II. Review of Literature
Plants have provided man with all his needs in terms of shelter, clothing, food, flavours, fragrances, as well as medicines. Plants have formed the basis for sophisticated traditional medicine systems that have been in existence for thousands of years, and continue to provide mankind with new remedies (Ameenah, 2006). The extraction and characterization of active compounds from medicinal plants have resulted in the discovery of new drugs with high therapeutic value (Asakawa, 2007 and Nisar et al. 2007). The use of medicinal plants has a long history throughout the world and herbal preparations, including herbal extracts, can be found in the pharmacopoeias of numerous countries. Ayurveda, Unani, Kampo and traditional Chinese medicine have flourished as systems of medicine in use for thousands of years (Ameenah, 2006). The number of higher plant species (angiosperms and gymnosperms) on this planet is estimated at 250,000 (Farnsworth, 1990), with a lower level at 215,000 and an upper level as high as 500,000 (Schultes, 1972). Of these, only about 6% have been screened for biological activity, and 15% have been evaluated phytochemically (Schultes, 1972). World Health Organization estimates that 80% of the people in developing countries of the world rely on traditional medicine for their primary health care needs, and about 85% of traditional medicine involves the use of plant extracts. This means that about 3.5 to 4 billion people in the world rely on plants as sources of drugs (Farnsworth et al. 1985).

There is a scientific discipline known as ethnobotany (or ethno pharmacology), whose goal is to utilize the impressive array of knowledge assembled by indigenous peoples about the plant and animal products they have used to maintain health (Georges, 1949; Vanden Berghe, 1986; Rojas, 1992 and Silva, 1996). Plants have an almost limitless ability to synthesize aromatic substances, most of which are secondary metabolites, of which at least 12,000 have been isolated, a number estimated to be less than 10% of the total (Schultes, 1978). In many cases, these substances serve as plant defense mechanisms against
predation by microorganisms, insects, and herbivores. Some, such as terpenoids, give plants their odors; others (quinones and tannins) are responsible for plant pigment. Many compounds are responsible for plant flavour (e.g. the terpenoid capsaicin from chilli peppers), and some of the same herbs and spices used by humans to season food yield useful medicinal compounds. The use of alternative medical therapy has increased the interest of pharmacologists and herbalists over the past decade.

Numerous plant based drugs have entered the international market due to pharmaceutical companies made renewed strategies in favour of natural product based drug development and discovery. It can be noted that these drugs were isolated from natural source, many of which have been used by various cultures throughout history. Some of them are morphine, strychnine, quinine and colchicine etc. (Brent Jason, 2005).

Pharmaceutical research took a major leap when alongside natural products chemistry; pharmacologists, microbiologists and biochemists began to unravel the chemistry of natural processes in human, animals, plants and microorganisms. Advances in synthetic organic chemistry led to the identification of many key chemical molecules that offered more opportunities to develop novel compounds. Many new drugs emerged by this route, particularly those now being used to treat infections, infestations, cancers, ulcers, and heart and blood pressure conditions. Many drugs were developed through random screening of thousands of chemicals synthesized as dye-stuffs and the like; many others resulted from serendipity arising from sharp-eyed observations of physicians and scientists. Examples of such drugs include sulphonamides, isoniazid, anti-psychotics, anti-histamines and penicillin (Clark, 1996).

The review of analysis of the drugs developed between 1981 and 2003 showed that natural products or natural product derived drugs comprised 68% of
all new chemical entities launched on to the market. In addition, 44% of these were semisynthetic or natural mimic compounds, based on the study of pharmacophores related to natural products (Newman et al. 2003). This much bulky percentage suggests that natural products are important sources for new drugs and are also good lead compounds suitable for further modification during drug development. The large proportion of natural products in drug discovery has stemmed from the diverse structures and the intricate carbon skeletons of natural products. Since secondary metabolites from natural sources have been elaborated within living systems, they are often perceived as showing more “drug-likeness and biological friendliness than totally synthetic molecules” making them good candidates for further drug development (Balunas and Kinghorn, 2005; Drah et al. 2005; Koehn and Carter, 2005).

Indian systems of medicine have a deep root in our culture heritage and cater to the Medicare of large sections of our population. These systems mainly use herbs. If we dwell for a moment on our hoary past, the Rigveda, one of the oldest repositories of human knowledge, mentions the use of 67 plants for therapeutic use, the Yajurveda enlist 81 plants whereas the Atharveda written during 1200 BC describes 290 medicinal plants of medicinal value. Charak Samhita written during 990 BC describes 341 medicinal plants. The land mark in Ayurveda was Sushrut Samhita written during 600 BC mentioned 395 medicinal plants. Dhanwantari Nighantu mentions 750 medicinal plants, 450 are mentioned in the Bhavaprakash, 480 in Madanapala Nighantu and 450 in the Kaiyadeva Nighantu. India unquestionably occupies the top position in the use of herbal drugs. It is one of the foremost countries exporting plant drugs and their derivatives (Agarwal and Paridhavi, 2007).
1. PHARMACOGNOSY

The increasing demand for herbal medicines both in the developing and developed countries inevitably led to maintaining the quality and purity of the herbal raw materials and finished products. Further, unlike the past ages, safety today is an issue due to, complexity of herbal extracts specially when the identity of an herb is questionable or extraction method is new, possibility of contamination due to heavy metals, microbiological load, pesticide residues or mycotoxins. So it is important that plant drugs and their products are prepared following standardized procedure to ensure product uniformity and quality. For standardization and quality assurance purpose, authenticity, purity and assay are desirable. Authenticity corresponds to the right identity, purity pertains to devoid of adulteration and assay part of standardization is chemical and biological profiling by which the chemical and biological effects could be assessed and curative values are established. It is practically impossible to avoid some naturally occurring inorganic (sand and inorganic constituents of soil) and organic (other parts of the same plants or parts of the neighbouring plants of another species) contaminants. The evaluation of these standardization parameters gives a clear idea about the specific characteristic of crude drug under examination (Mukherjee, 2002a).

The standardization problem relating to the herbal drugs arises from the complex composition of drugs that are used in the form of whole plant, plant parts or extracts obtained there from. To ensure reproducible quality of an herbal remedy, proper control of the starting material is utmost essential. Usually plants cannot be identified to species using only rhizomes, roots or barks, which for many medicinal plants are the parts found in market. As a result, the development of evermore sophisticated or molecular methods to be employed in quality control has become necessary, especially in such morphologically problematic species. However, such methods are costly enough that they should not be employed when
simpler methods would serve. Pharmacognostic study involving morphological and organoleptic identification is the oldest, simplest and cheapest of all methods, thus to be preferred when its use is feasible along with the other parameters like ash value, extractive value and qualitative chemical tests serve as source of information. Hence, the studies on pharmacognostic parameters are useful tools to determine the purity of certain plants and to avoid adulteration in the process of commercialization of raw material.

The pharmacognostic studies have been extensively studied on different plants *viz.* in *Jatropha curcas* an important Ayurvedic drug known as ‘Dravanti’ (Gupta, 1985); *Ligaria cuneifolia* (Loranthaceae) used as substitute for *Viscum album*, which is used in elevated blood pressure (Wagner et al. 1998). Bassols and Gurni, (2000) studied the anatomical features of four species of *Lippia* (Family: Verbenaceae), known under the trivial name “poleo”, in order to distinguish them from each other. Kola et al. (2003) investigated the comparative pharmacognostic and antimicrobial studies on leaves of two varieties of *Heinsia crinita*. Recently pharmacognostic investigations were carried out considering various parameters like organoleptic characters, microscopy, stomatal number, stomatal index, vein islet number, vein termination number, palisade ratio, soluble extractives, loss on drying, ash values & total foreign organic matter for the characterization of plants *viz.* *Coleus forskohlii* (Shrivastava et al. 2002); *Actaea racemosa* L. (Applequist, 2003), *Uncaria tomentosa* and *Uncaria guianensis* (Gattuso et al. 2004), *Maytenus ilicifolia*, (Duarte and Debur, 2005), *Gisekia physnacioides* (Musa et al. 2006), *Crateva nurvala* (Sikarwar, 2009), *Annona squamosa* Linn. (Sharma et al. 2009), *Capparis sepiaria* (Kalidass et al. 2009) and *Holoptelea integrifolia*, (Padmaja, 2009), *Tecomella undulata* (Nitin Kumar et al. 2010), *Tecoma stans* (Dharmesh Kumar et al. 2010), *Polygonum nepalense* (Rakesh and Garg et al. 2011), *Ficus hispida* (Ravichandra et al. 2011), *Viola betonicifolia* (Naveed Muhammad et al. 2012) and *Xanthium Strumarium* (Bhogaonkar et al. 2012).
2. PHYTOCHEMISTRY

Phytochemistry deals with chemicals obtained from the plant source. These chemicals are the secondary metabolites synthesized in the plants, which most of the time protect the plants from insect and microbial attack. However, these secondary metabolites are of medicinal interest as they have got a vast range of biological activity.

In the ancient times, substances obtained from plants and animals, with or without purification have been employed for medicine. But the pure medicinal chemicals obtained from these plants have got their own advantages, since the physiological effects of such compounds are fixed and definite. The actual active constituents of many crude drugs are still unknown. The pharmacological action of the crude drugs is determined by the nature of its active constituents. The plant species may contain vast range of compounds such as alkaloids, terpenoids, flavonoids, glycosides etc. These secondary metabolites are responsible for the desired therapeutic properties. In recent years, a renewed interest in obtaining biologically active compounds from natural sources has been observed, notwithstanding the impressive progress of new competing methodologies, as for example, combinatorial chemistry and high throughput screening or genetic engineering. Contributing to this world-wide attention towards formulations based on natural products are their low or absent toxicity, their complete biodegradability, their availability from renewable sources, and in most cases, their low-cost if compared, with those of compounds obtained by total chemical synthesis. In developed countries this could be connected with the trend favourable to the so-called ‘sustainable development’, and to some extent with the observed decline of patent applications in organic chemistry, paralleled by the rise of life sciences applications (Corrado, 2001).
In developing countries, this is sustained by the search for biologically active compounds obtainable from locally available plants, particularly with a view to reducing public health costs which have significantly been raised due to acquisition of synthetic drugs from industrialized countries. The study of active principles involved in traditional medicine treatments can also lead to an improvement of these remedies. A further drive to the study of compounds obtainable from natural sources is the increasing consciousness that destruction or severe degradation of rain forests and other wild habitats, including seas and oceans, will unavoidably result in the loss of unexamined species and consequently of potentially useful compounds. In fact, individual plant species may contain over one thousand chemical substances and only a minor fraction of the estimated total of 250,000 to 300,000 plant species has been studied for biomedical application; on the other hand, the marine ecosystem is still, to a large extent, unexplored. Thus, the urgent need for protection of biodiversity is, at molecular level, a need for protection of the chemical diversity, that is the variety of natural ‘libraries’ of compounds not yet identified and characterized. Owing to this renewed attention to pharmaceuticals, agrochemicals and nutraceuticals (functional foods) obtained from natural sources, the study of bioactive secondary metabolites, traditionally carried out mainly by chemists, has increasingly attracted the attention of pharmacologists, pharmacognosists, biologists, botanists, agronomists etc. stimulating cooperative work. Chemo diversity in nature, e.g. in plants, microorganisms and marine organisms, still offers a valuable source for novel lead discovery, but rapid identification of the bioactive compounds of natural product mixtures remains a critical factor to ensure that this tool of drug discovery can compete with recent developed technologies such as chemical compound libraries and high-throughput screening of combinatorial synthetic efforts. Rapid screening of natural product mixtures requires the availability of a library of reference of natural compounds and methods for simple identification of putative lead structural classes avoiding, to a large extent, the potential for false-
positive results. The coupling of chromatographic methods such as high pressure liquid chromatography (HPLC) with diode array detection, mass spectrometry (MS) or nuclear magnetic resonance spectroscopy (NMR) or, and with, on-line bioactivity assays is an important tool for high throughput screening of natural product mixtures. The introduction of a dereplication step after extraction by using a reproducible preseparation method would enable the rapid elimination of false positives (Verpoorte, 1998) the effective use of automated procedures and databases in the isolation, identification and biological profiling of bioactive compounds from natural sources will be the best guarantee to the continued discovery of novel chemotypes from nature (Hook et al. 1997). Structure-activity studies of these leads, preferentially combined with computer graphic model building, should result in molecules with optimal activity and bioavailability, fewer side effects and an acceptable therapeutic index and, consequently in good candidates, for the development to new drugs.

Although the first chemical substance to be isolated from plants is benzoic acid in 1560, the search for useful drugs of known structure did not begin until 1804 when morphine was separated from Papaver somniferum L. Since then many useful drugs from higher plants have been discovered but less than 100 with defined structure are in common uses. But less than half of them are accepted as drugs in industrialized countries (Framesworth, 1984). Among some of the earliest successes in developing drugs from natural products, one can mention the isolation of the antimalarial agents such as the cinchona tree alkaloids, pain relievers such as the morphine alkaloids as well as the development of aspirin. Quinine (Croteau, 2000) originally isolated from the bark of cinchona trees, Cinchona succirubra, was one of the principal antimalarial agents. Morphine (Newman, 2000) the major alkaloid of Papaver somniferum was first isolated between 1803-1806. It was widely used for pain relief beginning in the 1830’s, but was also recognized as addictive. The “Ebers papyrus”, the Egyptian pharmaceutical record, indicates the
use of willow leaves as an antipyretic agent. Following on this knowledge, chemists began to isolate the compounds responsible for the remedy, and salicin was isolated from the bark of the white willow, *Salix alba* in 1825-26 (Viktorin, 1999). It was subsequently converted to salicylic acid (Wallach, 1887) via hydrolysis and oxidation, and proved potent as an antipyretic that was manufactured and used worldwide (Viktorin, 1999). To overcome the severe gastrointestinal toxicity of salicylic acid, it was converted into acetylsalicylic acid (ASA) (Ruzicka, 1953) via acetylation and started to be marketed under the trade name aspirin in 1899 (Viktorin, 1999). Aspirin is still the most widely used analgesic and antipyretic drug in the world. More recently, the vinca alkaloids, vinblastine (Loomis, 1973) and vincristine (Whittaker and Banthorpe, 1972) were isolated as antineoplastic agents from the Madagascan periwinkle, *Catharanthus roseus*, and subsequently derivatized to vinorelbine and vindesine, the drugs that are currently in use for cancer treatment (Newman, 2000). Similarly, a potent antimalarial drug, a sesquiterpenoid endoperoxide, named artemisinin (Croteau, 1981) was isolated from *Artemisia annua* as a remedy against the multidrug resistant strains of *Plasmodium*, following on the long use of this plant material as an antimalarial drug in the traditional Chinese medicine. Using the basic structure of artemisinin, semisynthetic compounds were synthesized with the aim of optimizing the pharmacology of the principal molecule leading to the identification of artemether (Bryant, 1969) and dihydroartemisinin (Roberts, 1972) as potent antimalarial agents that are now in a widespread use around the world (Newman, 2000). Paclitaxel, marketed as Taxol was initially isolated from the bark of the Pacific yellow tree *Taxus brevifolia*, is the best selling drug obtained from natural products. This drug was developed by ‘Bristol-Myers Squibb’ and marketed for the treatment of ovarian and mammary cancers, and became available for use in the USA in 1993 (Michael et al. 2004).
Anogeissus latifolia is widely used in the Indian indigenous system of medicine and is reported to contain leucocyanidins and tannoid principles like ellagic acid and its derivatives (Reddy et al. 1965). The acetone extract of Anogeissus latifolia leaves yields a phenolic fraction and a carboxylic acid fraction. From the phenolic fraction gallotonin and from carboxylic acid fraction chebulagic acid, trigallic acid and gallic acid have been isolated and identified by Deshpande et al. (1976) using fractional crystallization and preparative chromatographic techniques.

The bark of Anogeissus latifolia was first examined by Reddy et al. (1965) who isolated (+) leucocyanidin, ellagic acid and 3, 4, 3'-tri-O-methyl ellagic acid. They also reported that “while the leaves contained purely hydrolysable tannins and related compounds, the bark and wood extractives contained both flavanoid tannins and compounds related to hydrolysable and flavanoid tannins”. Reddy et al. (1965) were able to isolate a fourth product 3, 4, 3'-tri-O-methyl favellagic acid. Later ellagic acid and two new glycosides of ellagic and flavellagic acid were reported. Other known chemicals from the bark includes chebulagic acid, sitosterol, rutin, quercetin, myricetin, procyanidin along with gallotannins, shikimic acid, alanine and phenyl amine (Reddy et al. 1965 and Deshpande et al. 1976).

The natural gum of Anogeissus latifolia is a calcium salt of polysaccharide acid, ghattic acid, which is a complex mixture of pentoses and galactoses. Its molecular weight is 11860 daltons (Hanna and Shaw, 1941). Ghattic acid is obtained by the precipitation of the aqueous solution of the gum with acidified alcohol. A vigorous hydrolysis of the gum gives aldobiouronic acid from D-Glucoronic acid (Hanna et al. 1939).
3. PHARMACOLOGY

A. Hepatoprotective activity

Liver is considered to be one of the most vital organs that functions as a centre of metabolism of nutrients such as carbohydrates, proteins and lipids and excretion of waste metabolites. Additionally, it is also handling the metabolism and excretion of drugs and other xenobiotics from the body there by providing protection against foreign substances by detoxifying and eliminating them. The bile secreted by the liver has, among other things, plays an important role in digestion. Liver cell injury caused by various toxicants such as certain chemotherapeutic agents, carbon tetrachloride, thioacetamide, chronic alcohol consumption and microbes is well studied. Enhanced lipid peroxidation during metabolism of ethanol may result in development of hepatitis leading to cirrhosis. Since time immemorial, mankind has made the use of plants in the treatment of various ailments. The Indian traditional medicine like Ayurveda, Siddha and Unani are predominantly based on the use of plant materials. Herbal drugs have gained importance and popularity in recent years because of their safety, efficacy and cost effectiveness. One of the important and well-documented uses of plant products is their use as hepatoprotective agents. Hence, there is an ever increasing need for safe hepatoprotective agent (Agarwal, 2001).

Bilirubin is a breakdown product of ‘heme’ (a part of haemoglobin in red blood cells). The liver is responsible for clearing the blood of bilirubin. It clears the bilirubin by following mechanism: Bilirubin is taken up into hepatocytes, conjugated (modified to make it water-soluble), and secreted into the bile, which is excreted into the intestine. Increased total bilirubin causes jaundice, and can signal a number of problems such as Prehepatic: due to a number of causes, including hemolytic anemias and internal hemorrhage. Hepatic: problems with the liver, which are reflected as deficiencies in bilirubin metabolism (e.g. reduced
hepatocyte uptake, impaired conjugation of bilirubin, and reduced hepatocyte secretion of bilirubin). Some examples would be cirrhosis and viral hepatitis. Posthepatic: obstruction of the bile ducts, reflected as deficiencies in bilirubin excretion (obstruction can be located either within the liver or in the bile duct).

A bilirubin test measures the amount of bilirubin in a blood sample. The bilirubin test is used to,

- Check liver function and watch for signs of liver disease, such as hepatitis or cirrhosis, or the effects of medicines that can damage the liver.
- Find out if something is blocking the bile ducts. This may occur if gallstones, tumors of the pancreas, or other conditions are present.
- Diagnose conditions that cause increased destruction of red blood cells, such as hemolytic anemia or hemolytic disease of the newborn.
- Help make decisions about whether newborn babies with neonatal jaundice need treatment.

**Hepatitis**

Hepatitis is an inflammation and/or necrosis of liver cells. This may be due to chemical and biological contamination of food and water due to deterioration in environmental conditions, eating fine and with less fiber contents are some of the important factors attributed for the rising liver dysfunction. Liver infection (viral hepatitis) and dysfunction results into jaundice (Sinha and Shweta Sinha, 2001).

**Types of hepatitis**

**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. Hepatic inflammation and necrosis continues at least for 6 months. Milder forms are non progressive or only slowly progressive, while more severe forms may be associated with scarring and architectural organization, which when advanced leads ultimately to cirrhosis. 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.

Drug induced hepatitis: Jaundice due to drugs and chemicals arise as a result of accidental, suicidal or therapeutic exposure to the agent. The exposure may be of an acute or a slow, prolonged and chronic type. Certain drugs and chemicals, which are poisonous to human system, produce jaundice by hepatocellular damage. In mild cases jaundice may be absent or slight whereas in severe cases death may occur before jaundice becomes apparent. In other cases jaundice is seen in association with other manifestations like albuminuria, diarrhoea, and vomiting, renal failure or blood dyscrasias. In some cases increased haemolysis may contribute to jaundice of hepatocellular damage. The Table 1 provides information about some hepatotoxic agents and their effects on liver cells.

Carbon tetrachloride (CCl₄) is widely used in animal models to induce acute liver injury. Prolonged administration of carbon tetrachloride can lead to cirrhosis (Cameron and Karunaratne, 1936) and hepatic carcinoma (Reuber and Glover, 1970). Most of the acute and chronic hepatic injury appears to result from the action of metabolite of the toxin (Recknagel and Glende, 1973). Chemically CCl₄ is a simple, strongly non-polar molecule (Von Oettingen, 1964), which undergoes metabolism in the smooth endoplasmic reticulum. It is generally believed that the toxicity of CCl₄ results from its reductive dehalogenation by the cytochrome P450 enzyme system into the highly reactive free radical
trichloromethyl radical (Recknagel et al. 1989). Liver fibrosis induced by the CCl₄ leads to the impairment in hepatocellular functions this in turn causes obstruction in detoxification mechanism leads to the clinical conditions such as hyperbilirubinemia, hypoprothrombinaemia etc.

Table 1: Hepatotoxic agents and their effects

<table>
<thead>
<tr>
<th>Toxicity agent</th>
<th>Mechanism</th>
<th>Histological lesion</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct cytotoxic</td>
<td>Direct physiochemical distortion and destruction of structural basic cell metabolism</td>
<td>Necrosis (zonal) and/or steatosis</td>
<td>CCl₄, CHCl₃, Phosphorous</td>
</tr>
<tr>
<td>Indirect cytotoxic</td>
<td>Interference with specific metabolic pathways leading to structural injury</td>
<td>Steatosis or necrosis</td>
<td>Ethionine, Mycotoxins</td>
</tr>
<tr>
<td>Cholestatic</td>
<td>Interference with hepatic excretory pathways leading to cholestasis</td>
<td>Bile casts</td>
<td>Ictirogenin C-17 alkylated anabolic and contraceptive steroids.</td>
</tr>
</tbody>
</table>

The investigations of Karandikar et al. (1963), Rubin et al. (1963), Vaishwanar and Kowale, (1976) and Recknagel, (1983) proved that administration of CCl₄ in rats tend to cause centrilobular hepatic necrosis or toxic hepatitis and the injury caused by this toxic substance is similar to that of human infective hepatitis. Similarly, the other hepatotoxic substances like alcohol (Gulati et al. 1995); paracetamol (Chattopadhyay et al. 1992 and Ahmed and Khater, 2001); aflatoxin B₁ (Dwivedi et al. 1990); D-galactosamine (Anandan and Devaki, 1999) etc. were also known to cause hepatic cirrhosis or necrosis in albino rats. Human beings are exposed to these compounds through polluted environment, consumption of contaminated food, synthetic drugs during diseases etc. which produces toxic manifestations. Biochemical damage is produced by the reactive
oxygen species and free radicals are fundamental aspects of liver injury. Conventional drugs are often inadequate and hence it’s necessary to screen for alternative drugs that can replace currently used drugs of doubtful efficacy and safety.

In the traditional systems of medicine, various plants have been used as hepatoprotective. Many investigators reported the hepatoprotective activity in the various plant extracts such as *Embelica officinalis Gaertn*, (Pillay and Iyer, 1958; Hemadri, 1984 and Sarwat sultana et al. 2005); *Picrorhiza Kurroa* (Chaturvedi and Singh, 1965 and Atal, et al. 1985); *Phyllanthus amarus* (Thyagarajan and Jayaram, 1992); *Elephantopus scaber*, *E. mollis* and *Pseudoelephantopus spicatus* (Chun-Ching Lin et al. 1995); *Berberis aristata* (Janzaz and Gilani, 2000); *Cassia angustifolia* Vahl (Ilavarsan et al. 2001); *Aptium graveolens* Linn; *Croton oblongifolius* Roxb. (Ahmed et al. 2002); *Thespesia populnea* (Havarasan et al. 2003); *Vitex negundo* (Srinivas et al.2004); *Boerhaavia erecta* (Krishna and Shanthamma, 2004a & b); *Diospyros cordifolia* (Krishna et al. 2005); *Polygala arvensis* (Dhanabal et al. 2006); *Beta vulgaris* (Agarwal et al. 2006) and *Pergularia daemia* (Sureshkumar and Mishra, 2007); *Cichorium intybus* (Madani et al. 2008); *Phyllanthus reticulatus* (Biplab et al. 2008); *Annona squamosa* (Raj et al. 2009); *Cassia roxburghii* (Arulkumaran et al. 2009); *Spondias pinnata* (Ganga Rao and Jaya Raju, 2010), *Aegle marmelos* (Sumitha and Thirunalasundari et al. 2011) and *Indigofera tinctoria* (Gnanasekaran et al. 2012).

Silymarin is a flavonoid isolated from *Silybum marianum* that heralded widespread world research on hepatoprotective agents (Wagner et al. 1968; Abraham et al. 1970 and Pelter and Hansel, 1975). Silymarin has been reported to protect liver cells from a wide variety of toxins, including acetaminophen, ethanol, carbon tetrachloride and D-galactosamine. Silymarin has also been found to protect liver cells from ischemic injury, radiation, iron toxicity, and viral hepatitis.
The mechanisms which provide silymarin's hepatoprotective effects are many and varied, and include antioxidation, anti-lipid peroxidation, enhanced detoxification, and protection against glutathione depletion. Silymarin has been found to inhibit the formation of leukotrienes from polyunsaturated fatty acids in the liver, via its inhibition of the enzyme lipoygenase. These leukotrienes are known to be some of the most damaging chemicals found in man. *Picrorhiza kurroa*, on the other hand, though less well researched than silymarin, appears to have similar applications and mechanisms of action. When compared with silymarin, the hepatoprotective effect of *picrorhiza* was found to be similar, or in many cases superior, to the effect of silymarin. Other important antihepatotoxic drug discoveries from plant sources include cynarin from *Cynara scolymus* (Panizzi and Scarpti, 1954) and schisandrin from *Schisandra sphenanthera* (Liu et al. 1978). The discovery of diverse chemical compounds from the natural products and synthetic compounds used in protective liver therapy such as phospholipids, sugar alcohols, pyrimidine, purine derivatives, vitamins, cysteine, glutathione, corticoids, androgens, penicillamine, ricinin etc. does not confine the activity to any particular class of compounds (Shirwaikar et al. 1991), but emphasizes once again the complexity of liver disorders in addition to the different action, mechanisms of different pharmaceutical preparations.

Search for hepatoprotective drug has been investigated by several workers utilizing different plant species. Visen et al. (1990) isolated an active constituent andrographolide from *Andrographis paniculata* which was found to possess the hepatoprotective activity against paracetamol induced hepatic damage. Two iridoid glycosides isolated from the plant *Picrorhiza kurrooa* exhibited significant hepatoprotective and anti-cholestatic activity against CCl₄ induced hepatitis (Dwivedi et al. 1991 and Saraswath, 1993). Lin and Shieh, (1997) studied the hepatoprotective activity of the constituents baicalein, baicalin and wogonin,
isolated from *Scutellaria rivularis*. Koul and Kapil (1999) observed that, the piperine isolated from black and long peppers has got significant hepatoprotective activity. Lim, *et al.* (2000) has evaluated the hepatoprotective effect of bergenin a major constituent of *Mallotus japonicas*. Bergenin has a potent hepatoprotective action against CCl₄ induced hepatic damage in rats which was indicated by controlling the serum enzyme levels. Bhattacharya *et al.* (2000) reported that glycowithanolides, isolated from *Withania somnifera* have protective effect against iron induced hepatotoxicity. 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 seeds 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. Hepatoprotective activity of isolated bioactive compound indigotone from *Indigofera tinctoria* (Singh *et al.* 2001) showed significant hepatoprotective activity against CCl₄ induced liver damage in rats and mice. Tran *et al.* (2001) also observed that the triterpene and saponins from *Panax vietnamensis* has showed the hepatoprotective activity. Khalid *et al.* (2002) isolated rutin from *Artemisia scoparia* and investigated its hepatoprotective activity against paracetamol and CCl₄ induced hepatotoxicity. The ethanol extract fractionation of *Cnidium monnieri* 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. Yoshikawa *et al.* (2003) noticed that the triterpene and saponins isolated from *Panax notoginseng* has hepatoprotective
effects. 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 (Choi *et al.* 2006). Echinacoside, is a phenylethanoid isolated from the stems of *Cistanches salsa* (Fam: Orobanchaceae), in carbon tetrachloride-induced hepatotoxicity showed significant result by reducing serum ALT, AST levels, hepatic MDA content, ROS production, and hepatic SOD activity and GSH content were restored remarkably in rats. Moreover, the histopathological damage of liver and the number of apoptotic hepatocytes were also significantly ameliorated by echinacoside treatment (Wu Yu *et al.* 2007). Bacoside-A (B-A) pretreatment (isolated from *Bacopa monniera* Linn; Fam: scrophulariaceae), for 21 days in dose of 10 mg/kg of body weight once daily on oral administration reduced the elevated levels of serum ALT, AST, ALP, GGT and LDH (Sumathi and Nongbri, 2008). Colchicine, the major alkaloid and its derivative trimethylcolchicinic acid (TMCA) of *Colchicum autumnale* (fam: Colchicaceae) was found to possess protective effects in the liver of experimental animals against several hepatotoxins *i.e.* D-galactosamine & paracetamol (Muriel and Rivera-Espinoza, 2008). Picroliv or Kutkin is a glucoside obtained from 3 - 4 years old roots and rhizomes of an endangered medicinal plant - *Picrorhiza kurroa* (kutki) used mainly for the treatment of a variety of liver ailments. It is an iridoid glycoside mixture containing 60% picroside I and kutkoside in the ratio of 1:1.5. Picroliv has shown efficacy comparable to silymarin in rodent models of galactosamine, paracetamol, thioacetamide and CCl₄ induced hepatic damage (Verma *et al.* 2009). The *in vitro* hepatoprotective effect of the methanolic extract from *Irvingia gabonensis* on CCl₄ induced liver cell damage effect were investigated. The phytochemical investigation of this methanolic extract led to the isolation of seven compounds identified as: 3-friedelanone (1); betulinic acid (2); oleanolic acid (3); 3, 3', 4'-tri-O-trimethylellagic acid (4); methyl gallate (5); hardwickiic acid (6) and
3-β-acetoxyursolic acid (7). The hepatoprotective activity of these compounds was tested in vitro against CCl4-induced damage in rat hepatoma cells. Compounds (3), (7), (5) and (2) showed significant hepatoprotective activity as indicated by their ability to prevent liver cell death and LDH leakage during CCl4 intoxication (Hubert Donfack et al. 2010). The diterpene isolated from methanol extract of Hedychium spicatum (Zinziberaceae) was subjected to in vitro hepatoprotective studies using paracetamol induced hepatotoxicity in primary rat hepatocytes. The isolated diterpene showed significant protective effect by restoring altered parameters (Joshi Uttara et al. 2011).

B. Anti hyperglycemic activity

Diabetes mellitus is a syndrome characterized by disturbed metabolism of carbohydrate, fat and proteins resulting in high blood glucose level due to lack or ineffective insulin action (Tuitoek et al. 1996). The rapidly increasing incidence of diabetes mellitus is becoming a serious threat to human health throughout the world (Malviya et al. 2010). The oral hypoglycemic agents and insulin preparations are the currently available forms of drugs for the treatment of diabetes mellitus but are not free from undesirable side effects (Ibrahim, 2010). The management of diabetes mellitus thus is global challenge that demands for alternative therapy. The need of the hour, therefore, is to develop indigenous safe and effective herbal formulations free from undesirable effects and cost effective too. Plant products are well known to mankind since time immemorial to treat a number of ailments by virtue of their contents. The phytoconstituents present in the herbal plants such as alkaloids, terpenoids, flavonoids, phenolics and some other chemical constituents have shown to possess antidiabetic potential (Bnouham et al. 2006 and Malviya et al. 2010).
Types of *Diabetes mellitus*

There are four major classifications of *Diabetes mellitus*

**Type I**

This is known as insulin dependent diabetes mellitus (IDDM)/ juvenile diabetes. About 5-10% of patients have type I diabetes mellitus. The pancreas produces inadequate amounts of insulin, resulting in the need for insulin injections to control the blood glucose. It is characterised by a sudden onset, usually before the age of 30 years (Mythili et al. 2004).

**Type II**

This is also known as the NIDDM (non-insulin dependent diabetes mellitus) and is the more common form of diabetes. It results from a decrease in the sensitivity of the cells to insulin and a decrease in the amount of insulin produced. About 90-95% of patients have type II diabetes. This type II diabetes is treated with diet and exercise, and if elevated glucose levels persist, diet is supplemented with oral hypoglycaemic agents.

**Other types (type III)**

This is where diabetes mellitus is associated with other conditions, for example, pancreatic disease, hormonal disorders and drugs such as glucocorticoids and oestrogen-containing preparations. Depending on the ability of the pancreas to produce insulin, the patient may require oral agents or insulin.

**Gestational diabetes mellitus**

The onset of gestational diabetes mellitus is during pregnancy, usually in the second or third trimester, as a result of hormones secreted by the placenta, which inhibit the action of insulin. It occurs in about 2-5% of all pregnancies.
About 30-40% of patients with gestational diabetes mellitus will develop type II diabetes within 5-10 years (especially if obese).

**Artificial induction of diabetes in rats**

In humans, diabetes mellitus is one of the most prevalent conditions with spontaneous manifestation. In animals, it can be induced by partial pancreatectomy or by the administration of diabetogenic drugs such as alloxan, streptozotocin, ditizona and anti-insulin serum. These agents selectively destroy the Langerhans islet β-cells. The best known drug-induced diabetes model is the streptozotocin and alloxan diabetes, which induces irreversible diabetes mellitus after 24 hours following its administration and the condition, proves to be chronic by laboratory tests after seven days.

The diabetes induced animals shows the following signs of the condition: polydipsia (abnormal thirst), polyuria (increased urine volume), weight loss (due to lean mass loss), asthenia (weakness due to the inability to use glucose as a source of energy), dehydration (due to the animal body’s attempt to get rid of the excess blood glucose as the normal process of storing glucose in the body cells is impaired).

**Streptozotocin**

Streptozotocin [IUPAC Name: 1-methyl-1-nitroso-3-[2,4,5-trihydroxy-6-(hydroxymethyl) oxan-3-yl]-urea, C₈H₁₅N₃O, (STZ)] is a naturally occurring chemical that is particularly toxic to the insulin-producing β-cells of the pancreas in mammals. It is used in medicine for treating certain cancers of the Islets of Langerhans and used in medical research to produce an animal model for diabetes.

Streptozotocin enters the pancreatic β-cell via a glucose transporter GLUT2 and causes alkylation of deoxyribonucleic acid (DNA). Furthermore, STZ induces
activation of poly adenosine diphosphate ribosylation and nitric oxide release. As a result of STZ action, pancreatic β-cells are destroyed by necrosis (Mythili et al. 2004). In adult rats, 60 mg/kg is the most common dose of STZ to induce insulin dependent diabetes (Patel et al. 2006), but higher doses are also used. STZ is also efficacious after intraperitoneal administration of a similar or higher dose, but single doses below 40mg/kg may be ineffective (Katsumata et al. 1992). In general, rats are considered diabetic if tail blood glucose concentrations in fed animals are greater than 200-300mg/dl, 2 days after STZ injection. A model of type II diabetes can be induced in rats by either i.v. (tail vein) or i.p. treatment with STZ in the first days of life.

Many investigators worked on indigenous plants to know the efficacy of antidiabetic property such as, Eugenia jambolana (Venkateswarlu, 1952); Syzygium cumini (Bhatia and Bajaj, 1975); Dietary Fish and Safflower Oil (Wong et al. 1984); Allium sativum (Sheela et al. 1992); Myristica fragrans (Arti Sharma, et al.1995 and Somani and Singhai, 2008); Allium sativum (Sheela et al. 1995); Salacia oblonga (Krishnakumar et al. 1999); Caralluma assttenuate (Venkatesh et al. 2003); Barleria lupilina (Suba et al. 2004); Annona squamosa (Shirwaikar et al. 2004); Persea americana (Antia et al.2005); Coccinia indica (Dhanabal et al. 2004); Acacia catechu (Ray et al. 2006); Cocculus hirsutus (Badole et al. 2006); Passiflora mollissima (Edwin et al. 2007); Ficus bengalensis (Sharad Sharma et al. 2007); Ichnocarpus frutescens (Rakesh Barik et al. 2008); Cassia auriculate (Surana et al. 2008); Carthamus tinctorious (Paramesha et al. 2009a); Anogeissus latifolia (Parvathi et al. 2009a); Cassia occidentalis (Emmanuel et al. 2010); Barringtonia acutangula (Khatib and Patil, 2011); Lagenaria siceraria (Prerona Saha et al. 2011); Glinus oppositifolius (Nazia Hoque et al. 2011) and Aristolochia indica (Sanjay Kumar Karan et al. 2012).
C. Hypolipidemic activity

Hyperlipidemia is a major risk factor in the initiation and progression of atherosclerotic lesions, conditions such as coronary heart disease, ischemic cerebrovascular disease and peripheral vascular disease. This leads to high mortality and morbidity rate in developed countries. This is mainly due to altered lipoprotein metabolism. It is considered as one of the five leading causes of the death in the world (NCEP, 2002 and Crowther, 2005). Since standard treatment of dyslipidemia with statins and with the other available agents have proven adverse effects (Anna Jamroz-Wisniewska and Jerzy Beltowski, 2005), now a days there is an increasing interest towards the potential health benefits of medicinal plants. Many indigenous Indian medicinal plants have been found to be useful to manage the hyperlipidemia such as Allium sativum (Garlic) (Julie et al. 2001), Curcuma longa (Turmeric) (Halim eshrat and Ali Hussain, 2002), Glycyrrhiza glabra (Asgary et al. 2006), Aloe barbadensis (Aloe vera) (Kim et al. 2009), Ocimum sanctum, (Tulasi) (Eshrat Halim et al. 2009) and others.

Lipoproteins and atherogenesis

The two main lipids in blood are cholesterol and triglyceride. They are carried in lipoproteins, which are globular packages that also contain proteins known as apoproteins. Cholesterol is an essential element of all animal cell membranes and forms the backbone of steroid hormones and bile acids; triglycerides are important in transferring energy from food into cells.

Lipoproteins are usually classified on the basis of density. Density is determined by the amounts of triglyceride and apoproteins. The least dense particles, known as chylomicrons, are normally found in the blood only after fat containing foods have been eaten. Chylomicrons rise as a creamy when nonfasting serum is allowed to stand. The other lipoproteins are suspended in serum and must be separated using a centrifuge. The densest (and smallest) family of particles
consists mainly of apoproteins and cholesterol and is called high-density lipoproteins (HDL). Somewhat less dense are the low-density lipoproteins (LDL). Least dense are the large, very-low-density lipoproteins (VLDL), consisting mainly of triglyceride. In fasting serum, most of the cholesterol is carried on LDL particles and is therefore referred to as LDL cholesterol; most of the triglyceride is found in VLDL particles. Specific apoproteins are associated with each lipoprotein class.

The plaques found in the arterial walls of patients with atherosclerosis contain large amounts of cholesterol, providing an early clue that serum cholesterol might be an important factor in their development. Epidemiologic studies have clearly established that the higher the level of LDL cholesterol, the greater the risk of atherosclerotic heart disease; conversely, the higher the level of HDL cholesterol, the lower the risk of coronary heart disease. This is true in men and women, in different racial and ethnic group and at all adult ages (Lawrence et al. 2005).

Studies have indicated that a diet low in fiber is associated with the incidence of adult disease including coronary heart disease (Kritchevsky and Story, 1978) and a colon cancer (Freudenheim et al. 1978). The health benefits of dietary fiber and pectin gums in reducing the risk of chronic diseases particularly serum cholesterol lowering effect have been hypothesized. Mechanisms proposed to explain antihypercholesterolomic effect of these include, 1) Altered intestinal absorption, metabolism and release of cholesterol through an influence on bile acids. 2) Altered hepatic metabolism and release of cholesterol with increased excretion of bile acids reducing the size of the bile acid pool and less cholesterol available for incorporation into lipoprotein and subsequent release into the circulation and 3) Altered peripheral metabolisms of lipoproteins. Fibers may also alter the proportion of cholesterol incorporated into chylomicrons and lipoprotein (Anderson and Wound Chen, 1979).
The hypolipidemic activity has been a matter of rigorous experimentation utilizing many medicinal plants viz. *Achyranthus aspera* (Khanna et al. 1992); *Terminalia chebula* (Khanna et al. 1993); *Myristica fragrans* (Ram et al. 1996); *Curcuma longa* (Godkar et al. 1996); *Psyllium* seed (Kotaro Segawa et al. 1997); traditional Chinese medicine –Kampo Medicine (Chun Zhen Wu et al. 1998); *Trigonella foenum* (Prasanna et al. 2000); *Allium sativum* (Augusti et al. 2001); *Cordyceps sinesis* (Jong-Ho Koh et al. 2002); *Phyllanthus niruri* (Khanna et al. 2002); *Ginkgo biloba* (Arun Kumar Dubey et al. 2004); *Clemode felina* (Nagarajan et al. 2005); *Salacia oblonga* and *Salacia reticulata* (Rabbani et al. 2006); *Strobilanthes heyneanus* (Mukunda et al. 2008); *Eclipta prostrata* (Dandapani et al. 2007); *Langanaria officinaria* (Mohale et al. 2008); *Aloe vera* (Mamata chandrakar et al. 2008); *Carica papaya* (Adeneye and Olagunju, 2009); *Mucuna purpuriens* (Murugan and Uma Maheshwara, 2009); *Mimosa pudica* (Rekha Rajendran and Ekambaram Krishnakumar, 2010); *Asparagus racemosus* (Ramachandran Vadivelan et al. 2011); *Vebesina encelioides* (Rakesh Sindhu et al. 2011); *Pleurotus ostreatus* (Nuhu Alam et al. 2011) and *Nyctanthes Arbortristis* (Krishna Murti et al. 2012).

D. Antiinflammatory activity

Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbial agents and is the body's effort to inactivate or destroy invading organisms, remove irritants, and set the stage for tissue repair (Mary, 1997). Upon interaction of foreign pathogens with innate immune cells like macrophage or monocytes, inflammatory immune response is trigger off. Inflammatory mediators elicit a complex series of cellular events upon interaction with invading microorganisms, including increased permeability of vessels, exudation of fluids and migration of leukocytes into the inflammatory focus, resulting in phagocytosis and killing of the microorganisms (Heumann and
Roger et al. 2002). The inflammatory responses are vigorous reactions that results in some collateral damage to the surrounding tissues but such effect is normally local and transient (Bosca et al. 2005).

Essentially there are two types of inflammation: acute and chronic. The classical signs of acute inflammation are warmth, redness, pain, swelling and loss of function. Chronic inflammation is also characterized by long lasting pain, redness and swelling and is caused by the persistence of an irritant, which may be biological, physical or chemical in nature.

Inflammation research involves a number of experimental models to study the anti-inflammatory activity. According to Lewis (1989) acute models are designed to test drugs that modulate erythema, changes in vascular permeability, leukocyte migration and chemotaxis, phagocytosis-polymorphonuclear leucocytes and other phagocytic cells, measurement of local pain, antipyretic activity and local analgesic action and rat paw edema (Barbosa-Filho et al. 2006) while, chronic models are designed to find drugs that may modulate the disease process and these include sponge and pellet implants and granulama pouches which deposit granulation tissue, adjuvant induced arthritis and rabbit monoarticular arthritis which have an immune etiology.

Natural products have long been recognized as an important source of therapeutically effective medicines for antiinflammation (Cragg et al. 2003). Different approaches used to analyze the anti-inflammatory potential of plant and plant derived compounds have been developed in the past years. Further, traditional herbal medicines like Commiphora mukul, Boswellia serrata, Harpagophytum procumbens and Pluchea indica have been used for antiinflammatory effect with success (Vohara and Dandiya, 1992).
Plants as anti-inflammatory agents

Practitioners of traditional Indian medicine, use formulation for anti-inflammatory action with considerable success. Dashmoola is standard ayurvedic remedy for anti-inflammatory diseases (Sharma and Sharma, 1973). The anti-inflammatory activity of many medicinal plants have been scientifically evaluated viz. *Rhododendron arboreatum* (Agarwal and Sharma, 1986); *Caralluma tuberculata* (Ahmed et al. 1993); *Rubia cordifolia* (Antarkar et al. 1994); *Mitracarpus scaber* (Ekpendu et al. 1994); *Curcuma amada* (Mujumdar et al. 2000) *Gochnatia polymorpha* (Moreira, 2000); *Goniothalmus andersonii* (Shigeo et al. 2001); *Cassia angustifolia, Rheum palmatum, Coptis chinensis, Phellodendron amurense* and *Scutellaria baicalensis* (Cuellar et al. 2001); *Clitoria fairchildiana* (Pereira da Silva and Paz Parente, 2002); *Leucas aspera* (Goudgaon et al. 2003); *Calendula officinalis, Hypericum perforatum, Plantago lanceolata* and *Glycyrrhiza glabra* (Herold et al. 2003); *Alchornea cordifolia* (Mavar et al. 2004); *Erigeron floribundus* (Asongalem, 2004); *Synurus deltoids* (Park et al. 2004); *Securidaca longipedunculata* (Okoli, 2005); *Vitex negundo* (Rasadah et al. 2005) *Bacopa monniera* (Shabana, 2006); *Ruta graveolens* (Ratheesh and Helen, 2007); *Aloe buettneri* (Metowogo, 2008), *Putranjiva roxburghii* (Wantana, 2009) and *Magnolia ovate* (Candida, 2009); *Cordia dichotoma* (Sharma, 2010); *Rubia Cordifolia* (Tailor Chandra Shekhar, 2010); *Filicium decipiens* (Paramaguru et al. 2011); *Boswellia Serrata* (Ramakrishnan et al. 2011) and *Leptadenia pyrotechnica, Haloxylon salicornicum* and *Ochradenus baccatus* (Saleh Ibrahim Alqasoumi et al. 2012).

E. Analgesic activity

Pain is an unpleasant sensation which informs structural and functional changes in body and acts as a warning signal against disturbances in the body. Even though pain is an unpleasant sensation, is mainly a protective mechanism for
the body (Kanodia, 2008). It is a consequence of complex neurochemical processes in the central and peripheral nervous systems (Mary, 1997). Typically, it is a direct response to an event associated with tissue damage, such as injury, inflammation or cancer, but severe pain can arise independently of any obvious predisposing cause or it can also occur as a consequence of brain or nerve injury.

An analgesic (also known as a painkiller) is any member of the diverse group of drugs used to relieve pain (achieve analgesia). The word analgesic derives from Greek an- ("without") and algos ("pain"). Analgesic drugs act in various ways on the peripheral and central nervous systems; they include paracetamol (para-acetaminophenol), the non-steroidal anti-inflammatory drugs (NSAIDs) such as the salicylates, narcotic drugs such as morphine, synthetic drugs with narcotic properties such as tramadol, and various others. In choosing analgesics, the severity and response to other medication determines the choice of agent; the WHO pain ladder, originally developed in cancer-related pain, is widely applied to find suitable drugs in a stepwise manner (Anonymous, 1990). The analgesic choice is also determined by the type of pain: for neuropathic pain, traditional analgesics are less effective, and there is often benefit from classes of drugs that are not normally considered analgesics, such as tricyclic antidepressants and anticonvulsants (Dworkin, 2003). Non-steroidal anti-inflammatory drugs (NSAIDS) and opioids are used in management of mild to moderate and severe pains respectively. These drugs have serious limitations due to their side effects (Mary, 1997 and Sathoskar, 1986). A natural agent with reduced or no toxicity is therefore, essential.

Evaluation of analgesic agents is done by several methods some prominent ones are -Physical stimulus (Tail-Flip method), Thermal stimulus, Hot plate method, Tail flick method, Tail immersion method, Chemical Stimulus, Writhing test, Writhing induced by 4% NaCl Solution and Writhing induced by aconitine etc.
In view of the side effects of the synthetic analgesic drugs, investigators on the lookout for the safer ways in plants have been well documented *viz.* *Caesalpinia ferrea* (Carvalho et al. 1996); *Psidium guajava* (Kulkarni et al. 1999); *Tragia involucrata* (Dhara et al. 2000); *Parkia biglobosa* (Kouadio et al. 2000); *Piperomia pellucid* (Peter et al. 2001); *Enhydra fluctuans* and *Polygonum hydropiper* (Rahaman et al. 2002); *Cleome viscosa* (Parimaladevi et al. 2003a); *Clitoria ternatea* (Parimaladevi et al. 2003b); *Datura fastuosa* (Abena et al. 2003); *Carthamus lanatus* (Bocheva et al. 2003); *Spilanthes camels* (Chakraborty et al. 2004); *Capparis zeylanica* (Chaudhary et al. 2004); *Zataria multiflora* (Jaffary et al. 2004); *Neem* (Patel et al. 2005); *Euphorbia deciensi* (Ahmad et al. 2005); *Sida acuta; Stylosanthes fruticosa, Toona ciliate, Bougainvilla spectabilis, Ficus glomerata* and *Polyalthia longifolia* (Malairajan, 2006); *Teucrium stocksianum* (Radhakrishnan, 2001); *Mahonia oiwakensis*, (Jung Chao, 2009); *Argyreia speciosa*, (Bachhav, 2009); *Citrus decumana* (Shailja, 2009); *Trapa natans* (Anuj et al. 2010); *Ficus bengalensis* (Sachdev Yadav, 2010), *Kaempferia galanga* (Amberkar et al. 2011) and *Ludwigia repens* (Muhammad Erfan Uddin et al. 2012).

**F. Anthelmintic activity**

Helminthiasis is prevalent globally, but is more common in developing countries with poorer personal and environmental hygiene. The World Health Organization estimates that a staggering two billion people harbour parasitic worm multiple infestations in the same individual are not infrequent. In the human body, gastro intestinal tract is the abode of many helminthes, but some also live in tissues. They harm the host by depriving food, causing blood loss, injury to organs intestinal or lymphatic obstruction and by secreting toxins. Helminthiasis is rarely fatal, but is a major cause of ill health (Tripathi, 2003). The main reasons responsible for the widespread nature of this disease in the developing countries are the lack of adequate sanitary facilities and supply of water, coupled with
poverty and illiteracy. The helminth infection can be acquired by contact with infected animal, ingestion of infected meat, animal or human excreta via ground water, by means of certain mosquitoes.

Diseases caused by helminth parasites in livestock continue to be a major problem, especially in small ruminants in the tropics and subtropics (Perry et al. 2002). Infections by gastrointestinal helminth parasites of livestock are among the most common and economically important diseases of grazing livestock (Monteiro, 1998). Adulteration of anthelmintics has been found to be a common practice (Dano and Bogh, 1999). Illiteracy and unfamiliarity with synthetic anthelmintics, resulting in incorrect usage, are also a problem leading to the same consequences. Moreover, these drugs are relatively expensive. As a consequence of these problems and difficulties, pastoralists and small holder farmer have continued to use indigenous plants as livestock dewormers (Waghorn and McNabb, 2003). Considerable research has shown that some plants not only affect the nutrition of animals, but also have antiparasitic effects (De Bairacli and Levy, 1991). For example, plants that contain condensed tannins have these effects. Anthelmintics are drugs that are used to treat infections with parasitic worms. This includes both flat worms, e.g. flukes and tapeworms and round worms, i.e. nematodes. They are of huge importance for human tropical medicine and for veterinary medicine.

Many plants have been used from ancient times to cure parasitic diseases of man and animals. For example Caesalpinia crista (Leguminosae), Melia azedarach (Meliaceae), Saussurea lappa (Compositae), Morringa oleifera (Moringaceae), Trachelospermum jasminoides, Butea frondosa (Leguminosae) etc. have been quite commonly used (Nadkarni, 1954). The fruit of Mallotus philippinensis (Euphorbiaceae) has been used as an anthelmintic; it has also been used in external applications for the control of parasitic infections of the skin, as an antiseptic for ears and systemically for urinary disorders (Chopra et al. 1956;
Ikram & Hussain, 1978 and Satyavati *et al.* 1987). Seeds of *Butea superba* are extensively used as sedative and anthelmintic in the indigenous system of medicine (Chopra *et al.* 1958). The powdered seeds and various extracts of plant *Peganum harmala* have been used as narcotic, analgesic, and antispasmodic in colic and as a remedy against tapeworm infection in man and animals (Chopra, 1956 and Said, 1969). *Vernonia anthelmintica, Embellia ribes, Psoralea corylifolia* and *Punica granatum* have been reported to possess anthelmintic, laxative, expectorant, diuretic and tonic properties (Nadkarni, 1954; Chopra *et al.* 1956; Said, 1969; Ikram and Hussain, 1978; Awan 1981 and Akhtar and Riffat, 1985). Various parts of *Lagenaria siceraria* have been used to treat tapeworm infections in children (Awan, 1981). *Fumaria parviflora* is traditionally used as an antidiabetic, diaphoretic, diuretic, anthelmintic (Nadkarni, 1954 and Chopra *et al.* 1956). *Nigella sativa* is used as an anthelmintic, stimulant and diuretic (Nadkarni, 1954 and Said, 1969). The roots of *Morus* are considered as an anthelmintic and vermifuge, whereas root bark and stem bark are reported to be vermifuge and purgative (Nadkarni, 1954).

Eventhough indigenous system of medicine reports a number of plants for their anthelmintic efficacy but their scientific evaluation as compared to commercial anthelmintics is limited. Alkaloid hydrochlorides extracted from seeds of *Butea frondosa* proved 100% lethal to earthworms within 24 h indicating their anthelmintic activity (Kalesaraj and Kurup, 1962). Garg and Atal (1963) reported remarkable vermicidal activity of Calotropain (proteolytic enzyme isolated from the latex of *Calotropis procera* and Bromelain (an enzyme obtained as a by-product from pineapple industry) against *Oesophagostomum columbianum* and *Bunostomum trigonocephalum* of sheep origin compared to phenothiazine.

*In vitro* anthelmintic activity is matter of several investigations in various plants *viz.* *Ananas sativus, Embellia ribes, Mucuna prurita* and *Melia azedarach* has significant activity against *Taenia canina* and *Paramphistomum cervi*;
Macuna prurita was especially quite active against trematodes (Neogi et al. 1964); Anacardic acid form Semecarpus anacardium and its sodium salt have been found to be potent anthelmintic agent (Chattopadhyaya and Khare, 1969); Zingiber zerumbet; Allium sativum; Alpinia calcarata; Citrus acida; Citrus aromatic; Citrus medica; Cucuruma aromatic, and Punica granatum (Kalesaraj and Kurup 1962); Lantana camara var. aculeate (Avadhoot et al. 1980 and Girme et al. 2006); Eugenol from Ocimum sanctum (Asha et al. 2001); Balanites roxburghii (Basavaraj Padmashali et al. 2001); Cordia dichotoma (Kuppasta and Nayak, 2003); Artemisia brevifolia (Iqbal et al. 2004); Bacopa monnieri (Ghosh et al. 2005), Enhydra fluctuans, Ananas comosus, Azadirachta indica, Caesalpinia crista, Vernonia anthelmintica, Fumaria parviflora and Embelia ribes (Hordegen et al. 2006), Flemingia vestita (Tandon and Das, 2007) and Euphorbia tirucalli (Asha et al. 2009); Carthamus tinctorious (Paramesha et al. 2009b); Anogeissus latifolia (Parvathi et al. 2009b) and Chlorophytum borivilianum (Deore and Khadabade, 2010), Aerva lanata (Rajesh et al. 2010), Cassia auriculata (Sucheta et al. 2011) and Carica papaya (Lakshmi kanta kanthal et al. 2012).