2. REVIEW OF LITERATURE

2.1 Hepatoprotective herbs

Herbal based therapeutics for liver disorders has been in use in India for a long time and has been popularized world over by leading pharmaceuticals. Despite the significant popularity of several herbal medicines in general, and for liver diseases in particular, they are still unacceptable treatment modalities for liver diseases. The limiting factors that contribute to this eventuality are

(i) Lack of standardization of the herbal drugs.
(ii) Lack of identification of active ingredient(s) principles(s).
(iii) Lack of randomized controlled clinical trials (RCTs).
(iv) Lack of toxicological evaluation. (Radha et al., 2005)

The use of natural remedies for the treatment of liver diseases has a long history, starting with the Ayurvedic treatment, and extending to the Chinese, European and other systems of traditional medicines. The 21st century has seen a paradigm shift towards therapeutic evaluation of herbal products in liver disease models by carefully synergizing the strengths of the traditional systems of medicine with that of the modern concept of evidence based medicinal evaluation, standardization and randomized placebo controlled clinical trials to support clinical efficacy. (Thyagarajan et al., 2002)

A large number of plants and formulations have been claimed to have hepatoprotective activity. Nearly 160 phytoconstituents from 101 plants have been claimed to possess liver protecting activity. In India, more than 87 plants are used in 33 patented and proprietary multi ingredient plant formulations. (Handa
Inspite of the tremendous advances made, no significant and safe hepatoprotective agents is available in modern therapeutics. Therefore, due importance has been given globally to develop plant based hepatoprotective drugs effective against a variety of liver disorders. The present review is aimed at compiling data based on reported works on promising phytochemicals from medicinal plants that have been tested in hepatotoxicity models.

2.1.1 Flacourtia indica

The extracts of the aerial parts of Flacourtia indica (Burm. f.) Merr, were evaluated for hepatoprotective properties. In paracetamol induced hepatic necrosis in rat models, all extracts were found to reduce serum aspartate transaminase (AST), serum alanine transaminase (ALT) and serum alkaline phosphatase (ALP). The most significant reduction of the serum level of AST and ALT were exhibited by petroleum ether and ethyl acetate extracts at a single oral dose of 1.5g/kg of bw with a reduction of 29.0% AST and 24.0% ALT level by petroleum ether extract, and 10.57% AST and 6.7% ALT level by ethyl acetate extract compared to paracetamol (3 g/kg of bw) treated animals. Histopathological examination also showed good recovery of paracetamol induced necrosis by petroleum ether and ethyl acetate extracts. On the other hand, the methanol extract did not show any remarkable effect on paracetamol induced hepatic necrosis. The hepatoprotective effects exhibited by petroleum ether and ethyl acetate extract might be mediated through the inhibition of microsomal drug metabolizing enzymes. (Marina et al., 2009)
2.1.2 Annona squamosa

The extracts of Annona squamosa (300 and 350 mg/kg bw) were used to study the hepatoprotective effect in RIF+INH induced hepatotoxic model in albino wistar rats. There was a significant decrease in total bilirubin accompanied by significant increase in the level of total protein and also significant decrease in ALP, AST, and ALT in treatment group as compared to the hepatotoxic group. In the histopathological study, the hepatotoxic group showed hepatocytic necrosis and inflammation in the centrilobular region with portal triaditis. The treatment group showed minimal inflammation with moderate portal triaditis and their lobular architecture was normal. (Saleem et al., 2008) In another study, the protective effect was evaluated in diethylnitrosamine induced hepatotoxicity. (Raj et al., 2009)

Silybum marianum The protective effects of polyphenolic extracts of Silybum marianum and Cichorium intybus on thioacetamide induced hepatotoxicity in rat was investigated. (Madani et al., 2008)

The extracts were injected to the rats, at a dose of 25 mg/kg body weight together with thioacetamide at a dose of 50 mg kg body weight. Significant decrease in the activity of aminotransferases, alkaline phosphatase and bilirubin was observed in the groups treated with extracts and thioacetamide compared with the group that was treated only with thioacetamide. The level of Na⁺, K⁺ and liver weight between different groups was not significantly altered. This findings suggested the hepato protective effect of Silybum marianum and Cichorium
intybus extracts on liver cells due to the presence of flavonoids and their antioxidant effects. (Madani et al., 2008)

2.1.3 Coccinia grandis

Alcoholic extract of the fruits of Coccinia grandis Linn (Curcubitaceae) was evaluated in CCl₄ induced hepatotoxicity in rats and levels of AST, ALT, ALP, total proteins, total and direct bilirubin were evaluated. At a dose level of 250 mg/kg, the alcoholic extract significantly (p<0.05) decreased the activities of serum enzymes (AST, ALT and ALP) and bilirubin which were comparable to that of silymarin revealing its hepatoprotective effect. (Vadivu et al., 2008)

2.1.4 Wedelia calendulacea

The hepatoprotective activity of ethanolic extract of Wedelia calendulacea L. (Family: Asteraceae) was studied against CCl4 induced acute hepatotoxicity in rats. The treatment with ethanolic extract of Wedelia calendulacea showed a dose dependent reduction in CCl₄ induced elevated serum enzyme activities with parallel increase in total proteins and bilirubin, indicating the extract could enhance the return of normal functional status of the liver comparable to normal rats. The weight of the organs such as liver, heart, lung, spleen and kidney in CCl₄ induced hepatic damaged animals that received ethanolic extract of Wedelia calendulacea showed an increase over CCl₄ treated control group. (Murugaian et al., 2008)

2.1.5 Prostechea michuacana

Methanol, hexane and chloroform extracts of Prostechea michuacana (PM) were studied against CCl₄ induced hepatic injury in albino rats. Pre
treatment with methanolic extract reduced biochemical markers of hepatic injury levels demonstrated dose dependant reduction in the in vivo peroxidation induced by CCl₄. Likewise, pretreatment with extracts of PM on paracetamol induced hepatotoxicity and the possible mechanism involved in this protection were also investigated in rats after administering the extracts of PM at 200, 400 and 600mg/kg. The degree of protection was measured by monitoring the blood biochemical profiles. The methanolic extract of orchid produced significant hepatoprotective effect as reflected by reduction in the increased activity of serum enzymes, and bilirubin. These results suggested that methanolic extract of PM could protect paracetamol induced lipid peroxidation thereby eliminating the deleterious effects of toxic metabolites of paracetamol. This hepato protective activity was comparable with silymarin. Hexane and chloroform extracts did not show any apparent effect. The findings indicated that the methanolic extract of PM can be a potential source of natural hepatoprotective agent. (Rosa and Rosario, 2009)

2.1.6 Aegle marmelos

_Aegle marmelos_ leaves (Bael, family of Rutaceae) which is also called as Bilva in ancient Sanskrit, was used as herbal drug in the Indian System of medicine. The hepatoprotective effect of _Aegle marmelos_ in alcohol induced liver injury was evaluated rats using essential marker biochemical parameters. The results indicated that, the Bael leaves have excellent hepatoprotective effect. Similar findings were also reported by other workers. (Vinodhini _et al._, 2007).

2.1.7 Cassia roxburghii

The Seeds of _Cassia roxburghii_ had been used in ethnomedicine for
various liver disorders for its hepatoprotective activity. The methanolic extract of *Cassia roxburghii* reversed the toxicity produced by ethanol and CCl$_4$ combination in dose dependent manner in rats. The extract at the doses of 250 mg/kg and 500 mg/kg are comparable to the effect produced by Liv 52®, a well established plants based hepatoprotective formulation against hepatotoxins. (Arulkumaran *et al.*, 2009)

2.1.8 *Orthosiphon stamineus*

The hepatoprotective activity of the methanol extract of *Orthosiphon stamineus* was assessed in paracetamol induced hepatotoxicity rat model. Change in the levels of biochemical markers such as AST, ALT, ALP and lipid peroxides were assayed in both paracetamol treated and control (untreated) groups. Treatment with the methanolic extract of *O. stamineus* leaves (200 mg/kg) has accelerated the return of the altered levels of biochemical markers to the near normal profile in the dose dependent manner. (Maheswari *et al.*, 2008)

2.1.9 *Ficus carica*

The methanolic extract of the leaves of *Ficus carica* Linn (Moraceae) was evaluated for hepatoprotective activity in CCl$_4$ induced liver damaged rats. The extract at an oral dose of 500 mg/kg exhibited a significant protective effect reflected by lowering the serum levels of AST, ALT, total serum bilirubin, and malondialdehyde equivalent, an index of lipid peroxidation of the liver. (Krishna *et al.*, 2007)

2.1.10 *Lepidium sativum*

The role hepatoprotective of methanolic extract of *Lepidium sativum* at a
dose of 200 and 400 mg/kg was investigated in CCl₄ induced liver damage in rats. Significant reduction in all biochemical parameters were found in groups treated with *Lepidium sativum*. The severe fatty changes in the livers of rats caused by CCl₄ were insignificant in the *Lepidium sativum* treated groups. *(Afaf et al., 2008)*

### 2.1.11 Sargassum polycystum

The protective effect of ethanol extract of *Sargassum polycystum* was evaluated in D galactosamine induced hepatitis in rats. Prior oral administration of *S. polycystum* extract [125/mg/kg bw/day for 15 days] significantly attenuated (P<0.05) the D galactosamine induced increases in the levels of diagnostic marker enzymes (AST, ALT and ALP) in plasma of rats. It has also demonstrated antioxidant activity against Dgalactosamine induced hepatitis by inhibiting the activation of lipid peroxidation and by preserving the hepatic enzymatic and non enzymatic antioxidant defense system at near normal. The antihepatotoxic potential of *S. polycystum* might possibly due to its antioxidant property and membrane stabilizing action. *(Meena et al., 2008)*

### 2.1.12 Solanum nigrum

The effects of *Solanum nigrum* extract (SNE) was evaluated on thioacetamide (TAA) induced liver fibrosis in mice. Mice in the three TAA groups were treated daily with distilled water and SNE (0.2 or 1.0 g/kg) via gastrogavage throughout the experimental period. SNE reduced the hepatic hydroxyproline and α smooth muscle actin protein levels in TAA treated mice. SNE inhibited TAA induced collagen (α1), transforming growth factor β1 (TGF β1) and mRNA levels in the liver. Histological examination also confirmed that
SNE reduced the degree of fibrosis caused by TAA treatment. Oral administration of SNE significantly reduces TAA induced hepatic fibrosis in mice, probably through the reduction of TGF β1 secretion. (Chang et al., 2008)

In other study, the protective effects of aqueous extract of SN (ASNE) against liver damage were evaluated in CCl₄ induced chronic hepatotoxicity in rats. The results showed that the treatment of ASNE significantly lowered the CCl₄ induced serum levels of hepatic enzyme markers, superoxide and hydroxyl radicals. Liver histopathology showed that ASNE reduced the incidence of liver lesions including hepatic cells cloudy swelling, lymphocytes infiltration, hepatic necrosis, and fibrous connective tissue proliferation induced by CCl₄ in rats. Therefore, the results of this study suggest that ASNE could protect liver against the CCl₄ induced oxidative damage in rats, and this hepatoprotective effect might be contributed to its modulation on detoxification enzymes and its antioxidant and free radical scavenger effects. (Hui Mei et al., 2008)

The presence of plant extracts of Solanum nigrum and Cichorium intybus in the reaction mixture containing calf thymus DNA and free radical generating system protect DNA against oxidative damage to its deoxyribose sugar moiety. The effect was dependent on the concentration of plant extracts. However, the effect of Cichorium intybus was much pronounced as compared to the effect of Solanum nigrum. These studies suggested that the observed hepatoprotective effect of these crude plant extracts may be due to their ability to suppress the oxidative degradation of DNA in the tissue debris (Sultana et al., 1995).

Since these herbs are commonly known as hepatoprotective agents and have shown their efficacy in protecting against CCl₄ induced hepatic injury
(Bardhan et al., 1985) it may be proposed that their efficacy may be attributed to their free radical scavenging ability.

2.2 Marketed formulation of hepatoprotective:-

**Baidyanath's Kumariasava:** Ghrit kumari, Iron, Triphala, Trikatu, Chaturjat, Dhaniya, Chitrakmoool, DeodarPunarnava, Rasna, Danti, Motha, Aparajita, Chavya, Pippal, Dhataki, Jaggery etc.

**Dose:** 15 to 30 ml with equal quantity of water

**Ayulab's Ayuliv Capsules / Syrup:** *Picrorrhiza kurrooa* (katuk), *Andrographis paniculata* (kalmegh)

**Baidyanath's Punarnawa Ark:** Ingredients: *Boerhavia diffusa* (Punarnawa)

**LIMARIN® Capsules**

Each capsule of LIMARIN® 70 contains Silymarin 70 mg.
Each capsule of LIMARIN® 140 contains Silymarin 140 mg.

**LIMARIN® Suspension**

Each 5 ml (One teaspoonful) contains Silymarin 35mg in a flavoured base.

Dosage:
- Hepatitis A: LIMARIN® 140 mg, one capsule thrice daily for 1 month.
- Alcoholic Liver disease and other indications: LIMARIN®140 mg, one capsule thrice daily for 3-6 months or as directed by the Physician.
- Maintenance dose: LIMARIN®70 mg, one capsule thrice daily or as directed by the Physician.

**LIMARIN® SUSPENSION**

Mild to moderate: 10mg/kg body weight in 3 divided doses.
Severe: 20 mg/kg body weight in 3 divided doses.

Mfg by: Serum India.

**Table 2.1: Plants investigated for their hepatoprotective activity**

<table>
<thead>
<tr>
<th>Plant Name</th>
<th>Part used</th>
<th>Experimental model</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Abutilon indicum</em></td>
<td>Leaves</td>
<td>CCl₄</td>
<td>Porchezhian <em>et al.</em>, 2005</td>
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<td>Bhattachary <em>et al.</em>, 2005</td>
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<td>Paracetamol and thioacetamide</td>
<td>Singh <em>et al.</em>, 1995</td>
</tr>
<tr>
<td><em>Apium graveolens</em></td>
<td>Seeds</td>
<td>CCl₄</td>
<td>Bahar <em>et al.</em>, 2002</td>
</tr>
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<td><em>Aronia melanocarpa</em></td>
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<td>Valcheva Kuzmanova <em>et al.</em>, 2004</td>
</tr>
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<td>Anwar <em>et al.</em>, 1995</td>
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<td><em>Artemisia vulgaris</em></td>
<td>Aerial parts</td>
<td>D Galactosamine (D GalIN) and Lipopolysaccharides</td>
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</tr>
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<td>Plant Name</td>
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<td>Substance</td>
<td>Reference</td>
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<td>Shivashagari et al., 2004</td>
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<td>Chattopadhyay et al., 2003</td>
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<td>Leaves</td>
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<td>Jung et al., 2004</td>
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<td>CCl₄</td>
<td>Agarwal et al., 2006</td>
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<td>Mrouesh et al., 2004</td>
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<td>Acetaminophen</td>
<td>Mantena et al., 2005</td>
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<td>Cudrania tricuspidata Breau</td>
<td>Root Barks</td>
<td>Nitrofurantoin</td>
<td>Tian et al., 2005</td>
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<tr>
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<td>Part of Plant</td>
<td>Stimulation/Compounds</td>
<td>Authors</td>
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<td>Tasduq et al., 2005</td>
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<td>Stem</td>
<td>D galactosamine</td>
<td>Matsuda et al., 2004</td>
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<td>Acetaminophen</td>
<td>Mohd et al., 2005</td>
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<td>Helminthostachys zeylanica</td>
<td>Rhizomes</td>
<td>CCl₄</td>
<td>Suja et al., 2004</td>
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<td>Nymphaea stellata Willd</td>
<td>Flower</td>
<td>CCl₄</td>
<td>Manoj et al., 2004</td>
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<td>Mature leaves</td>
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<td>Acetaminophen</td>
<td>Devi et al., 2004</td>
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<td>Asha et al., 2004</td>
</tr>
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<td>Premna tomentosa</td>
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<td>Acetaminophen</td>
<td>Pandimadevi et al., 2004</td>
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<td><em>Quercus aliena acorn</em></td>
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<td>Jin <em>et al.</em>, 2005</td>
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<td>Hoefler <em>et al.</em>, 1987</td>
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<td><em>Trichilia emetica</em></td>
<td>Root</td>
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<td>Germano <em>et al.</em>, 2005</td>
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</tbody>
</table>
2.2 Selected Plants – A Review

i) Adina cordifolia

**Plant name**: Adina cordifolia

**Family**: Rubiaceae

**Common name**:  
  
  Bengali : Keli kadam  
  Hindi : Haldu  
  Sanskrit : Dharakadanba

**Synonyms**: Haldina cordifolia, Adina ledermanii (hallealedermannii), Adina pilulifera (Cephalanthus), Adina rubella, Nauclea cordifolia.

**Parts used**: Leaf, root, seed and bark.

**Habitat**: A moderate sized deciduous tree grows up to 35 meter in height. Leaves large, cordate, abruptly acuminate. Flowers yellow in globose pedunculate heads; fruits capsules, splitting into two dehiscent cocci, seeds many, narrow, small, and tailed. It occurs frequently but scattered in deciduous forest in the lowland and lower hills. In Burma (Myanmar) and Thailand it is often associated with teak (Tectonagrandis L.f.) India, Sri Lanka, Burma (Myanmar), Indo China Southern China, Thailand and Peninsular Malaysia.

**Chemical Constituents**: It contains 10 deoxyadifoline, 10 deoxycordifoline indole alkaloid, cordifoline, difoline. Di OH tetra OMe flavone has been isolated from defatted heartwood. Oleoresin obtained from incision of trunk yields
essential oil (5.2 6.8 %). Stem contains yellow coloring matter, napthaquinone and adinin. The leaves contain ursolic acid and quercetin. It also contains 7 hydroxycoumarin (umbelliferone), D glucosycoumarin (skimmin).

**Properties:** *A. cordifolia* is a medium weight to heavy hardwood with a density of 570 895 kg/m cubic at 15 % moisture content. Yellow when fresh, Turning pale yellow or reddish brown on exposure.

**Uses:** It has been used in oriental medicine since ancient times as an essential component of various antiseptic and febrifuge prescriptions. *(Chopra et al., 2006b)* The bark is acrid and bitter and is used in biliousness. The roots are used as an astringent in dysentery. *(Chadha et al., 1985)* The *A. cordifolia* stem has been evaluated for its antiulcer potential. It is also used as febrifuge, antiseptic, anti fertility, anti inflammatory, anti rheumatoid, bitter tonic, anti cancer, anti microbial.
Figure 2.1: Leaves of *Adina cordifolia*
ii) *Sida veronicaefolia*

**Botanical name** : *Sida veronicaefolia*

**Family** : Malvaceae

**Common name**

- Bengali : Junka
- Hindi : Bhiunli
- Tamil : Palampasi

**Synonyms:** Rajbala, Bhumibala, Farid buti, Shaktibala etc.

**Plant Classification**

- **Kingdom** : Plantae
- **Subkingdom** : Tracheobionta
- **Division** : Magnoliophyta
- **Class** : Magnoliopsida
- **Subclass** : Dilleniidae
- **Order** : Malvales

**Family** : Malvaceae

**Genus** : Sida L.

**Species** : *veronicaefolia* (heartleaf)
Habitat: It is a straggling way side herb found very often growing in shady places. It grows mainly in clearing in the forest and as weeds in the over grown grass of public parks and gardens. (Lutterodt, 1988b; Warrier et al., 1996)

Chemical constituents: Phenethylamines, quinazoline, gossypol, sterculic acid, linoleic acid etc. It has muscarine like active principle. (Lutterodt, 1988a; Warrier et al., 1996)

Uses: It has haemostatic, analgesic and wound healing properties. Paste of either root or leaves is used in bleeding disorders and wounds. Being a nerveine and brain tonic, it is useful loss of memory and vata disorders unctuous, laxative, useful in acid peptic disorder and constipation. (Warrier et al., 1996) It is effective in cough, dyspnoea, bronchitis, tuberculosis and hoarseness of voice. Aphrodisiac and useful in semen debility. Being diuretic, it is used in retention of urine, dysuria and gonorrhea. Useful in fevers. Being a tonic it is useful in general debility and muscle wasting. Soup of this plant is taken in the last days of pregnancy. It has a capability to remove the three doshas from the body, and to provide strength and glow to the body. (Lutterodt, 1988a)
Figure 2.2: Leaves of *Sida veronicaefolia*
iii) *Nyctanthes arbortristis*

**Plant name** : Harsingar

**Botanical Name** : *Nyctanthes arbortristis*

**Synonyms**

- **English** : Night Jasmine, Weeping Nyctanthes
- **Hindi** : Harsinghar
- **Mal.** : Manpumaram
- **Sanskrit** : Parijata
- **Tamil** : Manjapu
- **Telgu** : Pagadamalle
- **Punjabi** : Kuri
- **Bengali** : Seoli

**Plant Classification**

- **Kingdom** : Plantae
- **Division** : Magnoliophyta
- **Class** : Magnoliopsida
- **Order** : Lamiales
- **Family** : Oleaceae
- **Genus** : Nyctanthes.
Species: *Arbor tristis*

Part used: Stem bark

**Distribution**

Native to India, Thailand and Indonesia, growing wild in the sub-Himalayan region to Nepal, through Central India to northern Karnataka and Andhra Pradesh. It is cultivated in gardens almost throughout India and in many tropical countries for its flowers, which are used for making garlands and offering in temples. *(Tuntiwachwuttikul et al., 2003; Paul et al., 1997)*

**Description**

A large shrub or small tree up to 10 m tall with gray or greenish-white bark. Leaves opposite, 3.5-13 cm long and 2-9 cm wide, ovate, apex acute, base rounded, margins entire or few large distant teeth and rough. Flowers fragrant, small, white with orange centre and axillary. Fruits sub-orbicular, compressed, capsule 2 cm long and wide. *(Tuntiwachwuttikul et al., 2003)*

**Habitat:**

A shrub or small tree up to 10 m heights with gray or greenish rough bark with stiff whitish hairs: young branches sharply quadrangular. Leaves are opposite, 5-10 by 2.5-6.3 cm, ovate, acute or acuminate, entire or with a few large distant teeth, short bulbous hairs rounded or slightly cuneate; main nerves few, conspicuous beneath; petiol 6 cm long, hairy. *(Tuntiwachwuttikul et al., 2003)* Flowers are small, delightfully fragrant, sessile in pedunculate bracteates fascicles of 3-5; peduncles 4 angled, slender, hairy, auxiliary and solitary and in
terminal short trichotomous chymes; bracts broadly ovate or suborb. (Das et al., 2003)

Uses:

The bitter leaves, seeds, flowers and stem bark are used in traditional system of medicine for the treatment of rheumatism, sciatica and intestinal worms. (Das et al., 2003) The powdered seeds are recommended for the treatment of scurvy leaf juice is used to treat loss of appetite, piles, liver disorders, biliary disorders, intestinal worms, chronic fever, ophthalmic use, laxities mild bitter tonic. (Paul et al., 1997; Das et al., 2003; Khatune et al., 2001)
Figure 2.3: Tree of *Nyctanthes arboristis*
2.3 Literature review of the selected plants

- **Sabir (1970)**, Studied the anti-fertility activity of leaf extract of *A. cordifolia*. (Sabir and Razdan, 1970)

- **Srivatsava (1983)**, Isolated a new flavanone from *A. cordifolia*. (Srivatsava et al., 1983)

- **Rao (2002)**, Studied about the isolation and structural elucidation of 3,4,5,7 tetra acetyl quercetin from the heart wood of *A. cordifolia*. (Rao et al., 2002)

- **Yue (2009)**, Studies antiamoebic coumarins from the root bark of *Adina cordifolia* and their new thiosemicarbazone derivatives. In continuation of our search for potential antiamoebic agents from folklore Indian medicinal plants, we found that the benzene and ethyl acetate extracts from the root bark of *Adina cordifolia* exhibited strong antiamoebic activity with IC\(_{50}\) values of 2.92 and 2.50 microg/ml, respectively. Bioassay guided fractionation of benzene and ethyl acetate extracts led to the isolation of 7-hydroxycoumarin (umbelliferone 1) and 7-beta-D-glucosylcoumarin (skimmin 2), respectively. Umbelliferone 1 was converted into 7 acetoxycoumarin 1a, which on treatment with aluminium chloride afforded 7-hydroxy 8-acetyl coumarin 2a. A new series of thiosemicarbazones 3a-e of 7-hydroxy-8-acetyl coumarin with different thiosemicarbazides were synthesized. Umbelliferone was also converted into its methoxy derivative (7-methoxycoumarin). Subsequently, all the compounds were assessed for antiamoebic activity against HM1: IMMS strain of Entamoeba histolytica. Umbelliferone and skimmin were found to possess a very good activity with IC\(_{50}\) values of 6.38 and 4.35 microM/ml, respectively. The activity
drastically increased on converting compound 2a into its thiosemicarbazone derivatives 3a-e with IC\textsubscript{50} values ranging between 1.06 and 4.46 microM/ml. Compounds 3b,c and e with IC\textsubscript{50} values of 1.49, 1.56 and 1.06 microM/ml, respectively, exhibited even higher antiamoebic activity than the standard drug metronidazole (IC\textsubscript{50}=2.62 microg/ml). The activity of 7 methoxycoumarin IC\textsubscript{50} = 8.92 micro/M/ml) was less than umbelliferone. Compounds 3b, c and e were tested for toxicity using H9c2 cardiac myoblasts cell line. The compounds exhibit >80% viability at 3.125 200 microg/ml. It is apparent from these results that umbelliferone and skimmin may be a useful lead for the development of new antiamoebic drugs. (Yue et al., 2009)

- **Zimmerman (1974),** studied alkaloids present in *Sida veronicaefolia* roots. Roots contain ephedrine, hypophorine, vasicine, vasicinol and vasicinone. *(Zimmerman et al., 1974)*

- **Lutterodt (1988\textsubscript{a}),** founds responses of gastrointestinal smooth muscle preparations to a muscarinic principle present in *Sida veronicaefolia*. The effects of the water soluble fraction from an alcoholic extract of *Sida veronicaefolia* leaves were studied on isolated guinea pig ileum and isolated rabbit duodenum. Agonist/antagonist studies, using atropine, hexamethonium and mepyramine, suggest that the active principle may be muscarine like. Preliminary biochemical investigations on the extract showed negative results for the presence of alkaloids, saponins and true tannins, but confirmed the presence of pseudotannins, oligosaccharides, flavonoids, choline, fructose, peptides, histidine, glycine, tyrosine, oxalic acid and phenolic acid.(Lutterodt, 1988\textsubscript{a})
• **Lutterodt (1988b)**, founds abortifacient properties of an extract from *Sida veronicaefolia*. A fraction from an alcoholic extract of *Sida veronicaefolia*, previously reported to be a potent oxytocic, was studied for its abortifacient effects in pregnant rats. Oral doses producing the abortifacient effects were greater than or equal to 32 ml/kg when administered from the 15th to 17th day of pregnancy. Similar effects were produced by intravenous doses of greater than or equal to 3 ml/kg. At the minimum effective oral dose of 32 ml/kg, those animals that carried the conceptuses to term (40%) had litters with reduced average number/litter and weight. At twice this dose, only 10% delivered and the litters were sickly. The effects of intravenous administration of the extract were similar but more pronounced and included also some unique acute effects. *(Lutterodt, 1988b)*

• **Lutterodt (1995)**, found interaction between oxytocin and 'sidaverin' on the gravid and non gravid rat uterus. Sidaverin, a crystalline compound extracted from a polar fraction of *Sida veronicaefolia*, elicited oxytocin like contractions in the non gravid rat isolated uterus preparation with a concentration response relationship. Equipotent concentrations of oxytocin and sidaverin, using matched responses, were approximately 0.16 U and 0.4 micrograms ml⁻¹, respectively. Sidaverin induced contractile response was atropine reversible. The concentration response curves for sidaverin and oxytocin were parallel, and both responses were inhibited by the specific oxytocin antagonist, Atosiban, indicating possible involvement of oxytocin receptors in the action of sidaverin. There were potentiations of action of one drug to that of the other, irrespective of the order of administration and even after washing off the first before introducing the second drug. In the gravid
uterus, sidaverin produced contractions in preparations from day 1 to day 6 or 7, caused relaxation in days 7 11, and elicited contractions in day 11 through term, the sensitivity of the preparations increasing exponentially toward term with strong sustained contractions. With the exception of days 7 11, when sidaverin antagonized oxytocin action, it potentiated action of oxytocin on the gravid uterus. (Lutterodt, 1995)

- **Pandey (2009),** founds the *Sida veronicaefolia* as a source of natural antioxidant the antioxidant activity of hexane, chloroform, hydro alcoholic and aqueous extract of whole plant of *Sida veronicaefolia* (family *Malvaceae*) was evaluated using *in vitro* models, DPPH free radical scavenging, scavenging of hydrogen peroxide and reducing power method. (Pandey et al., 2009)

- **Saxena (1984),** The water soluble fraction of its ethanol extract of *Nyctanthes arbortristis* demonstrates a significant anti inflammatory activity against acute inflammatory oedema produced in rats by different phlogistic agents, possibly by suppressing prostaglandin formation, like the other non steroidal anti inflammatory drugs. (Saxena et al., 1984)

- **Purushothaman (1985),** isolated arbortristoside A and B from the seeds of *Nyctanthes arbortristis*. (Purushothamam et al., 1985)

- **Saxena (1987),** screened the leaf extract of *Nyctanthes arbortristis* for analgesic, antipyretic and ulcerogenic activity. (Saxena et al., 1987)

- **Rathore (1990),** isolated arbortristoside D and E from the seeds of *Nyctanthes arbortristis*. (Rathore et al., 1990)
• **Tandon (1991)**, have reported that iridoid glucosides (arbortristosides A [1], B [2], C [3], and 6 beta-hydroxy-loganin [4] isolated from the traditional plant *Nyctanthes arbortristis*, show antileishmanial activity in both *In-vitro* (against amastigotes in macrophage cultures) and *In-vivo* (in hamsters) test systems. *(Tandon et al., 1991)*

• **Stuppner (1993)**, isolated 6,7-di-*O*-benzoylnyctanthoside, 6-*O*-trans cinnamoyl 6β hydroxyloganin and 7 *O* trans cinnamoyl 6β hydroxyloganin from the leaves of *Nyctanthes arbortristis*. *(Stuppner, 1993)*

• **Puri (1994)**, studied the leaf extract of *Nyctanthes arbortristis* for its impressive immunological activity. It strongly stimulates antigen specific and non specific immunity, as shown by an increase in humoral and delayed type hypersensitivity responses to sheep erythrocytes, and in macrophage migration index. *(Puri, 1994)*

• **Paul (1997)**, shows that the effect of the water soluble fraction of the ethanol extract of *Nyctanthes arbortristis* on tumor necrosis factor α (TNF α) level in plasma of arthritic and soluble protein A (SpA) treated mice. *(Paul et al., 1997)*

• **Khatune (2001)**, reported that flowers of *Nyctanthes arbortristis* have antibacterial activity against some gram positive and gram negative microorganisms (chloroform and ethyl acetate extracts) and significant cytotoxic activity (petroleum ether, chloroform and ethyl acetate extracts). *(Khatune et al., 2001)*
• **Saxena (2002)**, reported that the water soluble portion of the alcoholic extract of the leaves of *Nyctanthes arboristis* possess some CNS activities (viz. hypnotic, tranquilizing, local anaesthetic, hypothermic, anticonvulsant), antihistaminic and purgative activities. The extract produced general depression of spontaneous motor activity, significantly increased pentobarbitone sleeping time though it had no effect on righting reflex. (Saxena, 2002).

• **Paul (2002)**, have reported pharmacological effect of *Nyctanthes arboristis* leaf extract in the prevention of lung injury induced by silica particles. (Paul *et al.*, 2002)

• **Das (2003)**, shows that the ethanolic extracts of the flowers and seeds of *Nyctanthes arboristis* have CNS depressant activity, little antispasmodic activity and also have antipyretic and anti inflammatory activities. (Das *et al.*, 2003)

• **Tuntiwachwuttikul (2003)**, isolated an antiplasmodial cyclohexylethanoid, rengyolone (1), 6 *Otrans* cinnamoyl 7 O acetyl 6b hydroxyloganin, arborside C, 6b hydroxyloganin and nyctanthoside from the ethanol extract of the flowers of *Nyctanthes arboristis* L. Compound 1 and its acetate derivative exhibited antiplasmodial activity against *Plasmodium falciparum*. (Tuntiwachwuttikul *et al.*, 2003)

• **Gupta (2005)**, have reported that the ethanolic extracts, various fractional and two pure compounds isolated from the plant *Nyctanthes arbortris* were tested against Encephalomyocarditis Virus (EMCV) and Semliki Forest Virus (SFV). Pronounced *In-vitro* virus inhibitory activity was observed with the
ethanolic and n-butanol fractions as well as with the pure compounds arbortristoside A and arbortristoside C. (Gupta et al., 2005)

- **Gupta (2006)**, have reported that animal treated with methanol extract of *Nyctanthes arbortristis* Linn stem bark was administered orally to adult male albino rats at the dose level of 100 mg/kg showed a notable depression of spermatogenesis. There is significant reduction in testes weight, which can be attributed for the loss of germ cell. (Gupta et al., 2006)

- **Omkar (2006)**, have reported that the anti-inflammatory activity of the ethenolic extract of the orange tubular calyx of *Nyctanthes arbortristis* and pet.ether extract of root bark of *O echioides* was studied in albino rats of Wistar strain using the carrageenan induced paw edema model. The results indicated that all the extract produced significant (p<0.05) anti-inflammatory activity when compared with the standard drug (diclofenac sodium) and untreated control. (Omkar amrite et al., 2006)

- **Rathee (2007)**, studied the acetone soluble fraction of the ethyl acetate extract of *Nyctanthes arbortristis* (Harsingar) leaf showed impressive antioxidant activity as revealed by several in vitro experiments, e.g., DPPH, hydroxyl and superoxide radicals, as well as H$_2$O$_2$ scavenging assays. Moreover, its preventive capacity against Fe (II) induced lipid peroxidation of liposomes and c ray induced DNA damage also confirmed this. The strong reducing power and high phenolics and flavonoids contents could be responsible for the antioxidant activity. (Rathee et al., 2007)

- **Deshmukh (2007)**, have reported that leaves extract of *Nyctanthes arbortristis* linn was Used to treat hepatosuppression induced by carbon
tetrachloride (ccl4) which was evaluated in terms serum marker enzymes like viz. GOT, GPT, alkaline phosphate, glucose, cholesterol, and total protein concentration in blood. (Deshmukh et al., 2007)

- **Rathod (2007)**, have reported that the antidiabetic property of chloroform extract of *Nyctanthes arbortristis* leaves and flowers. In the present study antidiabetic properties of *Nyctanthes arbortristis* was investigated by hypoglycemic effect, potentiation action of exogenous insulin, oral glucose test and streptozotocin-induced diabetic rat model. (Rathod et al., 2007)

- **Rathore (2007)**, have reported that the comparative studies of the modulation effect of pro-and anti-inflammatory cytokines following long term use of water soluble ethanol extracts from different organs of *Nyctanthes arbortristis* (NAT) in mouse model of arthritis showed the evidence of lesser inflammation of the footpad and joint and associated histological observation support the therapeutic benefit of leaf and fruit extracts from *Nyctanthes arbortristis*. (Rathore et al., 2007)

- **Mahida (2007)**, have reported that the methanolic extract of *Nyctanthes arbortristis* exhibit significant antibacterial activity against multidrug resistant bacteria. (Mahida et al., 2007)

- **Kannan (2007)**, have reported that the leaf extracts of *Nyctanthes arbortristis* linn is used to treat arthritis, lung injury and some painful conditions such as cancer, chronic fever and rheumatism. An ethnolic extract of *Nyctanthes arbortristis* (NAEE) was screened in rats of humoral and cell-mediated immune responses. The chronic administration of NAEE increased the total
counts of white blood cells (WBC) and potentiated the strong immuno-bioactivities in extracts of *Nyctanthes arbor-tristis*. (Kannan *et al.*, 2007)

- **Sasmal (2007)**, have reported about comprehensive information on the chemical constituents and mainly pharmacological activities of the plant *Nyctanthes arbor-tristis*. The ethanolic, aqueous and hydro-alcoholic extracts of the leaves were established for antibacterial activity against both antibiotic resistant and nonresistant strains of *staphylococcus aureus*. (Sasmal *et al.*, 2007)

- **Sathiya (2008)**, have reported the *In-vitro* antibacterial studies on the ethanolic leaf extracts of *Nyctanthes arbor-tristis* linn. against ten medically important bacterial strains. The result of antibacterial assay revealed that the extracts showed good inhibitory activity against all the tested pathogens compared with standard antibiotics like streptomycin and penicillin. The inhibitory activity was found to be dose dependent. (Sathiya *et al.*, 2008)

- **Sasmal (2008)**, have reported the antianemic activity of ethanolic extracts of the flowers, barks, seeds and leaves of *Nyctanthes arbor-tristis*. (Sasmal *et al.*, 2008)