Review of Literature
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Medicinal plants are of great value in the field of treatment and cure of disease. Over the years, scientific research has expanded our knowledge of the chemical effects and composition of the chemical constituents, which determine the medicinal properties of the plants. It has now been universally accepted fact that the plant medicines and remedies are far more safer than that of synthetic drugs for curing the serious diseases like cancer, AIDS, hepatitis, epilepsy etc. Enormous number of alkaloids, glycosides and antibiotics have been isolated, identified and used as the curative agents. The modern developments in the instrumental techniques of analysis and chromatographical methodologies have added numerous complex and rare natural products to the armoury of phytomedicine. To mention few, Artemisinin as antimalarial, Taxol as anticancer, Forskolin as antihypertensive, Rutin as vitamin P and capillary permeability factor and Piperine as bioavailability enhancer are the some what recent developments.

In the western world, as the people are becoming aware of the potency and side effects of synthetic drugs, there is an increasing interest in the plant based remedies with a basic approach towards the nature. Mother earth has given vast resources of medicinal flora and fauna both terrestrial and marine. It largely depends upon the forthcoming phytochemists to explore the wonder drug molecules from this unexplored wealth.
The present study is focussing on the therapeutic efficacy of *D. cordifolia* and *P. marsupium* against toxic hepatitis, healing of wounds, analgesic, anti-convulsant and CNS depressant activities.

Hepatitis

Hepatitis is the condition where there is inflammation and/or necrosis of liver cells. The symptom of hepatitis is called ‘jaundice’ means yellow discoloration of sclera.

**Types of hepatitis: (Zimmerman, 1978)**

**Acute Hepatitis:** Acute (sudden in onset) infection of the liver e.g. infective hepatitis, serum hepatitis and toxic hepatitis. The common causes of acute hepatitis are hepatotropic viruses A, B, C, D and E, hepatotoxins and drugs.

**Chronic Hepatitis:** The injury to the liver is long standing and continuous. Many people with chronic hepatitis may not have any typical signs and symptoms and may therefore feel healthy e.g. chronic alcoholism, carriers of hepatitis viruses C & D It may only be detected through laboratory tests of liver function. Illness due to chronic hepatitis may last for more than six months.

The common causes of hepatitis are listed below.

Abiotic compounds
• Organic compounds like a) Halogenated aliphatic hydrocarbons e.g.,
carbontetrachloride, tetrachloroethylene, 
chloroform, etc. (Klatskin, 1975)
b) Halogenated aromatic compounds
Hexachlorobenzene, styrene, toluene, 
xylene, benzene, etc. (Klatskin, 1975, Felto, 
et. al., 1975, Reynolds, 1977)
c) Nitro aromatic compounds e.g.
Nitrobenzene, dinitrophenol, trinitrotoluene,
nitrosocompounds (Jones, et. al., 1974),

• Inorganic compounds like Arsenic, antimony, bismuth, thallium, 
cadmium, phosphorus, mercury etc. 
(Shapley, 1976)

• Pesticides e.g., Aldrin, dieldrin, endrin, DDT, etc (Webb, 1975).

Biotic compounds (Biotoxins).

• Mycotoxins e.g., Aflatoxin, Luteoskyin, Cyclochlorotine, Rubratoxin. 
(Palterson, 1978).

• Phytotoxins e.g., Pyrrolizidine alkaloids, seleniferous grains, lantana 
toxins, phalloidin, tannic acid. (Kraybill, 1973).

• Infectious agents e.g. \(E.\text{Coli}\) (endotoxin), \(E.\text{Coli}\) (ethionine), 
\(Corynebacterium\ \text{Diphtheriae}\) (exotoxin) (Shull, 
et. al., 1066).
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- Virus e.g., Canine hepatitis, Duck and turkey hepatitis, Rift valley fever virus (Zuckerman, et. al., 1978), Hepatitis A & B Viruses, Mouse hepatitis viruses, Yellow fever virus, Human herpes viruses (Okuds, et. al., 1976).

- Protozoa e.g. Entamoeba histolytica, Plasmodium knowlesi, Leishmania donovani, Schistosomiasis sps., Echinococcus granulosus.

- Helminthes e.g. Ascaris lumbricoides, Fasciola hepatica.

Viruses that can cause acute hepatitis include hepatitis A, B, C, D, E and G viruses. Majority of medical profession opines that hepatitis G does not cause a disease. Hepatitis A, B, C, D & E viruses together are responsible for more than 98% cases of viral hepatitis. Only 2% cases are due to other viruses.

Hepatitis A (HAV)

It is a small un-enveloped, symmetrical RNA virus classified as enterovirus. HAV belongs to the group picornavirus. It replicates only in the liver and is able to survive in wet environment for long periods. Infection is via faeco-oral route, commonly by drinking or eating contaminated food or water. It is common in persons travelling more, where public hygiene is poor. It can also be transmitted as a result of close contact, food prepared with the infected or cleaned with contaminated water (salad, raw vegetables & fruits).
Symptoms

Headache, nausea, vomiting, diarrhoea, abdominal pain, jaundice and yellowish colored stool characterize acute phase. The incubation period is two to six weeks. The risk is low but increases with age and the patient may feel tired. Infected patient confers life long immunity to this type of hepatitis.

Treatment

Avoiding ingestion of contaminated food and water, and maintaining good personal hygiene can reduce risk. Vaccination is also available either for short term (immunoglobulin) or long term protection (Harvix, Avaxim).

Hepatitis B (HBV)

HBV is a double stranded DNA virus that replicates by reverse transcription. The mode and rate of transmission is hundred times higher than that of AIDS virus. It spreads via contaminated body fluids, saliva, blood, semen, vaginal smear and by sharing contaminated needle, razors, body piercing and other sharp instruments. It can be transmitted from infected mother to newborn child.

Symptoms
• Acute hepatitis: The people infected with HBV develop acute hepatitis. The following symptoms appear in about 1 to 6 months after infection. jaundice, rash, pain in joints, inflammation of the kidneys and blood vessels and anaemia due to bone marrow depression. Most of the people may develop severe symptoms with liver failure and death may occur.
• Asymptomatic HBV carriers: About 10% adults infected with HBV do not clear virus from their bodies. Although the virus is present in the blood, it does not cause any symptoms and therefore such people are called asymptomatic carriers. It is desirable to take active immunization that come in close contact with, or have sexual relationship with asymptomatic carriers. In such persons a large numbers of viruses multiply, grow rapidly and chronic active hepatitis develops. This may lead to liver cirrhosis or some times even to liver cancer.

• Cancer of the liver: Chronic active hepatitis due to HBV infection can lead to liver cancer. This occurs more commonly in Asians and people who contact the infection in infancy or childhood. The risk of liver cancer increases with smoking, consumption of alcohol.

Treatment

HBV may be prevented by vaccination, e.g., Energix-B, H-B-Vax II, and Twinix. Three doses of vaccine are given at time zero, after one month and again six months later. Levels of antibodies are checked after 2 months. A booster dose may be given after five years for full immunization.

But once the person is infected with this strain, it is very difficult to get rid off it. No specific allopathic drug has been developed against this virus. The only available treatment is interferon. It is too costly and given for two to six months three times a week.
Hepatitis C (HCV)

HCV is an enveloped single stranded virus of 9.4 kilobases. The RNA is a plus strand and can serve directly as mRNA for viral proteins, once the virus infects the host cell. The viral genome contains one long open reading frame that could encode a protein of 3011 amino acids. The amount of virus required for successful transmission is much lower than HIV, but more than HBV. Further, the virus may survive in heat, cold and drying.

Mode of Transmission

1. Infected body fluid (blood) mainly via injection.
2. Sexually.
3. Mother to child during pregnancy.

Symptoms

The incubation period for the acute phase is 1 to 26 weeks. Patient is often asymptomatic, or may have mild symptoms of fatigue. Chronic infection may lead to cirrhosis and liver cancer.

Treatment

Treatment for HCV is only alpha-interferon for which only 50% of patients respond. However, half of these will relapse and only 15-20% will have benefit. Alpha-interferon is given 3 times a week for minimum of 3 months. It may be continued upto one year. Effectiveness of alpha-interferon increases after combination with antiviral agents. Side effects are dose related and include nausea, influenza like symptoms, lethargy and depression.
Hepatitis D (HDV)

HDV is a defective virus and contains a unique genome. A small single stranded RNA of ~ 1700 nucleotides with an unusually secondary structure (Polish, et. al., 1993). Hepatitis D occurs in only those who have HBV infection. It is a mutant strain of HBV and needs HBV to survive and cause disease. HDV infection can be detected through a blood test by the presence of antibodies to the virus. Acute viral hepatitis and chronic liver disease (cirrhosis and liver failure) caused by the combination of HBV and HDV are more severe than the disease caused by HBV alone.

Mode of Transmission

1. Contact with infected blood and contaminated needle.
2. Sexual contact with HDV infected person.
3. Infected mother to newborn child.

Treatment

There is no vaccine for HDV but people who are immunized against HBV are protected from HDV infection also. Interferon is effective with varying success.

Hepatitis E (HEV)

HEV is non-enveloped virus and virions containing a 7.5 kb, single stranded RNA genome with three partially overlapping open reading frames. HEV spreads similar to HAV infection. It affects adults more often than
children. It is more likely to cause epidemics. In India, it is the major cause of morbidity and mortality in pregnant women during out break.

Symptoms

It is often difficult to distinguish HEV from HAV infection. Its symptoms are lack of appetite, pain in abdomen, joint pain and fever. It can be serious in pregnant women in seventh to ninth month of pregnancy. During this period there is a high risk of life for mother and child.

Incubation period

Symptoms of HEV normally appear about two to nine weeks after (average 40 days) the virus enter the body.

Mode of Transmission

HEV spreads in similar fashion to HAV.

1. Faeco-oral route.
2. Out break is associated with contaminated water and food.

Treatment

There is no vaccine currently available for preventing HEV. The antibodies that develop during the illness do not offer life long protection. Relapse of HEV is also common. Prevention is better than cure for this disease.

Interferon and treatment of hepatitis

Interferon is a natural protein in the cell that is formed when the cells are exposed to a virus or any other foreign agents. It protects the cells from viruses.
Different types of interferons are produced for different types of viruses. It stimulates body's natural defense mechanism that fights the hepatitis virus. Interferon forms a protective layer around the healthy cell of liver. This strong protective layer of interferon protects the cell from hepatitis virus. Normally interferon injections are recommended for four months. The success of treatment depends on the duration of infection. About 5% people with chronic HBV infections benefit partially with interferon.

Treatment for chronic HCV infection with interferon is likely to last longer than that for HBV infection. For chronic HCV, interferon is normally recommended three times a week for 12 months to two years. Treatment of chronic hepatitis with interferon can reduce the risk of cirrhosis or liver cancer. During treatment with interferon, regular blood tests to measure the levels of liver enzymes are often recommended. It is important that the test for hepatitis B antigen may be positive for several weeks or years after completion of the treatment. This is because HBV may continue to be in the blood in small number. It is also important to remember that even after the infection is controlled, the liver will need time to grow healthy cells to replace those that were damaged or destroyed by hepatitis virus infection. It may produce side effects such as a feeling of being unwell, fatigue, body-ache, irritability, loss of appetite, nausea, diarrhea etc.

Hepatitis continues to be a major cause of illness and death among all communicable diseases (Pradeep, et. al., 1999). In the developing countries
like India majority of the population rely upon the plant based traditional medicines to cure jaundice. The allopathic medical care is too costly and the interferon treatment is highly sophisticated and beyond the reach of people living below the poverty line.

The investigation of Karandikar, et. al., (1963), Rubin, et. al., (1963), Vaishwanar, et. al., (1976) and Recnagel, et. al., (1983) proved that administration of CCl₄ in rats is known to cause centrilobular hepatic necrosis or toxic hepatitis and the injury caused by this toxic substance is similar to that of human infective hepatitis. Roullier, et. al.,(1964) and Schotz, et. al., (1964) suggests that the fats were mobilized from the peripheral adipose tissues and were deposited in the liver. Similarly the other hepatotoxic substances like alcohol, paracetamol and aflotoxin B₁ were also known to cause hepatic cirrhosis or necrosis in albino rats (Pandey, et. al., 1990), Dwivedi, et. al., (1990), Gulati, et. al., (1991) and Chattopadhay, et. al., (1992).

Many indigenous drugs and herbs were clinically screened to evaluate the hepatoprotective activity against toxic hepatitis or cirrhosis.

Young, et. al., (1986) reported that the methanol extract of Wedelia chinensis possesses a strong anti-hepatotoxic property against CCl₄ induced hepatitis, using primary cultured rat hepatocytes.

Wagner, et. al., (1986) found that the ethyl acetate soluble fraction of Eclipta alba and the isolated active constituents of Wedelia calendulacea
(Wedelolactone and dimethyl wedelolactone) exhibited hepatoprotective activity, in assays employing CCl₄ cytotoxicity in rat hepatocytes. Besides they observed a significant stimulatory effect on liver cell regeneration.

Venkateswaran, et. al., (1987) observed the hepatoprotective activity of the crude extract of Phyllanthus niruri.

Two iridoid glycosides isolated from the plant Picrorhiza kurrooa exhibited significant hepatoprotective and anti-cholestatic activity against CCl₄ induced hepatitis, (Dwivedi, et. al., 1991; Tripathi, et. al., 1991; Shukla, et. al., 1991 and Saraswat, 1993).

Dwivedi, (1990) observed that administration of aflatoxin-B₁ causes significant increase in the serum bilirubin and the activities of serum enzymes like alkaline phosphatases, lipases and transaminases. But there was a reduction in total proteins and the albumin concentration. The pretreatment of rats with the glycoside fractions of Picrorhiza kurrooa for seven days significantly reversed the toxicity induced by the aflatoxin B₁. This indicates the hepatoprotective activity of Picrorhiza kurrooa against aflatoxin B₁ induced hepatic damage.

The active constituent Andrographolide isolated from Andrographis paniculata was found to possess the hepatoprotective activity against paracetamol induced hepatic damage (Visen, et. al., 1990). The constituent reduced the serum enzyme levels and increased the serum protein.
Gulati, et. al., (1991) reported that the indigenous herb *Boerhaavia diffusa* has been reported to be used in chronic alcoholism and jaundice. The root extract of this plant has been claimed to reduce the serum levels of transaminases and alkaline phosphatases but increased the liver ATPase activity in albino rats.

Chandra, et. al., (1991) reported that administration of CCl₄ or alcohol produced fatty infiltration in the hepatocytes whereas in animals treated with *Boerhaavia diffusa* there was significant reduction in the fat deposition.

Singh, et. al. (1991) screened the petroleum ether, benzene, acetone and 50% alcohol extracts of *Eclipta alba* for their hepatoprotective activity against CCl₄ induced hepatic damage. It was observed that the alcoholic extract showed significant hepatoprotective activity.

Chattopadhay, et. al., (1992) observed that the serum enzyme levels were significantly reduced in the animals treated with *Ocimum sanctum* leaf extract and paracetamol. Further histopathological studies of liver revealed that severe fatty degeneration of the cells around the portal tract in paracetamol treated animals were controlled.

In the year 1992, Thyagarajan, et. al., reported the medicinal use of *Phyllanthus amarus* in the treatment of hepatitis B.

Shukla, et. al., (1992) isolated an active constituent from the leaves of *Ricinus communis* and found to possess the hepatoprotective effect.
A synthetic compound named 2-cyano, 4-methyl, 5-vinyl pyridine was screened and found to possess significant hepatoprotective activity (Visen, et al., 1993).

The following authors have reported the hepatoprotective activity of the various plant extracts.

Lin, *et al.*, (1997) studied the hepatoprotective activity of the constituents baicalein, baicalin and wogonin, isolated from *Scutellaria rivularis*. Baicalin (10mg/kg) exhibited the best hepatoprotective effect on CCl₄ induced liver injuries indicated by reduction in serum transaminases and histopathological changes. Wogonin 5,10 mg/kg also decreased APAP-induced hepatoprotective toxicity.

Anandan, *et al.*, (1999) observed the hepatoprotective effect of the ethanol extract of *Picrorrhiza kurroa* in D-galactosamine-induced hepatitis in rats. The pretreatment with the extract prevented the increase in lipid peroxidation and decrease in the liver antioxidant enzyme levels like superoxide dismutase, catalase, and glutathione peroxidase. The antioxidant effect of the ethanol extract of *P. kurroa* is probably due to the increase of the activities of the free radical scavenging enzymes, or to a counteraction of the free radicals by the presence of the electrophilic constituent picroside I, or to an activated conjugation of D-galactosamine with reduced glutathione in liver.

Mookan Prabakan, *et al.*, (2000) has reported the protective effect of ethanol extract of roots of *Hemidesmus indicus* (100mg/Kg/day for 15 days) against rifampicin and isoniazid induced hepatotoxicity in rats.

Hwa-Kyung Lim, *et al.*, (2000) has evaluated the hepatoprotective effect of Bergenin a major constituent of *Mallotus japonicas* on CCl₄ intoxicated rats. Bergenin has a potent hepatoprotective action against CCl₄
induced hepatic damage in rats which was indicated by controlling the serum enzyme levels.

The aqueous and methanol extracts of *Ambrosia maritima* were evaluated for the hepatoprotective activity against acetaminophen induced liver damage by Mohamed Bastawy Ahmed, *et. al.,* (2001). There was marked increase in lipid peroxidation measured by malondialdehyde (MDA) (42%). This was associated with significant reduction of the hepatic antioxidant system e.g. reduced glutathione (65%), glutathione reductase (35%), total glutathione peroxidase (32%) and glutathione S transferase (16%). These biochemical alterations were inhibited by pretreatment with *A. maritima* L extract which suggest that the plant may act as a hepatoprotective and anti-oxidant agent.

Coumestans isolated from the leaves of *Wedelia calendulacea* was evaluated in paracetamol induced liver damage by Emmanuel, *et. al.,* (2001). Coumestans afforded a significant protective action in the alleviation of paracetamol induced toxicity by restoring the increased serum enzyme levels.

Murakami, *et. al.,* (2001) isolated the principle constituent Quercetin 3-sephorotrioside from the young seed pods of garden peas (*Pisum sativum*). The active constituent was found to have protective effects on liver injury induced by D-galactosamine and carbon tetrachloride in mice.

Bioassay-guided fractionation of water extract of the seeds of *Psoralea corylifolia* furnished Bakuchiol, a hepatoprotective compound on tacrin
induced cytotoxicity in human liver derived HepG2 cells (Cho, et. al., (2001). The EC$_{50}$ value of the compound was 1.0 micro g/ml. Silymarin as a positive control showed the EC$_{50}$ value with 5.0 micro g/ml.

Hepatoprotective activity of indigtone- a bioactive fraction of petroleum ether extract of aerial parts of *Indigofera tinctoria* (Singh, et. al.2001), showed significant dose related hepatoprotective activity against CCl$_4$ induced liver damage in rats and mice.

Rutin, a well-known flavonoid isolated from *Artemisia scoparia* was investigated by Khalid, et. al., (2002) for its hepatoprotective activity against paracetamol and CCl$_4$ induced hepatotoxicity. Pretreatment with 20 mg/kg of rutin prevented the paracetamol and CCl$_4$ induced rise in serum enzymes. The treatment with CCl$_4$ is known to cause damage to microsomal drug metabolizing enzymes in hepatocytes leading to substantial decrease in hepatic drug metabolizing capacity, being reflected in prolongation of pentobarbital induced sleeping time confirming its hepatoprotective activity. Paracetamol is converted to a toxic reactive intermediate called N-acetyl-p-benzoquinone imine (NAPQI) following metabolism by a number of isoenzymes of cytochrome P-450. The massive production of reactive species may lead to depletion of protective physiological moieties (glutathione and $\alpha$-tocopherol, etc.) ensuing wide spread propagation of the alkylation as well as peroxidation, causing damage to the macromolecules in vital biomembranes. The reactive species mediated hepatotoxicity can be effectively managed upon
administration of agents possessing anti-oxidant, free radical scavenger and anti-lipid peroxidant activities. The inhibitors of CYPs are known to reduce the toxicity of paracetamol as well as CCl₄. Hence the reported inhibition of CYPs by rutin might have contributed favourably toward the observed hepatoprotection. The presence of this compound in *Artemisia scoparia* explained the folkloric use of the plant in liver damage.

Bioassay–guided fractionation of the ethanol extract of *Cnidium monnieri* (Apiaceae) furnished two hepatoprotective sesquiterpenes, torilin and torilolone (Oh, et al., 2002). Both the compounds showed the hepatoprotective effects on tacrine induced cytotoxicity in human liver derived HepG2 cells. The EC50 values of compounds torilin and torilolone were 20.6 plus-1.86 and 3.6 plus-0.1 micro M, respectively.

Aniya, et al., (2002) observed the free radicals scavenging action of medicinal herb *Limonium wrightii* from the Okinawa islands. Gallic acid was identified as the active component of *Limonium wrightii*. The water extract and the active constituent gallic acid were found to have strong free radicals scavenging action. They prevented the elevation of serum transaminases in CCl₄ induced liver toxicity.

Venkatesan, et al., (2003) have reported the protective effect of aqueous extract of *Phyllathus amarus* linn, phyllanthin and nirocil against carbon tetrachloride induced liver and brain toxicity these drugs showed significant protection by reversing the elevated plasma amino transferase levels.
Jeong, et. al., (2003) have screened the hepatoprotective activity of the medicinal plant extracts on CCl₄ induced hepatotoxicity in rats. The MeOH extracts of the following plants showed the protective effect against increased the transaminases activity: Mentha arvensis, Sophora japonica, Benincasa hispida, Lonicera japonica (Lonicerae Flos), Agaricus blazei, Epimedium koreanum, Aralia continentalis, Lithospermum erythrorhizon, Cimicifuga foetida, Gastrodia elata, Sanguisorba officinalis, Cephalonoplos segetum, Bupleurum falcatum, Alisma Plantago- aquatica var. orientale, Lonicera Japonica (Lonicerae Folium) and Sinomenium acutum showed protective effect against increased serum alanine aminotransferase (ALT) and / or serum aspartate aminotransferase (AST) activities.

Kim, et. al., (2003) have screened the dibenzylbutyrolactone lignans, (-)-aretigenin, (-)-traxillagenin and (-) demethyltraxillagenin, isolated from the bark of Torreya nucifera for the hepatoprotective activity against CCl₄ induced toxicity in primary cultured rat hepatocytes. The lignans reduced the release of transaminases. They also preserved the levels of glutathione (GSH) and activities of superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase in CCl₄ injured rat hepatocytes. The lignans also ameliorated lipid peroxidation as demonstrated by a reduction in malondialdehyde (MDA)-related products. The lignans may protect hepatocytes from CCl₄ injury by maintaining the GSH level.
Asati, et. al., (2003) studied the hepatoprotective activity of Kushmanda ghirta against CCl₄ induced hepatotoxicity. Kushmanda ghirta is a herbal formulation containing *Benincasa hispida* and cow's ghee. It gave significant protection to liver against CCl₄ injury. The comparative histopathological study further corroborated the hepatoprotective activity of KG.

The total alkaloid fraction of the methanol extract of the leaves of *Solanum pseudocapsicum* was tested for its hepatoprotective activity against CCl₄ induced toxicity in freshly isolated rat hepatocytes, HepG2 cells and animal models by Vijyan, et. al., (2003). The total alkaloid fraction was able to normalize the serum levels of transaminases, ALP, triglycerides, total proteins and bilirubin. The antihepatotoxic effect of this fraction was observed at very low concentrations and was found to be superior to that of standard used. Its in vivo hepatoprotective effect at 20mg/kg was comparable with that of the standard at 250mg/kg.

Hepatoprotective activity of *Wrightia tinctoria* Roxb. has been studied by Chandrashekar, et. al., (2004). The alcoholic, petroleum ether and aqueous extracts were investigated for hepatoprotective activity against CCl₄ induced liver damage. The alcoholic and petroleum ether extracts showed significant hepatoprotective activity by restoring the elevated serum bilirubin and enzymes. The histopathological study of the liver tissues also supported the fact.
Wound

Wound may be caused by

- Trauma—either accidental or surgical.
- Physical, chemical and microbial agents.
- Ischaemia, which leads to infarction.

Types of wounds

- Incised wounds: These are usually caused by a sharp knife or glass. These wounds are relatively clean. After suitable exploration, in which the underlying structures are repaired, these wounds may be closed by primary suture.
- Lacerated wounds: These wounds commonly occur following road traffic accidents. The wounds usually have jagged edges with certain lacerated and devitalized structures inside the wound. Thorough debridement of these wounds is required if received within 6 hours of injury.
- Penetrating wounds: These are almost similar to incised wounds, except that its depth is more. The wound should be explored layer by layer followed by primary suturing if it has come within 6 hours of injury.
- Crushed wounds: These occur due to industrial, road traffic and war injuries. These wounds are managed by debridement and removal of all necrotic tissues often there is great tension to the deep fascia.

The word “healing” means replacement of destroyed tissue by living tissue. The process of healing involves two distinct processes.
i. Regeneration: In this healing takes place by proliferation of parenchymal cells and usually result in complete restoration of the original tissues.

ii. Repair: In this healing takes place by proliferation of connective tissue elements resulting in fibrosis and scarring.

Repair process involves following steps

- Formation of clot and crust: The clot thus formed holds together the sides of the wound. If it reaches the surface, it dries to form a crust or scab. The crust prevents oozing of fluid from the wound and also serves as a mechanical barrier against bacteria from outside.

- Formation of granulation tissue: This is a composite step made up of 2 processes. i). Vascularization: New blood vessels and lymphatics are formed in the area undergoing repair. ii). Proliferation of fibroblasts: This is the most important features of the healing process. For the first three days after the injury the intercellular spaces are full of proteinous fluid. Later the fluid becomes gelatinous and shows increasing quantities of mucopolysaccharides which are produced locally by fibroblasts. The intercellular fibres are laid down in this wound fluid. At first these are fine, coarsen and thicken. The collagen fibres run parallel and the formation of a tough membrane of laminated collagen takes place. By this time fibroblasts decrease in number.

- Organization: Newly formed capillaries and fibroblasts gradually replace the clot. The process is known as organization. The new tissue is known as
granulation tissue because it has the appearance of pink granules. As more and more collagen fibres are laid down, granulation tissue becomes less and less vascular.

• Epithelialization: Epithelial cells from the margin of the wound, flatten, elongate and begin to migrate as a continuous sheet. It lasts till the gap is completely covered and the normal architecture of the cover is reestablished. The newly formed film of epithelium is only one or two layer thick. It becomes stratified and keratinized later.

• Wound contraction: Wound contraction is the shrinkage of the area of the wound. It is a normal process, which hastens healing. The mechanism of contraction may be (i) drying up of the fluid in the wound, (ii) contraction of granulation tissue and (iii) contraction of narrow band of tissue at the edge of the wound. The eosinophilic stellate cells found in early wounds are myofibroblasts. The cells are derived from pericytes, generate contracting force. Further they can secrete collagen and elastin and store lipids. As granulation tissue matures into fibrous tissue they lose their myofibrilin obviously contraction reduces the size of the scar.

Breaking strength of wound

This is the strength of a healing wound and is measured experimentally by the amount of force required to disrupt it. In the beginning a wound will be having little breaking strength because the clot alone will be holding the edges together. Thereafter breaking strength increases rapidly as collagen deposition increases and cross linkages are formed between collagen fibers. Extracellular
matrix involves five main components, which includes collagen, adhesive glycoproteins, basement membrane, elastic fibers and proteoglycans which are responsible for wound strength.

Many drugs are available for healing various types of wounds. However, evaluation of drug from the natural source is of utmost importance to meet the demands of the ever increasing population.

In the traditional systems of medicine, various plants have been used to promote wound healing (Udupa, et al., 1991). The plant kingdom consists of number of medicinal plants claimed to be useful in wound healing. Sushruta has mentioned about the use of the medicinal plants in wound healing in his Sushruta Samhita.

Wound healing activity of seeds of *Trigonella foenum graecum* in rats was studied by Taranahalli, et al., (1996). The aqueous suspension was more effective in healing of wounds than the extract.

The wound healing potential of the methanol extract of *Hypericum mysorenses* was evaluated by Mukherjee, et al., in the year 2000. The methanol extract of the leaves of the plant in simple ointment was evaluated for wound healing potential in excision and incision wound models in rats. The extracts showed the significant responses in both the models in terms of wound contraction, wound closure time, regeneration of tissues at wound site, tensile
strength and histopathological characteristics, which were comparable to those of standard drug Nitrofurazone.

The methanol extract of the rhizomes of *Nelumbo nucifera* (Nymphaeaceae) were studied for its wound healing properties using different types of wound models in rats (Mukherjee, *et al.*, 2000). The extract showed significant effect in respect with wound contracting ability, wound closure time, tensile strength, regeneration of tissues at the wound site as well as the protein content.

The wound healing effects of dried extracts of *Ginkgo biloba* were tested on dead space and excision wound models in male rats (Bairy, *et al.*, 2001). It has significantly promoted the breaking strength and hydroxyproline content of granulation tissue in dead space wounds. In case of excision wound it reduced the epithelialization period and increased the collagenation.

Jaswanth, *et al.*, (2001) evaluated the wound healing activity of the methanol extract of *Aegle marmelos* on excision and incision models. The rate of wound contraction and epithelialization period was found to be higher. The extracts also increased the tensile strength in the incision model. The results were comparable to those of standard drug Nitrofurazone.

Wound healing effect of the various plant extracts has been reported by the following authors:

The ethanol extract of leaves of *Eucalyptus globulus* was evaluated for its wound healing property by Hukkeri, et. al., (2002). The extract showed significant wound healing activity on excision, incision and dead space wound models using male albino rats.

Aziz, et. al., (2003) developed the wound healing ointment from *Tridax procumbens*. The ointment showed the dose dependent and significant activity in excision as the level of hydroxyproline was increased when compared to control. The 15% ointment promoted better wound healing activity.

Marina, et. al., (2003) evaluated the wound healing activity of leaf extract of *Helianthus annuus* on excision, incision and dead space wound models and histopathological studies by using albino rats. The extracts significantly influenced the healing process in all the above mentioned models.

The chloroform, alcohol and aqueous extracts of *Quercus infectoria* galls showed significant wound healing activity in rats (Patil, et. al., 2003). All
the extracts also showed significant antimicrobial activity, which was comparable to standards used.

In the year 2003 the following plants have been screened for their wound healing effect on different experimental models in rats. *Terminalia arjuna* (Madhura, *et. al*), *Desmodium triquetrum* (Annie Shirwaikar, *et. al*), *Dodonaea viscosa* (Joshi, *et. al*), *Eclipta alba* (Patil, *et. al*), *Hyptis suaveolens* (Shirwaikar, *et. al*), *Centella asiatica* (Patil, *et. al*), *Lawsonia alba* (Mandawgade, *et. al*), *Cinnamomum zeylanicum* (Kamath, *et. al*).

A herbal drug combination of *Tridax procumbens*, *Azadiracta indica*, *Curcuma longa* and *Apis mellifica* was evaluated for wound healing potency by Shinde, *et. al*., (2004).

Kusum, *et. al*., (2004) have reported the wound healing property of *Eucalyptus globulus* leaf extract on excision, incision and dead space wound models in rats.

Taranahalli, *et. al*., (2004) have studied the influence of *Trigonella foenum-graecum* seeds on wound healing, growth hormone and folic acid levels in rats.

**Nociception**

Pain is an unpleasant sensory and emotional experience associated with actual tissue damage. It is a subjective experience, which cannot be objectively defined satisfactorily. There is no doubt that pain acts as a warning signal
against disturbance either in the body or in the external environment of an individual and thus, has a protective function. As a symptom, pain demands instant relief and in practice dramatic relief of pain by drugs highly impresses a layman. Pain receptor organs are distributed throughout the body. Clinically, pain can be considered as:

- superficial or cutaneous pain,
- deep non-visceral pain from muscles, joints, ligaments and bones,
- visceral pain,
- referred pain, and
- psychogenic or functional pain.

Pain arising from the skin and the deep structures like muscles, bones and joints is also termed as somatic pain. Somatic pain is usually well defined and is generally caused by inflammatory reaction in the tissues. Pain arising from the skin and superficial mucous membrane is felt as pricking, if brief, and stinging, burning if prolonged. The sensation of ‘pinprick’ elicits a withdrawal reaction of a part or the entire organism. Such a reflex is protective in nature. Deep nonvisceral pain usually has a dull character and it may be accompanied by a sickening sensation due to an autonomic response. Sometimes, it tends to spread to other areas and may even occur as referred pain.

Visceral pain, unlike the somatic pain, is diffuse, less easily localised and often ‘referred’. It is dull-aching or colicky in character and accompanied by sweating, nausea, fall in blood pressure and even shock. In practice, visceral
pain may be due to spasm, ischemia, inflammation or stimulation of the sensory nerve endings. Deep pain may sometimes be misinterpreted as if it is coming from some part other than the actual site of stimulation. This is called referred pain. Thus cardiac pain is commonly referred to the left arm. Usually, the pain is referred to a cutaneous area, which is supplied by the same spinal segments as the affected viscus.

Psychogenic or functional pain is usually a vague pain, which follows no definite anatomical pattern of distribution. Such pain is usually continuous from day to day and does not disturb sleep (Guyton, 1986).

Analgesics are drugs, which relieve pain without causing loss of consciousness. The analgesia is defined as a state of reduced awareness to pain and analgesics decrease pain sensation by increasing threshold to painful stimuli. The commonly used analgesics are aspirin, paracetamol (non-narcotic type) and pentazocine, morphine (narcotic type).

Analgesic activity of N-Isobutyl-4, 5-Decadienamide isolated from the flowers of Spilanthes acmella was reported by Ansari, et. al., in the year 1988.

Barbera, et. al., (1992) evaluated the analgesic activity of the extracts of Trema guineense and Trema micrantha in mice by the acetic acid induced writhing test and in rats by the hot plate method. The anti-inflammatory activity was also evaluated in rats by the carrageenine-induced edema assay. The effects were compare with indomethacin. The ether and ethanol extracts of
both the plants showed significant analgesic activity in both the tests. The ether extract of Trema micrantha produced the better anti-inflammatory activity.

Rapisarda, et. al., (1992) have studied the analgesic and anti-inflammatory activities of the leaves extracts of the plants Cordia francisci, C. martinicensis, C. myxa, C. serratifolia and C. ulmifolia. Of these significant activities was observed with the extract of C. francisci.

Kaempferol-3-O-{alpha-L-rhamnopyranosyl (1-6)-beta-D-glucopyranoside} and Kaempferol 3-O-{beta-D-glucopyranoside} were isolated from the leaves of Hedyosmum bonplandianum which is used in Columbia folk medicine as an analgesic (Cardenas, et. al., 1993). The n-butanol extract and the glycosyl flavonoids isolated exhibited significant analgesic activity in mice.

Miguel, et.al., (1996) isolated furosin and geraniin from the ethanol extract of the leaves and stems of Phyllanthus sellowianus (Euphorbiaceae). Both the constituents exhibited significant and dose related anti-nociceptive properties against acetic acid induced writhing in mice. They were about 6 fold more potent as analgesics than aspirin and acetaminophen respectively.

Many investigators have studied the analgesic activity of the medicinal plants in different experimental models. The details are as under, Mentha villosa (Almeida, et. al., 1996), Caesalpinia ferrea (Carvalho, et. al., 1996), Clinacanthus nutans Lindau (Satayavivad, et. al., 1996), Ochna obtusata (Sivaprakasam, et. al., 1996), Psidium guajava (Kulkarni, et. al., 1999), Melia
review of Literature


Kavimani, et. al., (2000) tested hispidulin (6-methoxy-5,7,4'-trihydroxy flavone) isolated from the flowers of Helichrysum bracteatum for the analgesic and anti-inflammatory activities. The constituent inhibited the rat hind paw edema by 50% when compared to diclofenac sodium. It also exhibited analgesic activity when tested by using hot plate and tail clip method.

Almeida, et. al., (2000) isolated dioclenol and dioflorin from the plant Dioeclea grandiflora. Both the constituents were found to be effective in the
acetic acid induced writhing and tail immersion tests in dose of 10 mg/kg i.p. The observations suggested that dioflorin and dioclenol possess central antinociceptive activity.

Amabcoku, et. al., (2001) investigated the water extract of Dodonaea angustifolia L. and Salvia africana-lutea L. for analgesic and anti-pyretic activities using acetic acid writhing, hot plate tests and lipopolysaccharide induced pyrexia test in mice and rats respectively. The extracts of both the plants significantly inhibited acetic acid induced writhing and delayed the reaction time of mice to thermal stimulation. Both the extract significantly reduced fever induced by lipopolysaccharide.

Muruganandan, et. al., (2001) have screened the following medicinal plants for their analgesic and anti-inflammatory activities. 70 % ethanol extracts (300mg/kg p.o.) Delonix regia (bark & flowers), Pongamia pinnata (seeds), Psidium gaujawa (leaves) and Aegle marmelos (bark) exhibited significant anti-inflammatory activity in rats. However, Butea frondosa (flowers), leaves of Pinus longifolia, Eugenia jambolana and Aegle marmelos did not exhibit significant activity. Pongamia pinnosa (seeds) and Delonix regia (bark % flowers) also exhibited significant analgesic activity.

Gonzalez, et. al., (2001) have reported the analgesic and anti-ulcerogenic effects of Maytenus aquifolium, Sorocea bomplandii and Zolernia ilicifolia against acetic acid induced writhing, tail flick tests and ethanol induced ulcers.
Ahmed, et. al., (2001) has evaluated the effect of sesquiterpene dilactone from Mikania cordata for analgesic activity. Deoxymikanolide (1,10-epoxy-4,11(13)-germacradi-ene 12,8,15,6-diolide), was isolated from the whole plant of Mikania cordata. The crude extract of M. cordata (1and 3g/kg, p.o.) and doxymikanolide (10mg/kg, p.o.) significantly inhibited acetic acid induced writhing in mice.

The petroleum ether and alcohol extracts of rhizome of Acorus calamus and Curcuma amada were screened for anti-inflammatory, analgesic and antipyretic activity in albino rats and mice (Derle Deelip, et. al., 2001). Both the extracts of C. amada showed inhibition of paw edema in the dose of 20 to 40 mg/kg while the extracts of A. calamus showed anti-inflammatory activity at the dose of 5 to 15 mg/kg. Both the drugs did not show any analgesic and antipyretic activities.

Okuyama et. al., (2001) have identified analgesic components of Saposhnikovia root (Saposhnikovia divaricata). Two new components divaricatol and hamaudol were found to be most potent analgesic and inhibited writhing at an oral dose of 1mg/kg in mice.

Centipedic acid and 12-acetoxy hawtriwaic acid isolated from flower buds of Egeletes viscosa (Asteraceae) were assayed in animal models of nociception and gastric ulcer (Guedes, et. al., 2002). Both diterpenes (25 and 50mg/kg) were found to exert potent antinociceptive action. However, these
compounds were found to ineffective against thermal nociception in the hotplate method. These diterpenes were also found to be effective in reducing the severity of ethanol induced gastric lesions in rats.

Bocheva, et. al., (2003) have reported the anti-inflammatory and analgesic activities of *Carthamus lanatus* aerial parts. Fractions of methanol, dichloromethane, water extracts and volatiles of *C. lanatus* aerial parts showed significant anti-inflammatory activity on oral administration in the dose of 2 mg/kg. On the contrary, only the water fraction of methanol extract possessed a significant analgesic activity.

Acosta, et. al., (2003) investigated the analgesic activity of aqueous extract of dried leaves of *Capraria biflora*. The extract (50-200 mg/kg. i.p.) produced moderate inhibition of acetic acid writhing in mice and better analgesic effect was observed on hot plate test.

Chakraborty, et.al., (2003) have evaluated the anti inflammatory and analgesic activities of the aqueous extract of *Spilanthes acmella* in experimental animal models. The extract showed anti-inflammatory activity in the doses of 100, 200 and 400 mg/kg. in the same dose levels the percentage protection against acetic acid writhing was 46.9, 51.0 and 65.6 respectively. In the tail-flick model, the extract in the above doses increased the pain threshold significantly after 30 minutes, 1,2, and 4 hour of administration. The results indicated that the plant has significant anti-inflammatory and analgesic properties.
The stem bark of the plant Mitragyna ciliata was extracted with hexane followed by methanol (Dongmo, et. al., 2003). The methanol extract inhibited carrageenin induced paw edema by 70% in the dose of 50 mg/kg after one hour. The extract significantly decreased sensitivity to pain in the dose of 50mg/kg. Chemical analysis of the extract showed the presence of alkaloids and kempferol derivative, which may be responsible for the anti-inflammatory properties.

Thangathirupathi, et. al., (2003) screened the methanolic and aqueous extract of the leaves of Coccina grandis (Linn) voigt for analgesic, anti pyretic and anti inflammatory activities. Analgesic activity was compared with pentazocine for narcotic type by tail immersion method and diclofenac sodium for non-narcotic type by writhing method. The anti pyretic activity was compared with paracetamol in yeast induced pyrexia in albino rats. The anti-inflammatory activity against Carrageenin induced paw edema in albino rats was compared with diclofenac sodium. In all the methods, both the extracts showed good results with statistical significance.

Anti-inflammatory, analgesic and anti-pyretic activities of the methanol extract of Clitoria ternatea root has been reported by Parimala Devi, et. al., in the year 2003. Oral administration of the extract inhibited the carrageenin induced rat paw edema in rats. Moreover, the extract exhibited a significant anti-pyretic activity in yeast-induced pyrexia in rats. In the acetic
acid induced writhing response, the extract markedly reduced the number of writhings at doses of 200 and 400 mg/kg (p.o.) in mice.

Costa, et. al., (2003) has assessed the anti inflammatory and analgesic activity of the crude extract of dried leaves of *Bouchea fluminensis*. The extract inhibited the carrageenin induced paw edema in the doses of 1 to 30 mg/kg. At the same doses, it also exhibited analgesic effect in acetic acid induced and hot plate models in mice.

Chaudhary, et. al., (2004) have studied the anti-inflammatory and analgesic activity of the various extracts of roots of *Capparis zeylanica*. The petroleum ether methanolic and water extracts were effective against thermal models and also inhibited carrageenin induced rat paw edema.

Anti inflammatory and analgesic activity of the topical preparation of *Glaucium grandiflorum* methanol extract were studied by Morteza-Semnani, et. al., (2004) using carrageenan induced edema and formalin test. The extract showed better anti- inflammatory effect at the dose of 5% w/w at 3 hour after Carrageenan injection. Topical preparation containing the methanol extract showed analgesic effect in the concentration more than 4% w/w.

**Epilepsy**

The word epilepsy is derived from the Greek verb epilamvanein ("to be seized" or "to be attacked" indicating that the person having a seizure is
Epilepsy affects about 45 million people worldwide (Madhusudhanan, 2000). The incidence of epilepsy is highest among children of below 7 years of age, which is about 0.8%. It is less common in the middle aged people and again higher in individuals above 55 years of age. In India the reported prevalence of epilepsy is about 5.5 to 7.8 per 1000 people, which is about 1/8\textsuperscript{th} of the world population (Nag Devika, 2000).

Epilepsy occurs due to abnormal activity of brain tissue. It may be idiopathic (primary) or symptomatic (secondary) epilepsy. The symptomatic or secondary epilepsy may be caused by several factors such as: (a) birth trauma and head injury, (b) toxicity including drug intoxication, lead poisoning, consumption of alcohol and psychotropic drugs, (c) degenerative cerebral diseases, (d) metabolic disorders such as hypercalcaemia, hypoglycemia and uremia, (e) CNS infections and (f) cerebrovascular diseases (e.g. infarction). In susceptible individuals, even physical stimuli such as sound, touch or stroboscopic light may precipitate seizures.

The commonly occurring types of epileptic seizures are

- Grand mal or major epilepsy.
- Petit-mal or miner epilepsy.
- Psychomotor epilepsy.
- Status epilepticus.
Drug treatment for epilepsy

Commonly employed drugs in the treatment of epilepsy are those effective in petit mal epilepsy like ethosuximde, sodium valproate, clonazepam, acetazolamide and those effective in all other types phenytoin sodium, phenobarbitone, primidone, carbamazepine, diazepam etc.

Limitations with conventional anti-epileptic drugs, highlighted the need for developing newer agents for epilepsies and therefore several new anti-epileptic drugs like gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate and vigabatrin have been invented. Many other drugs are in various stages of development eg. Remacemide, losigamone, flunarizine, loreclezole etc. (Gupta, et. al., 2000).

There are many medicinal plants, which are claimed to be useful in the treatment of epilepsy and have the mention in the Indian traditional system of medicine. But there are no reports of the scientific basis for this. Hence it becomes essential to evaluate the antiepileptic potential of these plants.

The aqueous and alcoholic extracts of the rhizomes of Acorus calamus reduced the severity of maximum electric shock induced seizures in rats and the extracts significantly increased the pentylenetetrazole induced seizure latency (Martis, et. al., 1991). The extracts did not exhibit any sedative effects, but potentiated the barbiturate-induced hypnosis.
Akah, *et. al.*, (1993) have screened eleven Nigerian plants, *Alstonia boonei, Boerhavia diffusa, Calliandra porloricensis, Cleome cileata, Cynodon dactylon, Emilia coccinea, Holarrhena floribunda, Hoslundia opposita, Hyptis suaveolens, Newboldia laevis* and *Tetrapleura tetraptera* for their anti-convulsant activity. All the plant extracts exhibited anti-convulsant activity and this activity was linked to their ability to depress central nervous system.

Neutral fraction from *Nerium oleander* leaves caused sedation in low doses in mice, while at high doses it produced hypnosis (Haque, *et. al.*, 1993). In addition marked reduction in locomotor activity was observed. It also blocked the convulsions induced by the GABA antagonist, picrotoxin.

The protective effect of various doses of the methanolic extract of *Withania somnifera* against pentylenetetrazole-induced convulsions in mice has been reported by Kulkarni, *et. al.*, (1993). The methanolic extract in lower dose (30 and 100 mg/kg) produced delay in extensor phase while in higher dose (200 mg/kg) completely abolished the tonic extensor phase. The extract also significantly reduced the mortality rate in higher dose only.

Tortoriello, *et. al.*, (1996) evaluated the CNS effects of the methanolic extract of *Baccharis serraefolia*. The extract showed dose dependent spasmolytic activity. It also significantly delayed the onset of tonic seizures induced by strychnine and pentylenetetrazole and diminished the death rate. It produced Potentiation of the hypnotic effect of pentobarbital.
Various authors have reported the anti-convulsant activity of the different plants against maximal electroshock and strychnine induced convulsions in rats as mentioned under.


Ha, et. al., (2000) isolated 4-Hydroxybenzaldehyde from *Gastrodia elata* B 1 and found to be active in the antioxidation and GABA ergic neuromodulation of the rat brain. Ether fraction of *G. elata* methanol extract significantly inhibited the severity induced by pentylentetrazole treatment. 4-hydroxybenzaldehyde showed an inhibitory effect on the GABA transaminase. It also reduced the brain lipid peroxidation. The antioxidation and GABA ergic neuromodulation of 4-Hydroxybenzaldehyde partially contribute to an anti-epileptic and anti-convulsant activity of *G. elata* B1.
Sukma, **et. al.**, (2002) have studied the pharmacological profile of barakol, a major constituent of *Cassia siamia* in rodents. Barakol reduced the spontaneous motor activity, prolonged the thiopental sleeping time, indicating a sedative effect. Only a high dose of barakol (100 mg/kg i.p.) prolonged the latency of clonic convulsions induced by picrotoxin.

Zetola, **et. al.**, (2002) studied the CNS effects of liquid and spray dried extracts of leaves from *Lippia alba* (Verbenaceae). The extract in 80 % ethanol (200 mg/kg oral) exhibited sedative effect indicated by the prolongation of barbiturate sleeping time. It also protected mice against pentylenetetrazole induced seizures. The extract was found to contain a flavonoid.

Sayyah, **et. al.**, (2002) have studied the anti-convulsant activity of the seed acetone extract of *Ferula gummosa* against seizures induced by pentylenetetrazole and electroconvulsive shock in mice. The extract protected mice against maximal electroshock (200 mg/kg) and especially pentylenetetrazole (55 mg/kg).

Monforte, **et. al.**, (2002) has reported the anti-convulsant and sedative activity of the extract of the stem bark of *Salvadora percica*. The extract potentiated pentobarbital activity and extended sleeping time. In addition, it showed protection against pentylenetetrazole induced convulsion by increasing the latency period and diminishing the death rate.
The decoction of *Mimosa pudica* leaves given intraperitoneally at dose of 1000-4000 mg/kg protected mice against pentylenetetrazole and strychnine induced seizures (Ngo Bum, *et. al.*, 2004). *M. pudica* had no effect against picrotoxin-induced seizures.

**Insomnia**

Physiologically, sleep is regarded as absence of wakefulness. Every one needs sleep. It is believed that restoration of natural balance among the neuronal centres in the brain take place chiefly during sleep, and the association between sleep and growth in the early years of life is generally accepted. Based on electrophysiological studies, sleep has been classified into two types: non-rapid eye movement (NREM) and rapid eye movement sleep (REM).

While falling asleep, one passes sequentially through stages 1, 2, 3 and 4 of NREM sleep. After about 90 minutes of NREM sleep, REM sleep occurs and lasts for 5-30 minutes. This NREM-REM cycle repeats itself throughout the night, with progressive lengthening of the REM sleep bouts until one awakens from REM (not NREM) sleep in the morning. NREM sleep is very peaceful with preponderance of the parasympathetic system activity and diminution of the metabolic rate, heart rate, cardiac output and peripheral vascular resistance. Dreaming is frequent and the dreams are rarely recalled on awakening. The sleep is not so restful. 75% of the dreams occur in this type of sleep. Increased heart rate, blood pressure cardiac output and metabolic rate...
accompany these dreams. There is no eyeball movement during NREM sleep, where as the eyeballs move rapidly and jerkily during REM sleep. Growth hormone secretion occurs during NREM sleep but none during REM sleep (Guyton, 1986).

REM sleep normally occupies about 25% of the sleeping time. However, various diseases alter this pattern, sleep disorders and drugs. A normal person spends approximately one-third of his life in sleep. Adequate sleep is a necessity of life. In practice, significant numbers of individuals complain of lack of sleep, ‘insomnia’.

People are either ‘good sleepers’ or ‘poor sleepers’. The latter, on the whole, take longer to fall asleep, sleep less, awaken more and have higher physiological arousal than good sleepers. Insomnia is said to be present when an individual complains of inability to fall asleep, of reduction in the total sleep period or of sleep that does not refresh. Transient and short-term insomnia (less than 3 weeks) may occur in the absence of disease and is then due to stresses caused by environmental factors, job requirements etc. Other than this insomnia may be due to physical discomfort such as pain, fever, anxiety etc. Chronic insomnia lasts for at least 3 weeks and needs detailed evaluation. It is associated with increased risk of automobile accidents, increased alcohol consumption and daytime sleepiness.

Drugs such as, ephedrine, chloroquine, metronidazole, diuretics, systemic glucocorticoids etc. may cause insomnia and in the elderly age-related
changes in the sleep cycles, anxiety and loss of family support. In such cases only improvement to some extent can be achieved rather than total relief of insomnia.

A hypnotic drug is one, which produces sleep resembling natural sleep. Hypnotics and sedatives both induce depression of the central nervous system, the difference being mainly quantitative. The requirements of ideal hypnotics are:

- the drug should be effective orally quickly for a longer time,
- the sleep induced should resemble natural sleep,
- the drug should be non-irritant, non-toxic and should not cause hangover,
- tolerance, habituation and dependence should not develop,
- it should be cheap.

There is no such agent available. However barbiturates and benzodiazepines are the drugs in common use. They also have many side effects.

The various plants can produce CNS depression. The CNS depressant may be useful in the treatment of many conditions like, insomnia, aggressiveness etc. The CNS depressants reduce the locomotor activity, aggressiveness and act as additive with other depressants.
Lanthers, *et al.*, (1990), have studied the behavioral effects of *Euphorbia hirta* L. The aqueous extract of *Euphorbia hirta* exerted sedative effect in the dose of 100 mg/kg in rats. It also exhibited anxiolytic properties.

An aqueous extract of seed of *Myristica argentea* depressed the motor activity and caffeine induced excitement. It also prolonged pentobarbitone induced sleep in mice (Takahashi, *et al.*, 1991).

The sedative effects of the alcohol extracts of flowers of *Chrysanthemum indicum* and *Imperata cylindrica* were tested in mice (Albania-Aquitania, *et al.*, 1992). The extracts of *I. cylindrica* were more effective than *C. indicum*. The potency was comparable to that of pentobarbitone sodium but had shorter duration of action.

Pieretti, *et al.*, (1992) investigated a purified extract of *Orobanche hederae* composed of two phenylpropanoid glycoside, verbascoside and orobanchoside for its pharmacological profile. The mixture significantly prolonged the sleep induced by pentobarbital and also reduced locomotor activity in mice.

Xanthotoxol, 8-hydroxypsoralen, exhibited dose-graded (5-20 mg/kg oral) sedative activity in mice, rats, cats and dogs (Sethi, *et al.*, 1992). In mice it also reduced locomotor activity dose dependently it was also tested and found to be free of teratogenic effects.
Dried extracts of *Valerian officinalis* and *Melissa officinalis* were found to exert influence on the CNS of rats (Machoy-Mokarzynska, *et al.*, 1992). *V. officinalis* extract exerted CNS inhibitory effect while *Melissa* extract evoked the anti aggressive activity. Both the extracts did not disturb the motor coordination.

Okugawa, *et al.*, (1993) evaluated the central effects of benzene extracts of *Aquilaria malaccensis* in mice. The extract showed reducing effect in spontaneous motility, a prolonging effect on hexobarbitone induced sleeping time, a hypothermic effect and a suppressive effect on acetic acid writhing by oral administration.

Achliya, et. al., (2003) has observed the CNS effects of Bramhi Ghrita, a polyherbal formulation with cow’s ghee. The formulation (500 mg/kg oral) exhibited reduced alertness, spontaneous motor activity and reactivity in mice. Amphetamine induced locomotion was inhibited and pentobarbitone sleeping time was potentiated by Bramhi Ghrita.

The LD50 value of the methanolic extract of *Abies webbiana* was 986 mg/kg. (Jha, et. al., 2003). Alone the extract failed to produce any effects on CNS. However, significant synergistic activity was exhibited in combination therapy with pentobarbitone sodium and diazepam.

The methanol extract of leaves of *Passiflora incarnata* was evaluated for various CNS effects in experimental animals (Dhawan, et. al., 2003). The extract (200 mg/kg) exhibited significant sedative, anti-convulsant, CNS depressant, analgesic and anti-inflammatory activities.

The petroleum ether and benzene extracts of *Dalbergia malabarica* were tested for the CNS depressant activity by using locomotor activity and pentobarbitone sleeping time in Swiss albino mice (Nagarajan, et. al., 2003). The benzene extract showed better CNS depressant activity than petroleum ether extract.

The hexane extract of *Quassia amara* bark (i.p.), reduced carrageenin induced paw edema, showed antinociceptive activity on hot plate test and on
acetic acid induced writhing (Toma, et. al., 2003). It also showed sedative effects on pentobarbitone induced sleep and muscle relaxant property.

Chindo, et. al., (2003) have reported the CNS depressant activity of the methanolic extract of Ficus platyphylla. The extract significantly reduced the locomotor activity scores and prolonged pentobarbitone sleeping time in mice dose dependently.

The methanolic extract of the leaves of Mallotus peltatus (Geist) Muell Arg. var acuminatus (Euphorbiaceae) showed significant reduction in SMA, muscle relaxant and potentiation of phenobarbitone sodium induced sleeping time in the dose of 200-300 mg/kg p.o. (Chattopadhyay, et. al., 2003).

Diospyros cordifolia

Singh, et. al., (1971) has studied the effect of alcoholic extract of the plant Diospyros cordifolia and found to have spasmolytic activity. In addition the extract also produced bradycardia and hypotension.

Kohli, et. al., (1972) evaluated the different fractions of the alcoholic extract of the plant Diospyros cordifolia and has reported to have anti-inflammatory and anti-pyretic activities.

The researchers have isolated different chemical constituents from various species and screened for their pharmacological activities. The details of these investigations are as mentioned under.
Recio, *et. al.*, (1995) have reported the anti-inflammatory activity of betulin, betulinic acid and ursolic acid.

Misra, *et. al.*, (1989) have evaluated the anti-tumor activity of betulin, betulinic acid and lupeol. All the three constituents were found to be active against the Walker-Carcinoma-256 (intramuscular) tumor system.


Cordel, (1995) observed that betulinic acid was found to possess highly selective activity against human melanoma *in vitro* and *in vivo*.

Ohigashi, *et. al.*, (1986) showed that ursolic acid inhibited 12-o-teradecanoyl-phorbal-13-acetate induced Epstein-Barr virus activation.

Singh, *et. al.*, (1994) showed that ursolic acid has potent inhibitory activity against HIV-1 protease.


Gupta, *et.al.*, 1981 observed that ursolic acid inhibited stress induced ulcers in rats and also decreased incidence of gastric ulceration induced by pyloric ligation.
Ursolic acid increased the blood sugar concentration, glycogen and ATP contents in muscles, heart and uterus on intragastric administration into rats (Golovina, et. al., 1976).

Hazra, et. al., (1984) observed that diospyrin inhibited the in vitro growth of Ehrlich Ascitis Carcinoma (EAC), in Swiss albino mice.

In the year (1987) Hazra, et. al., reported that diospyrin showed in vitro activity against the protozoan Leishmania donovani.

**Pterocarpus marsupium**

The effect of administration of different doses of *Pterocarpus santalinus* L. bark extracts in normal and diabetic rats, on blood glucose levels was evaluated by Kameswara Rao, et. al., (2001). Among the three fractions (aqueous, ethanol and hexane), ethanol fraction at the dose of 0.25g/kg showed maximum antihyperglycemic activity. The same dose did not cause any hypoglycemic activity in normal rats. The results were compared with that of glibenclamide.

The extracts of *Pterocarpus osun* elder stems showed significant antibacterial activity (Ebi, et. al., 2000).

The leaves, root and stem barks of *Pterocarpus indicus* were successively partitioned with petrol, dichloromethane, ethyl acetate, butanol and methanol (Khan, et. al., 2003). All the fractions exhibited a wide spectrum
of antibacterial activity. The activity was more pronounced in the butanol and methanol fractions. None were active against moulds.

Serum lipid levels in rats with hyperlipidemia induced by diet as well as by Triton were determined after oral administration of ethyl acetate extract of Pterocarpus marsupium heartwood. (Jahromi, et. al., 1993). Administration of ethyl acetate extract for 14 consecutive days produced a significant reduction of serum triglyceride, total cholesterol, LDL- and VLDL-cholesterol levels without any significant effect on the level of HDL-cholesterol. Hypoglycemic activity of the extract of Pterocarpus marsupium wood has been reported by Ahmed, et. al., in the year 1991.

Grover, et. al., (2002) have studied the effect of feeding aqueous extract of Pterocarpus marsupium on glycogen content of tissues and the key enzymes of carbohydrate metabolism. The Indian traditional system of medicine mentioned in Ayurveda is Pterocarpus marsupium. The aqueous extract of P. marsupium (1g/kg p.o.) was assessed for its effect on glycogen levels of insulin dependent (skeletal muscle and liver), insulin-independent tissues (kidneys and brain) and enzymes such as glucokinase, hexokinase and phosphofructokinase. Administration of the extract of P. marsupium led to decrease in blood glucose level by 38 and 60 % on 15th and 30th day of the experiment.

The hypoglycemic effect of the aqueous extract of the bark of Pterocarpus marsupium (PM), alcoholic extract of seeds of Trigonella foenum-graecum (FG) and leaves of Ocimum sanctum (OS) was investigated (Vats, et. al., 1994).
al., 2002) in both normal and alloxan-induced diabetic rats. The aqueous extract of PM (1g/kg p.o. for 21 days) significantly lowered the blood glucose level in alloxan-induced diabetes in rats. Similarly, reduction was seen with alcoholic extract of FG in normal rats and in diabetic rats. OS also reduced the serum glucose levels in the models.

Literature survey revealed that, so far no investigations was carried out on the evaluation of the hepatoprotective, wound healing, antinociceptive, anti-convulsant and CNS depressant activities of the crude extracts of the stem bark of Diospyros cordifolia and Pterocarpus marsupium. Simultaneously no clinical studies have been conducted on the evaluation of the active constituents isolated from the stem bark of Diospyros cordifolia for these activities. So, in view of the high medicinal value of these two species, the present investigation was undertaken.