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2.1 Epidemiology and Statistics of Drug induced Liver Injury

Drug induced liver injury is the most commonly cited reason for withdrawal of drugs from the market [1]. The data from the centers for disease control and prevention in the U.S reported approximately 1600 new acute cases of liver failure annually, of which Paracetamol hepatotoxicity accounts for approximately 41% [2].

Hepatoprotection or anti-hepatotoxicity is the ability to prevent damage to the liver. An example of a hepatoprotective medicine is silymarin, derived from Milk thistle, which selectively inhibits leukotriene formation by Kupffer cells. Drug induced liver damage is the most commonly encountered clinical entity of which anti-tubercular drugs constitute the major cause of hepatotoxicity in India. Isoniazid, Rifampicin, Pyrazinamide and Ethambutol are the most commonly used combination for treatment of tuberculosis in which Isoniazid, Rifampicin and Pyrazinamide combination is most hepatotoxic [3]. The antitubercular drug induced hepatotoxicity is found to be mediated through oxidative stress and free radical damage to hepatocytes.

2.2 Liver diseases

I. Drug-induced liver diseases

Liver cells may become temporarily inflammed or permanently damaged by exposure to medications or drugs. Some medications or drugs cause liver injury in high doses while others may cause the damage even in the normal prescribed dosage.
II. Alcoholic liver diseases

Alcoholic liver disease is a term that encompasses the hepatic manifestations of alcohol over consumption, including fatty liver, alcoholic hepatitis, and chronic hepatitis with hepatic fibrosis or cirrhosis. It is the major cause of liver disease in Western countries. Steatosis (fatty liver) may develop in any individual who consumes a large quantity of alcoholic beverages over a long period of time. This process is transient and reversible.

III. Fatty liver disease

Fatty liver is the name given to a condition in which there are too much fat in liver. Today it is one of the most common forms of liver disease and is known to lead to advanced conditions. The effects of fat in the liver over a long period may lead to inflammation causing swelling and tenderness (hepatitis) and then to scarring (fibrosis). This condition can be caused by excess alcohol consumption and is called alcoholic liver disease or it can have other causes, for example diabetes, known as fatty liver disease.

IV. Liver cancer

Liver cancer is primary malignant tumours of the liver. Benign tumours and tumours resulting from spread of cancer from other organs of the body also occur in the liver.

V. Other chronic liver disease

Deaths from conditions in this group are dominated by fibrosis and cirrhosis of the liver. Cirrhosis is the result of long-term, continuous damage to the liver and may be due to many different causes. The damage leads to scarring, known as fibrosis. Irregular bumps (nodules) replace the smooth liver
tissue and the liver becomes harder. Together, the scarring and the nodules are called cirrhosis.

VI. Hepatic pancreatic biliary (HPB) pancreatitis

This category is defined quite broadly; as alcohol is a major cause of pancreatitis, a proportion of patients with HPB will also have liver disease. Also, it can be difficult to discern whether jaundice and abnormal liver function tests have their cause in the liver, biliary tract or pancreas.

VII. Viral liver disease

Viral hepatitis: Hepatic inflammation caused by a virus. Specific hepatitis viruses have been labelled A, B, C, D, and E. Some other viruses, such as the Epstein-Barr virus and cytomegalovirus, can also cause hepatitis, but the liver is not their primary target.

It includes both acute and chronic hepatitis:

**Hepatitis A** is the most common viral hepatitis. This virus produces acute, but never chronic disease, so the individual infected may get sick for a few days or weeks, but once improvement occurs, the infection is over, and progressive destruction of the liver does not take place.

**Hepatitis B** gets better spontaneously in over 95 percent of cases. Only a few individuals with this infection are likely to develop chronic disease. An important exception to this rule applies to children. The younger the child at the time of infection, the more likely the infection will become chronic. For example, when the infection is acquired in infancy, more than 90 percent of cases become chronic. The majority of hepatitis B infections in this country
Chapter 2

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occur in late adolescents and adults. However, worldwide, infants are most likely to get hepatitis B infections.

**Hepatitis C** occurs primarily in late adolescents and in adults. Unlike hepatitis B, this infection ordinarily escapes the body’s immune system and so in most cases does not resolve itself. In fact, up to 85 percent of people who get infected with hepatitis C will retain evidence of infection indefinitely.

**Hepatitis D** is a strange virus. It occurs only in conjunction with hepatitis B, where it seems to function as a parasite. It may turn a smoldering but well-tolerated B infection into a more aggressive and destructive disease. The other three hepatitis viruses E, F, and G are not common among individuals residing in the United States.

**Table 2.1:** Commonly–reported drugs associated with drug induced-liver injuries.

<table>
<thead>
<tr>
<th>Drug category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-tubercular</td>
<td>Isoniazid, Rifampicin, Pyrazinamide</td>
</tr>
<tr>
<td>Non-Steroidal</td>
<td>Diclofenac, Ibuprofen, Naproxen</td>
</tr>
<tr>
<td>Anti-Inflammatory</td>
<td></td>
</tr>
<tr>
<td>Anti-pyretic</td>
<td>Paracetamol</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Amoxicillin+Clavulanate, Flucloxacin, Erythromycin, Ciprofloxacin</td>
</tr>
<tr>
<td>Immunosuppressant</td>
<td>Azathioprine, Cyclophosphamide</td>
</tr>
<tr>
<td>Anti-Epileptics</td>
<td>Phenytoin, Carbamazepine, Valproic Acid</td>
</tr>
<tr>
<td>Psychiatric Drugs</td>
<td>Chlorpromazine, Paroxetine</td>
</tr>
</tbody>
</table>
Table 2.2: Some Drugs reported to have hepatoprotective action in animals.

<table>
<thead>
<tr>
<th>Herb’s Scientific Name(s)</th>
<th>Effective dosage</th>
<th>Animal model</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Chamomile capitula</em></td>
<td>Ethanolic extract 400mg/kg</td>
<td>Paracetamol</td>
<td>Gupta, et al., 2006.[4]</td>
</tr>
<tr>
<td><em>Flacoourtia indica</em></td>
<td>Ethanolic extract 500mg/kg</td>
<td>Paracetamol</td>
<td>Nazneen <em>et al.</em>, 2009.[5]</td>
</tr>
<tr>
<td><em>Sargassum polycystum</em></td>
<td>Ethanol extract 125mg/kg</td>
<td>D-galactosamine</td>
<td>Meena <em>et al.</em>, 2008.[6]</td>
</tr>
<tr>
<td><em>Silybum marianum</em></td>
<td>Polyphenolic extract 25mg/kg</td>
<td>Thiocetamide</td>
<td>Madani <em>et al.</em>, 2008.[7]</td>
</tr>
<tr>
<td><em>Coccinia grandis</em></td>
<td>Alcoholic extracts 250 mg/kg</td>
<td>CCl₄</td>
<td>Vadivu <em>et al.</em>, 2008.[8]</td>
</tr>
<tr>
<td><em>Wedelia calendulacea</em></td>
<td>Ethanolic extracts 250 mg/kg</td>
<td>CCl₄</td>
<td>Murugaian <em>et al.</em>, 2008.[9]</td>
</tr>
<tr>
<td><em>Cassia roxburghii</em></td>
<td>Methanolic extract 250 mg/kg &amp; 500mg/kg</td>
<td>CCl₄</td>
<td>Arul <em>et al.</em>, 2009.[10]</td>
</tr>
<tr>
<td><em>Orthosiphon staminens</em></td>
<td>Methanol extract 200mg/kg</td>
<td>Paracetamol</td>
<td>Maheswari <em>et al.</em>, 2008[11]</td>
</tr>
<tr>
<td><strong>Ficus caria</strong></td>
<td>Methanolic extracts 500mg/kg</td>
<td>CCl$_4$</td>
<td>Krishna <em>et al.</em>, 2007. [12]</td>
</tr>
<tr>
<td>----------------</td>
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<td>-------------------------------</td>
</tr>
<tr>
<td><strong>Lepidium sativum</strong></td>
<td>Methanolic extract 200 &amp; 400mg/kg</td>
<td>CCl$_4$</td>
<td>Afat <em>et al.</em>, 2008. [13]</td>
</tr>
<tr>
<td><strong>Ziziphus oenoplia</strong></td>
<td>Ethanolic extract 150 and 300 mg/kg</td>
<td>INH+RIF</td>
<td>Rao <em>et al.</em>, 2012 [14]</td>
</tr>
<tr>
<td><strong>Hibiscus vitifolius</strong></td>
<td>Ethanolic extract 400mg/kg</td>
<td>INH+RIF+P YZ</td>
<td>Anbu <em>et al.</em>, 2012. [15]</td>
</tr>
<tr>
<td><strong>Bombax ceiba</strong></td>
<td>Methanolic extract 150, 300 and 450 mg/kg</td>
<td>INH+RIF</td>
<td>Ravi <em>et al.</em>, 2010 [16]</td>
</tr>
<tr>
<td><strong>Padina boergesenii</strong></td>
<td>Diethyl ether extracts 150 mg/kg</td>
<td>CCl$_4$</td>
<td>Rajamani <em>et al.</em>, 2010[17]</td>
</tr>
<tr>
<td><strong>Mentha arvensis</strong></td>
<td>Ethanolic extract 375 mg/kg</td>
<td>CCl$_4$</td>
<td>Kalpana <em>et al.</em>, 2012[18]</td>
</tr>
<tr>
<td><strong>Amorphophallus paeoniifolius</strong></td>
<td>Methanolic extract (300 mg/kg</td>
<td>Paracetamol</td>
<td>Pramod <em>et al.</em>, 2012[19]</td>
</tr>
</tbody>
</table>
### Table 2.1: Medicinal Plants and Their Extracts

<table>
<thead>
<tr>
<th>Plant</th>
<th>Description</th>
<th>Treatment</th>
<th>Adjuvant</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pergularia daemia</em></td>
<td>Ethanolic extract 200 mg/kg</td>
<td>CCl₄</td>
<td></td>
<td>Suresh et al., 2006[20]</td>
</tr>
<tr>
<td><em>Annona squamosa</em></td>
<td>Ethanolic and aqueous extract of 350 mg/kg and 300 mg/kg</td>
<td>INH+RIF</td>
<td></td>
<td>Saleem et al., 2008[21]</td>
</tr>
</tbody>
</table>

#### 2.3. Medicinal plants under present investigation

I. *Adenanthera pavonina*

II. *Erythrina indica*
1. *Adenanthera pavonina*

2.4 Introduction

*Adenanthera pavonina* belongs to the family Fabaceae [22]. The scientific name is derived from a combination of two Greek words *aden*, "a gland," and *anthera*, "anther". It is commonly known as Red wood. The main important constituents are flavonoid compounds [23]. It is used as an antiseptic paste and to treat boils and inflammations [24].

- **Vernacular names**
  - English : Red wood
  - Hindi : Ranjana
  - Tamil : Yanai Kuntamani

![Fig. 2.1 Exomorphic features of the leaves](image-url)
Distribution

In India it is found in sub Himalayan tract, ascending upto an altitude of 1,200 meters in Sikkim, West Bengal Assam, Meghalaya, Gujarat, Maharashtra, South India and in Andamans. It is also found in Peurto Rico, Cuba, Jamaica, Trinidad, Venezuela, Brazil, Costa Rica, Honduras and Southern Florida. [25].

Description [25-26]

Tree: A medium to large-sized deciduous tree, *A.pavonina* ranges in height from 6-15 m. It is generally erect, having dark brown to greyish bark, and a spreading crown.

Seeds: The hard-coated seeds are lens-shaped, vivid scarlet in color, and adhere to the pods. The seed coat is smooth, shiny, bony and very hard and generally has no fracture lines.

Pods: The leathery pods are curve and twist upon dehiscence to reveal 8-12 showy seeds.

Leaves: The leaves are bipinamate. They are dark green in upper surface and blue green in lower surface. They become yellow with ageing.

Bark: The bark is dark brown or grayish brown on outer surface and grayish white in inner surface. It is rough on old trees with longitudinal fissures.

Flowers: The small, yellowish flower grows in dense drooping rat-tail flower heads. They are small, creamy-yellow in color, and fragrant. Each flower is star-shaped with five petals.

Wood: The wood is red in colour and extremely hard. It is durable and used for building purpose. It is also used in making furniture.
Traditional uses

Wood is used as an antiseptic paste; seeds are used to treat boils and inflammations, fever and giddiness act as antiemetic,. The seed has been used in the treatment of disease like cholera and general paralysis. Decoction of the seeds is used in pulmonary infections and externally applied in chronic ophthalmia [27]. Leaves are used to treat gout and rheumatism, and bark is useful in colonorrhea, haematuria, and ulcers.

2.4.1 Phytochemical Review

Seeds: It contains amino acid viz. γ-methelene glutamic acid γ-methelene glutamine & traces of γ-ethylendine glutamic acid. The kernels contain pale yellow fat. The fatty acid presents are palmitic; stearic, archidic; lignoceric, eucosenoic. The kernels also contain stigmasterol and its glycoside, dulcitol and a polysaccharide. The amino acid presents are arginine, cystine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, tyrosine and valine [28-29].

Root: Oleanolic and echinocystic acid are isolated from roots [30].

Leaves: The leaves contain octacosanol, dulcitol, glucosides of β-sitosterol and stigmasterol. [28].

Bark: The bark contains saponin having glucose as the sugar moiety and oleanic acid and echinocystic acids as sapogenins [31].

Wood: The wood contains flavonoids- robenetin, chalcone, butein and the flavones [30].

Chemical composition and nutritive value study of the seed oil of *A. pavonina* L. (Fabaceae) growing in Democratic Republic of Congo [32].
Pavonin (active constituent): a new five-membered lactone from *Adenanthera pavonina* Linn. Pavonina with an exo-cyclic double bond has been isolated from the methanol soluble part of *Adenanthera pavonina*. The structure of pavonin has been established with the aid of spectroscopic techniques [33].

**Physico-chemical characterization of seed oil and nutrient assessment of *Adenanthera pavonina*, an underutilized tropical legume.**

The seed of *Adenanthera pavonina* contains appreciable amounts of proteins, crude fat and minerals. Total sugar low while starch constitutes the major carbohydrates. It concluded that *A. pavonina* seeds represent a potential source of oil and protein that could alleviate shortages of oils [34].

**Chemical constituents of leaves of *Adenanthera pavonina***

The dried powdered leaf of *A.pavonina* has been successively extracted with petroleum ether, chloroform and methanol. From the chloroform extract, the hydrocarbon nonacosane & hentriacontane, the triterpenoid squalene, and the long chain fattyacid ester palmitate have been isolated. The methanolic extract yields β-sitosterol, β-sitosterol-3β-D-glucoside [35].

**Stigmasterol glucoside a constituent of *Adenanthera pavonina* seed and leaf.**

Seed contains stigmasterol glucoside, dulcitol, polysaccharide and free stigmasterol from the seeds and octacosanol, dulcitol, glucosides of β-sitosterol and stigmasterol from the leaves have been isolated and characterised [28].
2.4.2 Pharmacological review of *A. pavonina*

➢ **Blood pressure lowering effect of *Adenanthera pavonina* seed extract on normotensive rats**

The effect of *A. pavonina* seed extract on the blood pressure of normotensive rats has been evaluated. The study shows that *A. pavonina* seed extract have the potential to cause a blood pressure lowering effect. The serum biochemistry changes suggest that the extract has a tonic effect on the kidneys and liver. [36].

➢ **Antifungal, Antioxidant and Cytotoxic Activity of *Adenanthera pavonina***

*Adenanthera pavonina* are widely used in various Ayurvedic herbal preparations for treating diseases such as diarrhoea, asthma, ulcers, itchy skin, scales, sores, rheumatism, cold and cough and boils, inflammations and gout (*A. pavonina*). Extracts of plants exhibit antibacterial activity against methicillin-sensitive and resistant strains of *Staphylococcus aureus, Enterococcus faecalis* and *Pseudomonas aeruginosa* [37].

➢ **Anti-inflammatory activity**

Anti-inflammatory and analgesic activity of seed extract of *Adenanthera pavonina* has been evaluated by Olajide et al, (2004). The extract produces statistically significant inhibition of the carrageenan-induced paw oedema in rats, as well as the acetic-acid-induced vascular permeability in mice [38].
Arzumand et al, (2010) have shown anti-inflammatory activity in petroleum ether, dichloromethane, ethyl acetate, methanolic and aqueous extracts of the leaves of *A. pavonina*. The dichloromethane, methanolic and aqueous extracts at dose of 200 and 400 mg/kg significantly inhibit the paw oedema of carageenan treated rats. The methanolic extract shows significant anti-inflammatory activity in a dose dependent manner [39].

- **Antihyperlipidimic and Antihyperglycaemic activity.**

  The anti-hyperglycaemic and lipid lowering effect of *A. pavonina* seed aqueous extract (APSAE) has been evaluated using streptozotocin induced diabetes in rats. Streptozotocin was given at the dose of 55 mg/kg, i.p. After induction of diabetes, treatment with APSAE shows significant reduction in plasma glucose when compared with diabetic control. The elevated levels of serum triglyceride and cholesterol levels significantly decreases (*P*<0.01) by APSAE. APSAE treatment for 30 days shows significant decrease in serum LDL-cholesterol and significant increase in serum HDL cholesterol level. Diabetic control significant decrease in HbA1c which significantly increase by treatment with APSAE. Hence, from the result obtained in this study it can be confirmed that *A. pavonina* has the potential to treat diabetes condition and associated lipid disorders [40].
II. Erythrina indica

2.5 Introduction

_Erythrina indica_ is a middle-sized quick growing tree found in Bengal and many parts of India especially in southern India. It belongs to the family Papilionaceae, commonly known as Mandara (in Hindi) and Indian coral tree (in English). It grows up to 18 m in height, the leaves are trifoliolate, and flowers are borne in dense racemes.

➢ Vernacular Name

<table>
<thead>
<tr>
<th>Language</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bengali</td>
<td>Pattemadar</td>
</tr>
<tr>
<td>English</td>
<td>Indian coral tree</td>
</tr>
<tr>
<td>Hindi</td>
<td>Dadap, Pharhad, Pamkara</td>
</tr>
<tr>
<td>Sanskrit</td>
<td>Paribhadrah</td>
</tr>
</tbody>
</table>

![Fig. 2.2 Exomorphic features of leaves of E. indica](image)
Distribution

This is found throughout the tropical region of the world (Africa, Madagascar, Srilanka, India and Burma). All over India in deciduous forest is common as fencing plant in villages and as wild in open forest areas. [41].

2.6 Traditional uses

Leaves are used for round, tape or thread worms, it acts as cathartic, it is used for relief for earache and as an anodyne for toothache. Crushed leaves applied for rheumatic joints to relieve pain. The juice of leaves is used to kill worms. Fresh leaves used internally and as galactagogue and emmenagogue. Leaf juice is said to have cured long standing dysmenorrhoea. The juice increases the secretion of milk during the period of lactation, and also used in diarrhoea, pain and fever. The bark is used in dysentery, worms and useful as colyrium in ophthalmia. Inner side of bark is used in purulent conjunctivitis and is bitter, acrid, thermogenic. It is used as, anti-inflammatory, sedative, vulnerary, carminative, digestive, stomachic, anthelmintic, diuretic, emmenagogue, depurative, febrifuge and is useful in condition of kapha and vada inflammation [42-43].

2.5.1 Phytochemical review

Erythrina indica contain several phenolic metabolites, such as pterocarpsans, isoflavones, flavanones and chalcones, some of which displays antiplasmodial activity, antimycobacterial activity and cytotoxic activity against various cancer cell lines. It also contain alkaloids like N-norprotosinomenine (I), protosinomenine (2), erysodienone (3),3-erythroidine, erysopine, erythraline, erythramine, erysodine, ersotrine, erythratine, N,N-dimethyltryptophan, hyparphorine and it also contains sterols like campesterol,
β-sitosterol, β-amyrin. The isoflavones named as indicanines D and E together with 11 known compounds including 6 isoflavones like genistein, wighteone, alpinum isoflavones, dimethyl alpinum isoflavone, 8-prenyl erythrinin ‘C’ and erysenegalensein E and one Erythrinassinate B. Flavonoids include apigenin, genkwanin, iso-vitexin, swertisin, saponarin, 5-O-glucosylswertisin and 5-O-glucosylisoswertisin. Glucoside swertiamarin, a triterpene betulin have also been isolated. The alcohol insoluble portion of the unsaponifiable matter has yielded n-hexosamol, heptacosine, nonacosane. The non saponifiable matter of the petroleum ether extract has yielded myristic, stearic and oleic acids [44-46].

2.5.2 Pharmacological review

➢ Anti-osteoporotic Effect

Study shows that *E. indica* suppresses the high rate of bone turnover induced by estrogens efficiency and improves the biomechanical properties of bone in the rats [47].

➢ Anti-diarrhoeal activity

The anti-diarrhoeal activity of ethanol and aqueous extracts of *E. indica* leaf at 500 mg/kg dose level has been evaluated using castor oil-induced diarrhoea model in rats. The results shows possible anti-diarrhoeal effect of the leaf extracts and substantiates the use of this herbal remedy as a non-specific treatment for diarrhoea in folk medicine [48].

➢ Anthelmintic activity

Ethanol, chloroform and ethyl acetate extracts of leaves of *Erythrina indica* (*EI*) has been evaluated for its anthelmintic property against Pheritima
Posthuma. The activity was assessed by the determination of time of paralysis and time of death of earth worms. Piperazine citrate (10mg/kg) was included as standard. All the three extracts of *Erythrina indica* exhibit good anthelmintic activity [49].

- **Anti ulcer activity**

  The methanol extract of *E. indica* leaves possess significant antiulcer properties in a dose dependent manner [50].

- **Diuretic Activity**

  *Erythrina indica* Lam is used in the traditional medicine as diuretic. In the present study, the diuretic activity of ethanol, chloroform and ethyl acetate extract of leaves of *Erythrina indica* was studied and the activity was compared with furosemide as standard. All the three extract exhibited significant diuretic activity as evidenced by increased total urine volume and the urine concentration of $\text{Na}^+$, $\text{K}^+$ and $\text{Cl}^-$. The result thus supports the use of *Erythrina indica* as diuretic agent [51].

- **Analgesic activity**

  Study shows that analgesic activity of methanolic leaf extract of *E. indica* in acetic acid induced writhing inhibition method. The inhibition of writhing in mice by the plant extract was compared against inhibition of writhing by a standard analgesic agent, aminopyrine given orally at a dose of 50 mg/kg body weight. The methanolic extract of leaf of *E. indica* possesses significant analgesic activity [52].
Antioxidant activity

Saraswathy et al., (2006) investigated the ethanolic extract of the stem bark of *E. indica* and screened for its *in vitro* antioxidant activity by Ferric thiocyanate (FTC) and thiobarbituric acid (TBA) methods. Ethanolic extract of the stem bark of *Erythrina indica* possess significant antioxidant activity [53].

Anti-cancer activity

It has been evaluated the effect of methanolic extract of *E. indica* (MEEI) root bark against Dalton’s Ascitic Lymphoma (DAL) in Swiss Albino mice. DAL cells were injected intra-peritonially (10^6 cells) to the mice. Two days after cells injection the animals were treated with 250 and 500 mg/kg of MEEI for 8 days. 5-fluorouracil (20 mg/kg) was used as reference drug. On day 11, cancer cell number, packed cell volume, decrease in tumor weight of the mice, increase in life span and haematological parameters were evaluated and compared with the same parameters in control. A significant increase in the life span and a decrease in the cancer cell number and tumor weight were noted in the tumor-induced mice after treatment with MEEI. The haematological parameters were also normalized by MEEI in tumor-induced mice. These observations are suggestive of the protective effect of MEEI against Dalton’s Ascitic Lymphoma [54].

Anti-hyperlipidemic effect

Administration of aqueous extract of *E. indica* leaf at two dose level 200mg/kg and 300mg/kg for 30 days resulted in the reduction in total cholesterol, triglycerides, low density lipoprotein level and significant increase
in high density lipoprotein level in the high fat diet which in dual hyperlipidemia in rats [55].

➢ **Cardiovascular effects**

Study shows that intravenous administration of the aqueous extract at a dose, varying from 0.1-0.4mg/kg produces a sharp and short lived fall in blood pressure both in cats and rats in acute experiments. The cats were sensitive as regards the hypotensive action than rats since a moderate fall was noted with 0.12 mg/kg while in rats the hypotensive response noted only after 0.4mg/kg. On the isolated frog hearts the extract has no action in smaller dose but at a dose of 5mg resulted a complete but reversible block of the heart [56].

➢ **CNS effects**

It is reported that the extract is relatively non-toxic and the mice can tolerate a dose more than 500 mg/kg, i.p of the extract. Pretreatment of mouse with the extract neither potentiated nor reduced the pentobarbitone induced sleeping time. Similarly the extract failed to protect the mouse significantly from pentylenetetrazol induced convulsions [56].
References


