1.0. GENERAL INTRODUCTION

1.1. Description of the Liver

The liver is among the most complex and important organs in the human body, weighs 1200–1500 g and comprises one-fiftieth of the total adult body weight. It is relatively larger in infancy, comprising one-eighteenth of the birth weight. Its primary function is to control the flow and safety of substances absorbed from the digestive system before distribution of these substances to the circulatory system. The liver is occupying a large region mostly on the right side of the body, below the diaphragm and behind the ribs. The liver is divided into 4 lobes: right, left, caudate and quadrate. The right and left lobes are the largest, while the caudate and quadrate are smaller and located posteriorly. Two ligaments are visible anteriorly. Superiorly, the falciform ligament separates the right and left lobes. The caudate lobe is located superiorly, approximately between the right and left lobes. Adjacent to the caudate lobe is the sulcus for the inferior vena cava. Inferior to the caudate lobe of the porta hepatis, where the hepatic artery and hepatic portal vein enters into the liver. The portal vein carries nutrient laden blood from the digestive system. Inferior to the porta hepatis is the bile duct which leads back to the gallbladder. Finally, the hepatic vein, where post-processed blood leaves the liver, is found inferior and adjacent to the sulcus
for the inferior vena cava. The liver is held on place by a system of mesenteries posteriorly and is also attached to the diaphragm via the falciform ligament. Most of the liver is covered by visceral peritoneum (Sherlock and Dooley, 2002).

Liver is a solid organ composed of tightly packed thin plates of epithelial cells called hepatocytes. The outer surface of the liver is covered by collagenous tissue called Glissons capsule over which is a layer of mesothelial cells from the peritoneum. The spaces between the plates of liver cells are called as sinusoidal spaces. The most of the connective tissue in the liver is in the form of portal tracts which contain the blood vessels running into the liver. Hepatocytes are large polyhedral cells with round nuclei with peripherally dispersed chromatin and prominent nuclei. The sinusoids are lined by endothelial lining cells which are readily distinguishable from hepatocytes by the flattened condensed nuclei and attenuated poor nature of cytoplasm. The largest terminal branch of hepatic portal vein is lined by thin
wall of epithelial cells. Smaller diameter thick walled vessels are terminal branches of hepatic artery with the structure of arterioles. The structural unit of the liver is considered as hepatic lobule. However, the physiology of the liver is more accurately represented by a unit structure known as hepatic acinus. The hepatic is roughly hexagonal in shape and centered on terminal hepatic venule. The portal tracts are positioned at the angles of hexagon. The blood from the portal vein and hepatic artery branches flows away from the portal tract to the adjacent central vein. The hepatic acinus is a roughly berry shaped unit of liver parenchyma centered on a portal tract. The acinus lies between two or more terminal hepatic venules and blood flows from the portal tracts through the sinusoids to the venules (Sherlock and Dooley, 2002).
**1.2. Functions of Liver**

The main function of the liver is synthesis of proteins *viz.*, albumin, coagulation factors, α-antitrypsin, very low density lipoprotein and many others that circulate in the blood. Stores glucose as glycogen and converts it back to glucose as needed. The liver can also synthesize glucose from amino
acids, lactate and glycerol, although this is less efficient than breaking down glycogen into glucose. Additionally, the liver metabolizes fatty acids, cholesterol and amino acids. The liver can convert excess amount of glucose and amino acids into fatty acids for storage. The liver synthesizes cholesterol and removes it from circulation. The liver can synthesize non-essential amino acids. Toxins are detoxified by the liver’s ability to metabolize lipophillic compounds. These compounds (bound to albumin) enter the liver sinusoids and then the area of disse. Enzymes in the hepatocytes (Cytochrome P-450 enzymes) are involved in the metabolism of the lipophillic compounds, which include toxins and many drugs. The liver cells can produce biles that can act as a detergent and breaks fats down into smaller components so they can be digested in the small intestine (Young et al., 2006).

1.3. Liver Damage - An Overview

Liver damage refers to any disorder of the liver and includes the steatosis or fatty deposits in the liver, fibrosis or scarring of the liver, hepatitis or inflammation of the liver, cirrhosis where scarring and inflammation spread through the liver and irreversibly disrupt its shape or function causing permanent cell damage and ultimately liver failure and leading to liver cancer. Liver damage mortality as one in 10 people in England has some form of liver disease (British Liver Trust, 2006) and many
of them die prematurely from this condition. Department of Health (2006) reported that, liver disease is currently the fifth most common cause of mortality in the UK for both men and women. The majority of liver deaths are due to cirrhosis and it has recently been reported that, there are about 4000-5000 deaths from cirrhosis in the UK each year (Iredale, 2003; Ryder, 2006). A population based study reported that 41% increase in new cases of cirrhosis each year (incidence) in the UK between 1992-2001. In this general practice study, 3,360 new cases were identified and the incidence rate was 14 cases per 100,000 populations. Median age at diagnosis was 56 years for men and 61 years for women (Fleming et al., 2008).

Department of Health (2007) reported that, regional trends within England, the greatest numbers of deaths from chronic liver disease are found in the North West and North East of England. These two regions were reported to have the highest rates of heavy drinking in England and alcohol-related hospital admissions. The other main cause of death from liver disease is due to liver cancer. It should be noted that, cirrhosis is a specific precursor of liver cancer (Perz et al., 2006). Liver cancer can either arise in the hepatobiliary system itself (primary liver cancer) or metastasize from a tumor elsewhere in the body (secondary liver cancer). Most liver cancer (95%) is a secondary cancer (Williams et al., 2007). Nevertheless, primary liver cancer caused 2091 deaths in England and Wales in 2001 and mortality
rates have steadily increased over the last three decades (West et al., 2006). Liver cancer is more common in men compared to women and it predominately occurs in older people (Khan et al., 2005). Moreover, primary liver cancer consists of either hepatocellular carcinoma (HCC) which arises in liver cells (hepatocytes) or cholangiocarcinoma (CCA) which arises in the bile ducts either within (intrahepatic) or outside of the liver (extra-hepatic). HCC is responsible for the majority (70-85%) of primary liver cancer worldwide (Perz et al., 2006). However, recent rises in primary liver cancer have been attributed to a rapid rate of increase in CCA (Khan et al., 2005). CCA is the commonest type of primary liver cancer in women and HCC increases have only the commonest type of primary liver cancer in men (West et al., 2006). According to Kaner et al. (2007) a large number of people die from liver disease each year, therefore drugs with novel mode of action required.

1.3.1. Types of Liver Damage

Types of the liver damage can be classified by their duration of the damage. A chronic disorder lasts for more than 6 months; a subacute disorder lasts for 3 to 6 months, while an acute disorder occurs over a period less then 3 months. A very severe disorder that leads to liver failure within 6 weeks is termed fulminant. Some of the common disorders of the liver include cirrhosis, viral hepatitis, alcoholic liver disease, hemochromatosis and liver cancer.
Cirrhosis is a widespread and progressive chronic liver condition in which hepatocyte activity is depressed due to excessive amounts of fibrous scar tissue inhibiting blood flow. This blood flow obstruction can cause portal hypertension, which leads to additional complications, including shunting of veins around the liver. Other complications of portal hypertension include swollen veins in the esophagus (varices) and accumulation of fluid in the abdomen (ascites). Other potential complications of cirrhosis include bleeding problems, kidney disorders, osteoporosis and liver cancer. Any chronic liver disease can eventually lead to cirrhosis, which is believed to be irreversible. The only treatment options are to treat the cirrhosis condition is liver transplantation.

Hepatitis refers to inflammation of the liver. Hepatitis can have several causes, the most common being viruses or alcoholism. Viral hepatitis comes in several forms, the most 9 common being hepatitis B (40%), hepatitis A (32%) and hepatitis C. Hepatitis virus B and hepatitis virus C are spread by the blood and can become
chronic conditions, which can lead to cirrhosis. A vaccine has been developed for hepatitis virus B, which has helped to control its spread. Hepatitis virus C often becomes chronic and thus can be life-threatening. Viral hepatitis has several treatment options, which frequently have undesirable side effects. Interferon is used for treating HBV and HCV. Interferons are so named because they interfere with viral replication. The body makes interferon naturally, but supplementing this with synthetically made interferon can sometimes be beneficial against viral hepatitis. However, the selection criteria for who should use interferons are quite stringent, attesting to the downsides of this therapy. Additionally, interferon is available by injection only and is quite expensive.

Alcoholic Liver Disease (ALD) comes in 3 major varieties: alcoholic fatty liver, alcoholic hepatitis and alcoholic cirrhosis. All 3 can occur alone or even together in the same patient. The primary form of treatment is abstinence from drinking alcohol.

Fatty liver is the most common and the least harmful. It can occur within days of moderate to heavy drinking. Fat accumulates in the cytoplasm of liver cells, causing the liver to swell, sometimes...
to large proportions. Fatty liver often has no symptoms and can disappear as quickly as it appears.

Alcoholic hepatitis is inflammation of the liver and can exist as either acute or chronic conditions. Symptoms can vary greatly, from asymptomatic to severe fever, nausea and abdominal pain. Acute hepatitis can often cause death and the chronic form often leads to cirrhosis. Alcoholic cirrhosis, like all forms of cirrhosis, is often life-threatening.

The disease is characterized by regenerative nodules of hepatic tissue completely surrounded by fibrous scar tissue. The scar tissue grows faster than liver cells can regenerate and the growing network of scar tissue inhibits blood flow as described earlier. Once cirrhosis develops, the risk of liver cancer elevates substantially, even if the patient abstains from drinking for several years.

Autoimmune hepatitis is caused by the body’s immune system attacking liver cells and causing inflammation, damage and eventually cirrhosis. Researchers believe genetic factors may make some people more
prone to autoimmune diseases. About 70 percent of those with autoimmune hepatitis are female.

Several different diseases can damage or destroy the ducts that carry bile from the liver, causing bile to back up in the liver and leading to cirrhosis. In adults, the most common condition in this category is primary biliary cirrhosis, a disease in which the bile ducts become inflamed and damaged and ultimately, disappear. Secondary biliary cirrhosis can happen if the ducts are mistakenly tied off or injured during gallbladder surgery. Primary sclerosing cholangitis is another condition that causes damage and scarring of bile ducts. In infants, damaged bile ducts are commonly caused by alagille syndrome or biliary atresia, conditions in which the ducts are absent or injured.

Hemochromatosis is a condition in which too much iron is contained in the body. It is the most common genetic disease in the United States among people of European origin, but does not
Chronic hemochromatosis can lead to cirrhosis, cancer, impotence and heart problems. Iron damages the body through its promotion of oxidation, increasing the level of free radicals in the body. Harmful levels of iron can be accumulated in the body simply by eating too much of the wrong foods and supplements. In hemochromatosis, the body cannot absorb iron as effectively and also cannot detect when iron levels are too high. This excess iron is then absorbed into the body’s organs particularly the liver and causes liver damage.

Liver tumors are not always malignant. One type of benign tumor is hemangioma, which is a non-malignant tumor filled with blood. Malignant tumors fall into two major categories, metastatic and primary liver tumors. A metastatic tumor is a malignant growth whose primary growth site is someplace other than the liver. The liver is a frequent target of metastatic cancers, as it is the primary filter of venous blood from several organs, such as the colon. The prognosis for patients with metastatic liver cancer is typically poor; most patients die within 1 year of diagnosis.
The most common primary liver malignant cancer is hepatocellular carcinoma (HCC). HCC is one of the most common cancers in the world, although it is currently relatively uncommon in the U.S. This is largely due to the higher incidence of viral hepatitis in Southeast Asia and Africa.

Drugs, toxins and microbial infections are the other causes of cirrhosis which includes drug reactions, prolonged exposure to toxic chemicals, parasitic infections and repeated bouts of heart failure with liver congestion.

### 1.4. Therapy of Liver Damage

Liver transplantation is often the best option for either liver cancer or cirrhosis. However, there is an extreme shortage in the number of donor organs available and there are restrictions on who can receive liver transplants. Due to these problems, alternatives are constantly being sought. Some of the primary areas of research involve antioxidants, ursodeoxycholic acid, S-Adenosylmethionine (SAMe), metformin, thiazolidinediones, corticosteroids, phosphatidylcholine, pentoxifylline and liver transplantation.
1.4.1. Chemotherapy for Non Alcoholic Liver Damage

(a) Vitamin-E

Oxidative stress is the main hit in the pathogenesis from steatosis to fibrosis. Therefore, using antioxidant substances seems to be rational in the treatment of steatohepatitis. Several in vitro and animal in vivo studies revealed that, application of vitamin-E decreased levels of profibrogenic TGF beta, improved liver histology and inhibited hepatic stellate cell activation (Parola et al., 1992a; Parola et al., 1992b; Houglum et al., 1997). Patients with presumed non alcoholic steatohepatitis were prescribed 400-1200 IU of oral vitamin-E. Post treatment of vitamin-E with steatohepatitis liver biopsy showed that, the degree of steatosis, inflammation or fibrosis also improved or remained unchanged and the plasma levels of TGF-β decreased significantly (Harrison et al., 2003).

(b) Polyenylphosphatidylcholine (PPC)

Phospholipids deficiency is associated with altered mitochondrial membranes and correlates with morphologic changes and impaired function in liver. Administration of PPC to primates corrected the ethanol induced decrease in phospholipid levels and prevented progression to alcohol induced septal fibrosis and cirrhosis (Li et al., 1994) with an associated reduction in the number of activated stellate cells. These had been found to be strikingly increased in alcohol fed baboons contributing to the progression
of fibrosis (Mak et al., 1984). A similar transformation of stellate cells was observed in patients with alcoholic liver disease (Mak and Lieber, 1988) and an attenuation of the activation of stellate cells to myofibroblast like cells was also observed in vitro (Poniachik et al., 1999).

(c) Silymarin

Silymarin was found to be effective against various liver injuries in rodents. In patients with alcoholic liver disease, some randomized controlled trials with silymarin showed beneficial effects such as improved survival (Ferenci et al., 1989). However, some clinical trials and non human primate studies (Pares et al., 1998) reflects poor compliance treatment thus indicates the inequity of silymarin, it might be justified to verify its effect in additional clinical studies.

(d) Betaines

Betaines are trimethyl amino acids derived either from choline or from the diet. They function as methyl donors and therefore, reduce lipid accumulation in the liver (Best et al., 1969). Betaines are important to form phosphatidyl choline (PC), a component of VLDL, which is the key molecule to export lipids from hepatocytes (Neuschwander-Tetri, 2001). Supplementation with betaine improves the export of lipids from hepatocytes.
(e) Ursodeoxycholic Acid (UDCA)

Hydrophilic bile acid is approved for the treatment of primary biliary cirrhosis. Ursodeoxycholic acid (UDCA) has been shown to reduce the portion of hydrophobic bile acids which contribute to oxidative stress. This is of particular importance, because fatty hepatocytes reveal an increased sensitivity to hydrophobic bile acids (Angulo, 2002). Laurin et al., (1996) reported that, the effect of UDCA on serum liver enzymes and histology in patients with non alcoholic fatty liver disease showed promising results. The mode of action of UDCA is speculated as cytoprotective, chemoprotective, antioxidant and immunomodulatory properties (Stiehl et al., 1998). The long term treatment of nonalcoholic steatohepatitis patients with UDCA in mono therapy or in combination with vitamin E is currently under investigation.

(f) S-Adenosylmethionine (SAMe)

SAMe is the activated form of methionine, has potential in alcoholic as well as in non-alcoholic liver disease. N-acetylcysteine, which is a glutathione prodrug and known to decrease oxidative stress and alcoholic steatohepatitis.

(g) Metformin

Metformin has been shown to be an effective treatment of fasting hyperglycemia in patients with non insulin dependent diabetes mellitus. It is decreasing the hepatic glucose output mostly due to an inhibition of the
gluconeogenesis (Stumvoll et al., 1995). Further evidence for beneficial effects of metformin was provided by Marchesini et al. (2001) with non insulin dependent diabetes mellitus. However, metformin should be used with caution in patients with advanced liver disease because of the risk of lactic acidosis (Marchesini et al., 2001; Phillips et al., 1978). Idiosyncratic hepatotoxicity of metformin also has been reported by several authors (Babich et al., 1988; Swislocki and Noth, 1988).

(h) Thiazolidinediones (TZDs)

Thiazolidinediones (Troglitazone, rosiglitazone and pioglitazone) improves insulin sensitivity enhancing glucose disposal and influencing lipid metabolism (Komers et al., 1998; Saltiel, 2001). TZDs activate PPARg, a nuclear receptor expressed in adipose tissue to maintain normal insulin sensitivity. PPARg activation reduces release of FFAs and TNFα by adipocytes (Hauner, 2002; Hube and Hauner, 2000; Hotamisligil and Spiegelman, 1994). In contrast to rosiglitazone, pioglitazone and troglitazone has been found to induce cytochrome P4503A4 (CYP3A4) predisposing it to drug interactions (Scheen, 2001). Nevertheless, there are also some reports of possible rosiglitazone-related hepatotoxicity (Forman et al., 2000; Salman et al., 2000) and pioglitazone-related hepatotoxicity (Maeda, 2001; May et al., 2002). Normalisation of ALT levels was observed in 70% of female patients who treated with 400mg. qd, for 6 months (Caldwell et al., 2001) but this
biochemical response was not paralleled by a significant histological improvement. Although rosiglitazone and pioglitazone do not share the hepatotoxic profile of troglitazone (Scheen, 2001).

1.4.2. Chemotherapy for Alcoholic Liver Damage

(a) Corticosteroids

Potential role of inflammatory factors in the pathogenesis of fibrosis and cirrhosis, anti-inflammatory therapy with corticosteroids has been used. Corticosteroids are a class of steroid hormones that are produced in the adrenal cortex. Corticosteroids are involved in a wide range of physiologic systems such as stress response and regulation of inflammation, carbohydrate metabolism, protein catabolism and blood electrolyte.

(b) Phosphatidylcholine

Phosphatidylcholine is an essential component of all cell membranes and is vulnerable to attack by lipid peroxidation. Through mechanisms that are as yet unclear, dietary supplementation with phosphatidylcholine has been shown to attenuate ethanol induced fibrosis in baboons. In a long term trial in patients with alcoholic cirrhosis, there was a trend toward improvement in transaminase and bilirubin levels in the phosphatidylcholine group for certain patient subgroups (heavy drinkers
and those with hepatitis C). Lieber et al. (2003) reported that, there was no overall improvement in mortality or histology for chronic studies.

(c) Pentoxifylline (PTX)

Pentoxifylline (PTX) is a nonselective phosphodiesterase inhibitor that has a moderate anticytokine effect attributed to reduce transcription of the tumor necrosis factor (TNF) gene). 40% of mortality reduction was reported by Akriviadis et al. (2000) when compared with placebo, the improvement survival was due to a decrease in mortality from hepatorenal syndrome. Further trials are needed to determine whether PTX should become a standard treatment for patients with alcoholic steatohepatitis.

1.4.3. Organ Transplantation Therapy

A liver transplant is considered when complications cannot be controlled by treatment. Liver transplantation is a major operation in which the diseased liver is removed and replaced with a healthy one from an organ donor. Transplantation surgery is a major undertaking and requires life-long anti-rejection medications afterwards. Extensive testing is required before a liver transplant to ensure that a candidate is in good enough health to proceed with a transplant operation. Additionally, transplant centers typically require some period of abstinence from alcohol (often at least 6 months) and/or formal alcohol and drug treatment for patients with alcohol-
related liver disease before transplantation. Not all patients with cirrhosis need a liver transplant and transplantation is not the best choice for all patients.

1.4.4. Alternative Chemotherapy

The liver disorders are treated using several alternative medicinal therapies viz., ayurveda, homoeopathy, siddha and naturopathy are some of the ancient and known methods for treating liver diseases. Sometimes, various home remedies are also applied for treating liver disorders. Most of these treatment methods make good use of various herbs and natural ingredients and provide an effective way for getting relief from liver disorders.

For treatment of liver disorders, the ayurvedic medicine first identifies the exact type of disorder and then prescribes a particular method. The ayurvedic treatment of liver disorders includes both medications and dietary restrictions. Ayurveda describes jaundice as kaamala and also consider this as one of the major diseases of yakrit (liver). There are many ayurvedic preparations used for treating liver diseases including panchakarma, rasayana therapies, pippalyadi choornam, pippali vardhamana yogam, panchagavyam, mahathiktakam, snehanam, kalyanaka gritham, pippalichitraka gritham, pippali gritham, chitraka gritham, rohitha gritham, maharohita gritham, etc. Ayurvedic medicines play a significant role in
protecting the liver from cirrhosis and from liver cancer. The herbs that are used commonly for making ayurvedic medicines for liver disorders include bhumyamalaki, bhringaraj, turmeric, guduchi, haritaki, kalmegha, kutki, musta, pippali, punarnava, licorice, triphala, amrutha, etc. Apart from these, the herbs like berberis, chicory, dandelion, gokulakanta, henna, indian aloe, indian sorrel, picrorrhiza, trailing eclipta, turpeth, etc. are also used for treatment of liver disorders. Among all these herbs, bhringaraj is considered the most useful ayurvedic drug and is used for almost all types of liver disorders.

Homoeopathy provides a useful and easy procedure for treating liver disorders. The homoeopathic medicines are by nature gentle and treat the patient as a whole. The individual based homoeopathic treatment prescribes remedies and dosages, depending on the strength of a person’s immune system. The medicines improve the overall functioning of the liver. They also prevent problems associated with a sluggish liver like depressed immune system, constant fatigue, obesity, sluggish digestive system, allergies, respiratory ailments, unhealthy skin, irritability, etc. The homoeopathic remedies improve gall bladder functioning, reduce inflammation, help dissipate gallstones and also neutralise toxins. They act as liver friendly antioxidant, vitamin and mineral supplements. The most frequently used homoeopathic medicines for treating liver diseases are bryonia, mercurius,
podophyllum, chelidonium, digitalis, myrica cerifera, nux vomica, lycopodium, carduus marianus, sulphur, phosphorus, taraxacum, etc.

Siddha is also used frequently for the treatment of liver disorders. The siddha system of medicine is well recognized as a definite approach to liver disease treatment and the medicines are made using the natural ingredients like venkaram (Borax), rasa karpooram (Mercuric sub chloride), manjal (Curcuma longa), elumichai charu (Lemon juice), etc.

In naturopathy, the treatment of liver disorders is done following various dietary restrictions and different exercises. According to naturopathy, detoxification of the liver is necessary if there is a liver problem. To do this, fasting for a day is suggested and after that, easily digestible food items should be consumed. Consumption of bitter vegetables like bitter gourd and bitter drumstick and goat`s or cow`s milk is prescribed. It is a necessity to add garlic in the diet. The patients are sometimes advised to eat beets, lemon, papaya, grape juice, radish juice and carrot juice to help curing liver diseases. They are also prescribed to undertake warm water anemia and eat the foodstuffs like raw nuts, almonds, home made cheese, sprouts and steamed vegetables like papaya and bitter gourd. They may sometimes follow the milk and fruit diet as well. However, consumption of
salt, sugar and alcohol are strictly prohibited in naturopathic treatment of liver disorders.

Drinking plenty of liquids, vegetable soups and taking complete bed rest are suggested in case of jaundice and hepatitis. Excluding all fats, fried foods, smoked foods, cakes, creams, pulses, legumes and all kinds of meat, etc. is also quite necessary for effective treatment of liver disorders. It is often advised to add tender neem leaves and flowers to the patient’s diet. Practising Yogic Asanas like Pranayama, twice a day along with mudpacks, mineral water drinks and mineral bath are a few other effective ways for treating liver disorders. There are also some home remedies used for treatment of liver disorders. Drinking a mixture of a little salt and some roasted cumin seeds with a glass of buttermilk is sometimes suggested.

However, though most types of liver disorders can be treated following the above mentioned treatment methods. Apart from these, the other preventive measures for liver disorders include practising good hygiene like washing hands well after using the restroom or changing diapers; avoiding drinking or using tap water while traveling; avoiding illegal drug use, especially sharing injection equipment; avoiding the sharing of personal hygiene items like razors or nail clippers; avoiding toxic substances and excess alcohol consumption; using medications only as
directed; using caution around industrial chemicals; eating a well balanced diet; getting an injection of immune globulin after exposure to hepatitis A; using recommended safety precautions in healthcare and day care work, etc.

All the siddha based treatments are depends on the dietary schedule and selective food intake. However, there is no scientific evidence on the side effects of the dietary supplements and hence compared with the chemotherapy and ayurvedic medicines. The siddha based drugs are not available in the market. The present study was made an attempt to find out the safe and efficacy of siddha based drug with scientific proof from the highly unexplored mangrove plants for the treatment of liver damage.
Picture showing the commercialized drugs for liver diseases

- Betaines
- Metformin
- Ursodeoxycolic acids (UDCA)
- Pentoxifylline (PTX)
- Phosphatidylcholine
- Thiazolidinediones (TZDs)
- Silymarin
- S-Adenosylmethionine (SAMe)