatitis activities remains in its infancy.
Silymarin from Experimental Pharmacology to Clinical Medicine

A number of herbals showed promising therapeutic activity, including Silymarin for liver cirrhosis, *Phyllantus amarus* in chronic hepatitis B, glycyrrhizin to treat chronic viral hepatitis, and some herbal combinations from China and Japan that have been scientifically proven for treatment of liver diseases (Stickel and Schuppan., 2007; Mohamed et al., 2011). Silymarin is a flavonolignan from the seeds of “milk thistle” *Silybum marianum* an edible plant, used medicinally for centuries as a herbal medicine for liver-related disorders. It is a mixture of mainly three flavonolignans, viz, silybin, silidianin, and silychristin, with silybin being the most active. Silymarin offers good protection in different toxic models of induced liver cirrhosis experiments by using laboratory animals. Its mechanism of action includes inhibition of hepatotoxin binding to receptor sites on the hepatocyte membrane; reduction of glutathione oxidation to enhance its level in the liver and intestine; antioxidant activity; and stimulation of ribosomal RNA polymerase and subsequent protein synthesis, leading to enhanced hepatocyte regeneration (Nitin et al., 2007). In A.D. 77 Pliny the Elder described the medicinal use of ‘Milk Thistl’ indicating it was excellent for carrying off bile. It was cultivated and traditionally used as a bitter digestive, liver tonic and poison antidote. It is widely prescribed by herbalists and has almost no known side effects. The plant is native to the Mediterranean and grows throughout Europe and North America (Luper, 1998; Pepping, 1999). It also grows in India, China, South America, Africa, and Australia. This herb is approved for sale in Canada in 70 different products and generates an annual business of $180 million in Germany alone (Luper, 1998; Nitin et al., 2007). Thus the ‘Milk Thistle’ is a good example for the future bio prospecting and scientific validation of herbal medicinal plants as well as ethnopharmacological research.

**Selection of Plants from Traditional or Tribal Knowledge:**

A detailed investigation and documentation of plants used in local health traditions and pharmacological evaluation of these plants and their taxonomical relatives can lead to the development of invaluable plant drugs for many dreaded diseases. Random screening of plants has not proved economically effective (Aszalos, 1980; Hari et al., 2011). And here traditional knowledge can serve as a powerful search engine, which will greatly facilitate intentional, focused and safe natural product drug discovery and help to rediscover the drug discovery process. By looking at the historical trends in drug and medical developments, it is possible to
understand how current drug development will benefit from this partnership (Bhushan, 2009). The Indian Traditional Medicine like Ayurveda, Siddha and Unani are predominantly based on the use of plant materials. Several Indian medicinal plants have been extensively used in the Indian traditional system of medicine for the management of liver disorders. Some of these plants have already been reported to possess strong antioxidant activity (Achuthan et al., 2003; Aniya et al., 2002; Priya et al., 2010)

**TBGRI Model/Pushpangadan's Model of Benefit Sharing**

Consequently, there is a need for efforts to support the ethno-ecological communities/systems that conserve this knowledge through everyday use and generate further knowledge. As for benefit sharing, the 1992 Convention on Biological Diversity places legal obligations on commercial users of traditional knowledge to share the benefits with the holders and their communities in a fair manner (Dutfield, 2010). In a benefit-sharing biodiversity model that has made the United Nations (UN) sit up and take notice, the Kani tribals of Kerala share the benefits of the licensing fee and royalties on the sale of the wonder drug Jeevani derived from the 'magical' Arogyapacha plant (*Trichopus zeylanicus* subsp. travancoricus). In the TBGRI Model/Pushpangadan's Model of Benefit Sharing the Tropical Botanic Garden and Research Institute (TBGRI) agreed to share the licence fee and royalty obtained for Jeevani with the tribal community on a 1:1 basis. Technology for the drug Jeevani has been transferred to a reputed Ayurvedic drug manufacturing company for a period of seven years. TBGRI received Rs 10 lakh as licence fee and 2% royalty on ex-factory sales. The Kanis have registered a trust called the Kerala Kani Samudaya Welfare Trust, which received half the licence fee (Rs 5 lakh) and receives a share of the royalty. The trust funds are being used for welfare activities of the Kanis.

**Hepatoprotective Plant Screening**

Hepatoprotective medicinal plants have been quite extensively investigated experimentally, but clinical trial in hepatitis or liver cirrhosis are not easy to carry out. In most of the cases, it is yet to be established by a detail study of a herb/formulation, which of their active ingredients/herb/combined, contribute most to the activities of liver protection and treatment. It is not clear whether one, several or all of these components are active ingredients for liver
protection. It is likely that some specific ingredients of each herb play a vital role in liver protection/treatment, thereby contributing to their therapeutic effects (Wang et al., 2007).

The traditional therapeutic indications of *Crepis rueppellii* and *Anisotes trisulcus* were confirmed by examining the ethanolic extracts of these two plants for their ability to reduce mortality of mice after ethanol intoxication and to lower the activities of plasma glutamic-pyruvic transaminase (GPT) after carbon tetrachloride-induced hepatitis in rats (Fleurentin et al., 1986).

The hepatoprotective activity of aqueous-ethanolic extract of leaves of *Cassia occidentalis* L. (Caesalpinaceae) was studied on rat liver damage induced by paracetamol and ethyl alcohol by monitoring serum transaminase, alkaline phosphatase, serum cholesterol, serum total lipids and histological alterations. The leaf extract was shown to possess significant hepatoprotective property (Jafri et al., 1999).

*Schisandra lignans* (Magnoliaceae) exhibited strong protective effect on phase I oxidative metabolism in the liver damaged by CCl₄. Pretreatment of *Schisandra*, 30 min before intoxication showed a more potent effect than that of the 6 hour pretreatment (Zhu et al., 1999).

The protective effect of aqueous extract of *Andrographis paniculata* (Acanthaceae) on hexa chloro cyclohexane induced severe liver damage in Swiss male mice was studied (Trivedi and Rawal, 2001).

*Ficus hispida* L. (Moraceae) leaves methanolic extract possessed significant hepatoprotection against paracetamol induced liver damage *in vivo* (Mandal et al., 2000).

The aqueous extract of *Cassia fistula* (Fabaceae) showed hepatoprotective effect on rat liver damage induced by carbontetrachloride (CCl₄) in rats (Illavarasan et al., 2000).

Alcoholic extract of leaves of *Acanthus ilicifolius* L. (Acanthaceae) showed significant liver protection against CCl₄- induced liver damage (Babu et al., 2001).

Petroleum ether, acetone and methanolic extracts of the fruits of *Luffa echinata* (Cucurbitaceae) showed significant hepatoprotective activity against CCl₄ induced hepatotoxicity in albino mice (Ahamed et al., 2001).

Mung bean, Achzuki bean, Black bean and Rice bean are food and folk medicines of Taiwan of which Mung bean aqueous extract showed best hepatoprotective effect on APAP induced hepatotoxicity (Wu et al., 2001).
Application of Kamadhenu Arka and Kushamanda Veleh showed relief of symptoms and decrease in serum enzyme levels of jaundice patients (Kunde and Ande, 2001).

Artemisia scoparia (Asteraceae) showed protective effect against APAP and CCl₄ induced hepatotoxicity. It contains a well known flavonoid Rutin which may responsible for the hepatoprotection (Janbaz and Glani, 1995).

The hepatoprotective property of Ginkgo biloba (Ginkgoaceae) was due to the ability to prevent lipidperoxidation and replenishing the glutathione level (Shenoy et al., 2002).

Kashadi Ghrita showed significant hepatoprotective action in CCl₄ intoxicated rats, it also decreased the serum enzyme levels (Pethe et al., 2002).

Treatment with Draksha Ghrita showed significant liver protection which was evident by decreasing serum biochemical parameters as well as liver histology (Fulzele et al., 2002).

The hexane extract of Ixora coccinea (Rubiaceae) flowers showed significant hepatoprotection against APAP over dose in Wistar rats. Both serum biochemical and liver histopathological studies supported the finding (Latha et al., 2003)

Indigofera tinctoria (Leguminosae) alcoholic extract showed hepatoprotective activity on liver antioxidant defense system during acute hepatitis induced by D-galactosamine (Malarvannan and Devaki, 2003).

Spilanthes ciliata (Asteraceae) ethanolic extract showed significant hepatoprotection against over dose of paracetamol in Wistar rats, besides increasing choleretic activity of anesthetised rats (Suja et al., 2004).

Pretreatment of Helminthostachys zeylanica (L.) Hook methanol extract showed significant hepatoprotection as evident from decreased levels of serum enzymes and an almost normal architecture of the liver, in the treated groups, compared to the controls (Suja et al., 2004).

The methanolic extract of Rhinacanthus nasuta (Acanthaceae) showed significant hepatoprotection against paracetamol and CCl₄ induced liver damage (Suja et al., 2004).

Glycyrrhiza glabra Linn. (Fabaceae) protected liver tissue from CCl₄ induced oxidative damage, and thus proved the antioxidant property of the plant (Rajesh and Latha, 2004).

Ethanolic extract of Commiphora opobalsamum (L.) Engl. (Burseraceae) showed significant antioxidant and hepatoprotective property (Al-Howiriny et al., 2004).
Ethanol-water extracts of aerial parts of *Barleria prionitis* (Acanthaceae) showed hepatoprotective activity in various acute and chronic animal test models of hepatotoxicity (Singh et al., 2005).

Hydroalcoholic extract of dried powdered root stalks of *Gundelia tourenfortil* (Asteraceae) showed hepatoprotection against CCl₄ induced hepatotoxicity *in vivo* in rats (Jamshidzadeh et al., 2005).

The ethanol and aqueous stem bark extracts of *Pterocarpus santalinus* L. (Fabaceae) showed significant protection against CCl₄ induced hepatocellular injury (Manjunatha, 2006).

The ethanolic extract obtained from the roots of *Operculina turpethum* (Convolvulaceae) showed significant hepatoprotection in rats of paracetamol induced liver damage (Kumar et al., 2006).

The *in vivo* hepatoprotective effects of *Rhoicissus tridentata* subsp. *cuneifolia*, (Vitaceae) a traditional Zulu medicinal plant, was investigated against carbon tetrachloride-induced acute liver injury in male Sprague-Dawley rats (Opoku et al., 2007).

Hepatoprotective activity of *Enicostema axillare* (Gentianaceae) against CCl₄ induced hepatic damage in rats showed significant reduction in serum biochemical parameters (Gite et al., 2007).

Ethanol extract and ethanol fraction from aerial parts of *Pergularia daemia* (Forsk.) (Asclepiadaceae) exhibited significant hepatoprotective effect against CCl₄ induced hepatotoxicity in rats (Suresh and Mishra, 2008).

The hydroalcoholic extract of *Aerva lanata* (Amaranthaceae) possesses hepatoprotective activity against paracetamol induced hepatotoxicity in rats as evident from significant reduction in serum enzyme alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and bilirubin (Manokaran et al., 2008).

Methanol, hexane and chloroform extracts of *Prostechea michuacana* (Lex.) W. E Higgins (Orchidaceae) were studied against carbon tetrachloride (CCl₄) induced hepatic injury in albino rats. The methanol extract of orchid *P. michuacana* produced significant hepatoprotective effect by decreasing the activity of serum enzymes and bilirubin, which suggests that EMM could protect liver from paracetamol-induced lipid peroxidation eliminating the deleterious effects of toxic metabolites from paracetamol. (Rosa et al., 2009).
The water extract of aerial parts of *Enicostemma axillare* (Gentianaceae) have shown significant hepatoprotection against CCl₄-induced hepatotoxicity in albino rats in reducing serum total bilirubin, SAKP, SGPT and SGOT levels (Gite et al., 2009).

The methanol extracts of *Casuarina equisetifolia, Cajanus cajan, Glycosmis pentaphylla, Bixa orellana, Argemone mexicana, Physalis minima, Caesalpinia bonduc*, belonging to the different families were studied for hepatoprotective activity against Swiss albino mice with liver damage induced by carbon tetrachloride (CCl₄). It was found that the methanol extract of *B. orellana, C. cajan, G. pentaphylla*, and *C. equisetifolia* at a dose of 500 mg/kg body weight exhibited moderate protective effect (Ahsan et al., 2009).

Aqueous extract of *Kohautia grandiflora* (Rubiaceae) on paracetamol induced hepatotoxicity in rats showed was slightly hepatoprotective at 300 mg/kg (Garba et al., 2009).

Aqueous extracts of Indian medicinal plants like *Phyllanthus amarus, Maytenus emerginata, Eclipta alba, Aloe vera, Solanum indicum and Aegle marmelos*, showed significant hepatoprotection against CCl₄ induced hepatotoxicity in rats (Parmar et al., 2009).

*Anogeissus latifolia*, (Combretaceae) one of the important medicinal plants in Ayurveda, is used in cardiac disorders, skin diseases, liver complaints, fever and epileptic fits. Hepatoprotective activity of *A. latifolia* against carbon tetrachloride induced hepatotoxicity in albino rats of Wistar strain was evaluated. They reported that CCl₄ treatment depleted the viability of hepatocytes by 65%. *A. latifolia* treated hepatocytes showed concentration dependent protective effect and restored the viability of the hepatocytes (Hulikere et al., 2009).

Extract of *Phyllanthus amarus, Maytenus emerginata, Eclipta alba, Aloe vera, Solanum indicum* and *A. marmelos* afforded protection from such paracetamol induced liver damage, where the aqueous extract of *Phyllanthus amarus and Maytenus emerginata* has shown the most pronounced hepatoprotective effect. These results showed their protective activity in the order of *M. emerginata > P. amarus > A. marmelos > S. indicum > A. vera > E. alba* (Parmar et al., 2010).

*Butea monosperma* (Fabaceae) is native to tropical Southern Asia. It contains active constituent(s) that could be attributed towards its hepatoprotective effect in paracetamol induced toxicity in rabbits. It may be one of the potential targets for the development of new therapies for the treatment of various hepatic diseases. It is a good anti-inflammatory agent. It improved
digestion and stimulates liver for adequate functioning. Its flowers were astringent, hemostatic and diuretic (Maaz et al., 2010).

*Orthosiphon stamineus* (Lamiaceae) as medicinal plant is commonly used in Malaysia for treatment of hepatitis and jaundice; the ethanol extracts were applied to evaluate the hepatoprotective effects in a thioacetamide-induced hepatotoxic model in *Sprague Dawley* rats (Alshawsh et al., 2011).

Experiments have clearly shown that plants such as *Picrorhiza kurroa, Andrographis paniculata, Eclipta alba, Silybum marianum, Phyllanthus madraspatensis* and *Trichopus zeylanicus* are sufficiently active against, at least, certain hepatotoxins. *P. kurroa, E. alba, Glycyrrhiza glabra, A. paniculata* and *P. amarus* were likely to be active against Hepatitis B virus (Hari et al., 2011).

Studies showed that hepatoprotective effect of *Calotropis procera* (Asclepiadaceae) root (methanolic extract) is due to the prevention of the depletion in the tissue glutathione levels. It was found that the root of *C. procera* contains quercetin-3-rutinoside and other flavanoids which was present in methanolic extract and hence the antioxidant and hepatoprotective property of the extract. Traditionally the plant has been used as antifungal, antipyretic, analgesic and root as an antidote for snake poisoning (Prakash et al., 2011).

Plants like *Tinospora cordifolia, Terminalia arjuna, Plumbago zeylanica* and *Berberis aristata*, have anti-oxidant and anti-inflammatory properties that help in preventing hepatic injury by certain hepatic insults (Rana et al., 2011).

Hepatoprotective activity was reported of *Clitoria ternatea* (Fabaceae) seed and root and *Vigna mungo* (Fabaceae) seed against acetaminophen and carbon tetrachloride-intoxicated rats. The liver functioning was evaluated by measuring serum marker enzymes and hepatic fibrosis was accessed by measuring collagen content in terms of p-hydroxyproline levels (Solanki and Jain, 2011).

The methanolic extract of *Ocimum gratissimum* (L.) (Lamiaceae) leaves was screened for analgesic and hepatoprotective activity in albino rats. It showed potent analgesic and antihepatotoxic effects (Uheqbu et al., 2012).

Hepatoprotective potential of the methanol extract of leaves of *Urtica dioica* L. (Urticaceae) was evaluated against CCl₄-induced hepatic injury in Wistar rats and significant hepatoprotective profile was observed (Kataki et al., 2012).
Plants used in traditional system of medicine require detailed investigation from an ethnopharmacological approach for the treatment of liver disorders because hepatic ailments remains a serious health problem caused by drugs, chemicals and alcohol. So investigation into the lead molecules, that may produce better therapeutic effects is required to overcome the pharmaceutical imbalance between remedies that protect the liver and drugs that induce hepatotoxicity (Dhiman et al., 2012).

**Hepatoprotective Herbal Formulations**

Single plant may not have all the desired activities. A combination of different herbal extracts/fractions is likely to provide desired activities to cure severe liver diseases. Development of such medicines with standards of safety and efficacy can revitalise treatment of liver disorders and hepatoprotective activity (Hari et al., 2011).

In India, more than 93 medicinal plants are used in different combinations in the preparations of 40 patented herbal formulations. However, only a small proportion of hepatoprotective plants as well as formulations (Sharma et al., 1991) used in traditional medicine are pharmacologically evaluated for their safety and efficacy. Six polyherbal hepatoprotective formulations, namely Liv 52, Livergen, Livokin, Octogen, Stimuliv and Tefroliv were selected and their efficacy against paracetamol (PCM) induced hepatotoxicity in mice was studied. It showed significant hepatoprotection (Girish et al., 2009). The list of six commercial poly herbals and the plants used in the formulations is shown in Table 3. List of some poly herbal formulations against liver diseases is shown in Table 4.

**Plants Having Antioxidant Property**

Free radicals play a major role in hepatic injury and hence the main mechanism of herbal drug to protect liver is its antioxidant property through enhancement of the antioxidant defense system in vivo via endogenous superoxide dismutase, glutathione peroxidase and catalase.

Ten plants (*Picrorrhiza kurroa, Tephrosia purpurea, Terminalia arjuna, Tinospora cordifolia, Glycyrrhiza glabra, Azadirachta indica, Apium graveolens, Swertia chirata, Phyllanthus amarus, and Aloe vera*) and their possible constituents responsible for its antioxidant property were compared by reducing power, 2, 2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity method. The plants described contained antioxidant principles that can explain and
justify their use in traditional medicine (hepatoprotective) in the past as well as the present (Vivek et al., 2011).

*Garcinia indica* Linn (Clusiaceae), a medicinal plant mentioned in Ayurveda has been used for treatment of liver disorders, dysentery, sunstroke, cancer and heart diseases. The aqueous and ethanolic extract of *Garcinia indica* Linn were studied for their antioxidant and hepatoprotective effects on carbon tetrachloride induced liver toxicity on Wistar albino rats. It showed significant protection (Deore et al., 2011).

**Plants against Hepatitis B Virus and Hepatocellular carcinoma**

Hepatitis B virus (HBV) infection is a worldwide public health problem, which can lead to life threatening chronic hepatitis, liver cirrhosis and cancer. Despite this, treatments for chronic HBV infections are still very limited. The current treatment strategy for hepatitis B is to eradicate replication and infection of hepatitis B virus (HBV) *in vivo* using anti-virus drugs such as interferon and nucleoside analogs such as lamivudine (Palumbo, 2008). However, because of their side effects, low antiviral potency, and long treatment period, the actual effects of these treatments are neither ideal nor adequate (Keeffe et al., 2008).

Hepatocellular carcinoma (HCC) is one of the most frequent tumour types worldwide. It is the fifth most common cancer and the third leading cause of cancer death (El-Serag and Rudolph 2007). There are multiple etiological agents that are associated with the development of HCC, the most frequent being chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, and long-term exposure to the alcohol, mycotoxin, aflatoxin B1 (Ha et al., 2010).

Extracts of *Phyllanthus amarus* (Euphorbeaceae) have been shown to inhibit the DNA polymerase of hepatitis B virus (HBV) and Woodchuck hepatitis virus (WHV) *in vitro*. Three of four recently infected WHV carriers treated i.p. with *P. amarus* extract lost WHV, animals infected for 3 months showed a decrease in virus levels. Preliminary results in human carriers treated orally with *P. amarus* for 1 month indicated that ≈ 60% of the carriers lost HBV during the observation period (Blumberg et al., 1990).

Alexander cell line, a human hepatocellular carcinoma derived cell line which has the property of secreting HBsAg in the supernatant was used to study the antiviral property of *P. amarus*. Aqueous extract of *P. amarus* was evaluated for its *in vitro* ability to inhibit HBsAg secretion in a dose dependent manner (Jayaram and Thyagarajan 1996).
An aqueous extract of the plant *P. amarus* inhibits endogenous DNA polymerase of hepatitis B virus and binds to the surface antigen of hepatitis B virus *in vitro*. The extract also inhibits woodchuck hepatitis virus (WHV) DNA polymerase and binds to the surface antigen of WHV *in vitro* (Venkateswaran et al., 1987).

The lipophilic fraction of root extracts of *Ferula ferulaeoides*, (Apiaceae) which has been used as a traditional Chinese medicine, showed a significant inhibitory effect against HBV in HBV-producing cell line Hep G2.2.15. In the experiment, extract reduced the HBsAg level and HBV replication by 87% and 36%, respectively (Zhai et al., 2011).

Ellagic acid from *Phyllanthus urinaria* (Euphorbeaceae) showed a unique anti-HBV function, did not inhibit either HBV polymerase activity, HBV replication or block HBsAg secretion. Rather, ellagic acid blocks effectively HBeAg secretion in HepG2 cells (IC$_{50}$=0.07 μg/ml). Since HBeAg is involved in immune tolerance during HBV infection, ellagic acid, a newly identified functional anti-HBV compound, may be a new candidate therapeutic against immune tolerance in HBV-infected individuals (Shin et al., 2005).

The inhibitory activity of *Agrimonia eupatoria* (Rosaceae) extracts on HBsAg secretion varied over the growing season and was the highest at mid-July. This inhibitory activity was also shown with the aqueous extracts of two other species of the genus *Agrimonia*: *A. pilosa* and *A. coreana pilosella*. These results suggest that some plants of the genus *Agrimonia* contain potential antiviral activity against HBV (Kwon et al., 2005).

*Orthosiphon stamineus* Benth (Lamiaceae) is widely used in Malaysia for treating hepatitis, jaundice, kidney problems, fever, hypertension, gout and diabetes. The hepatoprotective activity of *O. Stamineus* was assessed against thioacetamide-induced liver cirrhosis in rats, thus scientifically proving the traditional use of the plant against liver disorders (Alshawsh et al., 2011).

*Cocculus hirsutus* (L) (Menispermaceae) methanolic extract treatment significantly reduced the fibrosis induced by bile duct ligation, showing decreased levels of serum marker enzymes and this was further confirmed by histopathological results (Thakare et al., 2009).

**Plants Having Inhibitory Property of Reverse Transcriptase (RT)**

Crude extracts from plants *Cinnamomum loureiroi* (stem bark), *Quercus infectoria* (fruit), *Plumbago indica* L. (root), *Artocarpus heterophyllus* Lam. (seed), *Ocimum sanctum* L.
(leaves), *Allium sativum* L. (bulb) and *Acorus calamus* L. (rhizomes) showed strong HIV-1 reverse transcriptase inhibitory effects. The efficiency of anti-HIV-1RT activity was reported at 50% inhibitory concentrations (IC$_{50}$). This showed that the hexane crude extracts from *A. calamus* L. and *A. heterophyllus* Lam. contained potent activity against HIV-1 RT, with IC$_{50}$ of 32.96 ± 3.17 and 34.69 ± 2.41 µg/ml, respectively (Silprasit et al., 2011).

**Hepatoprotective Phytoconstituents**

Hepatoprotective plants have the phytoconstituents such as phenyl compounds, coumarins, essential oils, monoterpenoids, diterpenoids, triterpenoids, steroids, alkaloids and other nitrogenous compounds (Valan et al., 2010).

A diverse array of plant-derived compounds including saponins, polyphenols, iridoids and alkaloids have been reported to have a hepatoprotective effect in the TNF-α-dependent inflammatory liver injury models. Some of these compounds impede TNF-α-mediated hepatocyte apoptosis and consequently block the progression of liver injury, whereas others protect against hepatocyte necrosis occurring at the final stage (Hase et al., 2001).

**Tetrandrine in Liver Protection**

Five bisbenzyl isoquinoline alkaloids were isolated from *C. peltata* by Kupchan et al (1961). Tetrandrine is a bisbenzyl isoquinoline alkaloid and it is the major compound present in *C. peltata*. Tetrandrine (TET) is well known to possess activities including antioxidant, plasma glucose lowering (Chen et al., 2004), anti-inflammatory, immunosuppressive (Li et al., 1989), free radical scavenging (Cao, 1996), anti-fibrotic and anticancer properties. It is used clinically to treat hypertension and silicosis (Qian, 2002; Xie et al., 2002). TET exhibited anti-proliferative effect on Hep G2, PLC/PRF/5 and Hep 3B cells in a dose-dependent manner. TET also possesses a lower IC$_{50}$ and better SI value than cisplatin against Hep G2 and PLC/PRF/5 cells (Ng et al., 2006). TET and related compounds are potentially useful in the treatment of lung silicosis, liver cirrhosis, and rheumatoid arthritis (Kwan et al., 2002).

TET inhibits the expressions of types I, III and IV collagen genes being at the level of transcription. In liver fibrosis, TET could also lower the expression levels of mRNAs of PDGF, PDGF receptor β1 (PDGFR β1) and transforming growth factor β1 (TGF β1), suggesting that
TET indirectly reduces collagen synthesis through suppression of gene expressions of TGF β1, PDGF and other hepatofibrosis-related growth factors (Guo et al., 1998).

**Table. 3. Some important liver protective poly herbal liquid formulations and plants used in the formulations against liver damage (Girish et al., 2009)**

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<th>Si No</th>
<th>Name of the formulation</th>
<th>Plants used in the formulation</th>
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| 1     | Live 52 (Himalaya Drug Co, Bangalore) | *Achillea millefolium*  
*Caparisspinosa*  
*Cassia occidentalis*  
*Cichoriumintybus*  
*Solanumnigrum*  
*Tamarixgallica*  
*Terminaliarjuna* | Protects liver against various hepatotoxins, Promotes appetite and growth. |
| 2     | Livergen (Standard Pharmaceuticals, Serampore, West Bengal) | *Andrographispaniculata*  
*Apiumgraveolens*  
*Asteracantha longifolia*  
*Cassia angustifolia*  
*Trachyspermum ammi*  
*Trigonellafoenum-graecum* | Gastrointestinal and hepatic disorders. |
| 3     | Livokin (Herbo-med, Kolkata) | *Andrographispaniculata*  
*Apiumgraveolens*  
*Berberislyceum*  
*Carumcopticum*  
*Cichorium intybus*  
*Cypererotundus*  
*Ecliptatalba*  
*Ipomoeaturpethum*  
*Oldenlandiacorymbosa* | Hepatic dysfunction. |
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<th>Picrorrhiza kurroa</th>
<th>Hygrophila spinosa</th>
<th>Plumbago zeylanica</th>
<th>Solanum nigrum</th>
<th>Tephrosia purpurea</th>
<th>Terminalia arjuna</th>
<th>Terminalia chebula</th>
<th>Trigonella foenum-graecum</th>
<th>Octogen (Plethico Pharmaceuticals Ltd., Indore)</th>
<th>Arogyavardhini rasa</th>
<th>Phyllanthus amarus</th>
<th>Highly potent hepatoprotective.</th>
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<tr>
<td>5</td>
<td>Stimuliv (Franco-Indian Pharmaceuticals Pvt Ltd, Mumbai)</td>
<td>Andrographis paniculata</td>
<td>Eclipta alba</td>
<td>Phyllanthus amarus</td>
<td>Justicia procumbens</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Liver stimulant and tonic.</td>
</tr>
<tr>
<td>6</td>
<td>Tefroliv (TTK Pharma Pvt Ltd, Chennai)</td>
<td>Andrographis paniculata</td>
<td>Eclipta alba</td>
<td>Ocimum sanctum</td>
<td>Phyllanthus niruri</td>
<td>Picrorrhiza kurroa</td>
<td>Piper longum</td>
<td>Solanum nigrum</td>
<td>Tephrosia purpurea</td>
<td>Terminalia chebula</td>
<td></td>
<td>Effective hepatic regeneration.</td>
</tr>
</tbody>
</table>
Table. 4. Some important commercially available poly herbal products against liver damage.

<table>
<thead>
<tr>
<th>Herbal Product</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1   Pro-liver Pill</td>
<td>Yang et al., 2000</td>
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<tr>
<td>2   Liver Cure</td>
<td>Hikino et al., 1988</td>
</tr>
<tr>
<td>3   Liv-52</td>
<td>Huseini et al., 2005</td>
</tr>
<tr>
<td>4   Jianpi Wenshen Pill</td>
<td>Song and Song, 1994.</td>
</tr>
<tr>
<td>5   Binggan capsules</td>
<td>Han et al., 1997</td>
</tr>
<tr>
<td>6   Hepatomed</td>
<td>Sudhir et al., 1991</td>
</tr>
<tr>
<td>7   Binggan Tang</td>
<td>Pei et al., 1996</td>
</tr>
<tr>
<td>8   Stimuliv</td>
<td>Asha, 1998</td>
</tr>
<tr>
<td>9   Yizhu decoction</td>
<td>Jiang, 1999.</td>
</tr>
<tr>
<td>10  Brahmi gritha</td>
<td>Achilya et al., 2004</td>
</tr>
<tr>
<td>12  Tefroli</td>
<td>Handa et al., 1986</td>
</tr>
<tr>
<td>13  Panchagavya gritham</td>
<td>Achilya et al., 2004</td>
</tr>
<tr>
<td>14  Xiaochaihu Tang</td>
<td>Yamashiki et al., 1997</td>
</tr>
<tr>
<td>15  Livol</td>
<td>Chrungo et al., 1997</td>
</tr>
</tbody>
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