Chapter - 1
Introduction
1. INTRODUCTION

Plants have formed the basis for treatment of diseases in traditional medicine for thousands of years and continue to play a major role in the primary health care of about 80% of the world’s inhabitants [Farnsworth et al., 1985]. It is also worth noting that (a) 35% of drugs contain ‘principles’ of natural origin and (b) less than 5% of the 500,000 higher plant species have undergone pharmacological screening. Each plant has potentially 10,000 different constituents [Belle & Charlwood, 1980].

By definition, ‘traditional’ use of herbal medicines implies substantial historical use, and this is certainly true for many products that are available as ‘traditional herbal medicines’. In many developing countries, a large proportion of the population relies on traditional practitioners and their armamentarium of medicinal plants in order to meet health care needs. In this modern setting, ingredients are sometimes marketed for uses that were never contemplated in the traditional healing systems from which they emerged. An example is the use of Ephedra for weight loss or athletic performance enhancement [Shaw, 1998].

The discovery and development of efficacious therapeutic agents from natural sources provided convincing evidence that plants could be a source of novel drugs. Western medicine use many drugs extracted from natural products: atropine, cocaine, digitoxin, ephedrine, hyoscine, codeine, morphine, pilocarpine, quinine, reserpine, taxol, warfarin, menthol, etc. While the natural product isolated as the active compound might not always be suitable for development as an effective drug, it can provide a suitable lead for conversion into a clinically useful agent [Belle & Charlwood, 1980].

Ayurveda is a medical system primarily practiced in India for nearly 5000 years. It includes diet and herbal remedies, while emphasizing on the body, mind and
spirit in disease prevention and treatment [Morgan, 2002]. The word “Ayurveda” means literally the knowledge or science (Veda) of life (Ayu). The aim of Ayurveda is to improve the quality and span of life, in preserving and promoting the fitness of healthy individuals [Dahanukar & Thatte, 1993]. Ayurveda always gives a primary importance to the maintenance of sound health and the prevention of disease by the simple device of raising the individual resistance of the body and providing active immunity [Dash, 1991; Seth, 1996].

Plants and their secondary metabolites have a long history of use in modern ‘western’ medicine and in certain systems of traditional medicine. Monographs on selected herbs are available from a number of sources, including the ‘European Scientific Cooperative on Phytotherapy’ [ESCOP, 1999], ‘Natural Medicines Comprehensive Database’ [Jellin et al., 2000], ‘The complete German Commission E monograph’ [Blumenthal et al., 1998] and the ‘World Health Organization’ [WHO, 1999]. The WHO monographs, for example, describe the ‘herb’ itself by a number of criteria including synonyms and vernacular names and the herb part commonly used, its geographical distribution, tests used to identify and characterize the herb (including macroscopic and microscopic examination and purity testing), the active principles, dosage forms and dosing, medicinal uses, pharmacology, contra-indications and adverse reactions. Information about other available databases has been published [Bhat, 1995].

**Liver**

Liver is a soft, dark brown, highly vascular organ. It is the largest gland in the body. It has a weight range of 1.4 - 1.8 kg in adult males and 1.2 - 1.4 kg in adult females [Williams et al., 1995]. It occupies a substantial part of the abdominal cavity. It lies under the diaphragm. It occupies most of the right hypochondrium, part of the
epigastrum, and extending into the left hypochondriac region [Wilson & Waugh, 1996].

The liver is divided into two primary lobes. The two primary cells of the liver are the hepatocytes and kupffer cells [Sherwin & Sobenes, 1996]. Hepatocytes constitute about 80% of the liver by volume and 60% of the liver by number. They form a continuous system or murale of hepatic laminae. Hepatocytes are polyhedral with five to twelve sides. Their nuclei are euchromatic and polyplody. Their cytoplasm displays much granular and agranular endoplasmic reticulum, mitochondria, lysosomes, golgi bodies. They contain characteristic type of cytokeratin filaments. Hepatocytes mediate many activities [Williams et al., 1995].

**Functions of Liver**

More than 500 vital functions have been identified with the liver. Some of the more well-known functions include the following:

Production of bile, which helps carry away waste and break down fats in the small intestine during digestion, production of certain proteins for blood plasma, production of cholesterol and special proteins to help carry fats through the body, conversion of excess glucose into glycogen for storage (glycogen can later be converted back to glucose for energy), regulation of blood levels of amino acids, which form the building blocks of proteins, processing of hemoglobin for use of its iron content (the liver stores iron), conversion of poisonous ammonia to urea (urea is an end product of protein metabolism and is excreted in the urine), clearing the blood of drugs and other poisonous substances, regulating blood clotting, resisting infections by producing immune factors and removing bacteria from the bloodstream.

When the liver has broken down harmful substances, its by-products are excreted into the bile or blood. Bile by-products enter the intestine and ultimately
leave the body in the form of feces. Blood by-products are filtered out by the kidneys, and leave the body in the form of urine [Kaplan et al., 1988].

Diseases of the liver

The disturbances of metabolism occurring in liver diseases are largely the result of failure of the parenchyma cells to carry out vital functions because of: Infectious or noxious agents, decreased mass of functioning cells, decreased blood supply, impaired nutrition, reactions of other organs to liver damage [Hawk, 1979].

Some of the drugs, their metabolites and various chemicals are toxic to hepatic cells and induce various injuries that may range from cholestasis to cell injury of particular structures or organelles and may even cause cell necrosis. Liver cells develop only when needed to replace damaged cells. Capacity for regeneration is considerable and damage is extensive before it is evident.

The diseases that can affect the liver include, Hepatitis, alcohol related liver diseases, Jaundice, liver tumors and Reye’s syndrome [Isselbacher & Podolsky, 1994; Sherwin & Sobenes, 1996].

Hepatitis

Hepatitis is a general term which refers to ‘Inflammation of the liver’ is used to describe diseases resulting in hepatocellular damage.

Acute hepatitis is a systemic infection affecting the liver predominantly. It occurs after an incubation period that varies according to the responsible agent. Five categories of viral agents have been implicated. Hepatitis A virus (HAV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Hepatitis D virus (HDV) and Hepatitis E virus (HEV). Chronic hepatitis represents a series of liver disorders of varying causes and severity in which hepatic inflammation and necrosis continue for at least 6 months. Milder forms are non-progressive or only slowly progressive, while more severe
forms may be associated with scarring and architectural disorganization, which when advanced, lead ultimately to cirrhosis [Isselbacher & Podolsky, 1994].

**Alcohol related liver diseases**

This is a pathologically defined entity which is associated with a spectrum of characteristic clinical manifestations. The cardinal pathologic features reflect irreversible chronic injury of the hepatic parenchyma and include extensive fibrosis in association with formation of regenerative nodules. Cirrhosis may be usefully classified by a mixture of etiologically and morphologically defined entities as, alcoholic, cryptogenic and postural or post necrotic, biliary, cardiac, metabolic and inherited and drug related [Isselbacher & Podolsky, 1994].

**Jaundice**

Jaundice is a general condition that results from abnormal metabolism or retention of bilirubin. Jaundice causes a yellow discoloration of the skin, mucous membranes, and sclera. The three principal types of jaundice are prehepatic, hepatic and post hepatic [Isselbacher & Podolsky, 1994].

**Liver tumors**

Tumors are abnormal masses of tissue that form when cells begin to reproduce at an increased rate. The liver can grow both non-cancerous (benign) and cancerous (malignant) tumors.

Non-cancerous (benign) tumors are quite common and usually do not produce symptoms. Often, they are not diagnosed until an ultrasound, computed tomography (CT) scan, or magnetic resonance imaging (MRI) scan is performed. There are several types of benign liver tumors, including hepatocellular adenoma and hemangioma.
Cancerous (malignant) tumors in the liver have either originated in the liver (primary liver cancer) or spread from cancer sites elsewhere in the body (metastatic liver cancer). Most cancerous tumors in the liver are metastatic.

Hepatoma is also called hepatocellular carcinoma. This is the most common form of primary liver cancer. Chronic infection with hepatitis B and C increases the risk of developing this type of cancer. Other causes include cancer-causing substances, alcoholism, and chronic liver cirrhosis [Isselbacher & Podolsky, 1994].

Reye’s syndrome

Reye's syndrome is primarily a children's disease, although it can occur at any age. It affects all organs of the body but is most harmful to the brain and the liver causing an acute increase of pressure within the brain and, often, massive accumulations of fat in the liver and other organs. It is defined as a two-phase illness because it generally occurs in conjunction with a previous viral infection, such as the flu or chicken pox. The disorder commonly occurs during recovery from a viral infection, although it can also develop 3 to 5 days after the onset of the viral illness [Sherwin & Sobenes, 1996].

Hepatotoxins

The hepatotoxins are classified as chemicals producing, ‘zonal hepatocellular alterations’ (Carbon tetrachloride, chloroform, phosphorus, tannic acid, ethionine, ethanol, etc), ‘biliary dysfunction’ (Phenothiazine derivatives, antimicrobial agents, anabolic steroids and oral hypoglycaemics) and ‘hepatocellular necrosis’ (Iproniazid, MAO inhibitors and halothane) [Plaa & Charbonneau, 1994].

Liver function tests

Estimation of the presence or absence of hepatic dysfunction is complicated by the large functional reserve of the liver and its power to regenerate rapidly. A diffuse
minimal involvement of liver may produce more grossly abnormal laboratory test than a focal necrosis [Kaplan et al., 1988]. The reasons for requesting liver function tests are three fold. They may be for diagnosis, differentiation or prognosis purpose. The following are the different biochemical parameters which are normally estimated to assess the liver function:

Serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum alkaline phosphatase (SALP), serum gamma glutamyl transpeptidase (SGGTP), sugar, total bilirubin, protein, triglyceride, total cholesterol, HDL and LDL. Antioxidant assay includes estimation of superoxide dismutase (SOD), catalase, glutathione peroxidase, lipid peroxidation and glutathione transferase in liver tissues.

**Standard liver treatments**

Conventional medicine does not provide efficient remedies for liver diseases. Interferon-based therapy is a standard treatment in modern medicine for chronic viral hepatitis and its use is associated with the risk of relapse and danger of side effects such as depression and suicide. Ribavirin, corticosteroids, nucleoside analogs, and thymosin are the usual additives to this treatment. According to Hepatitis Foundation International, HBV is one of the most serious killers in the world with more than two billion people have been infected and more than 350 million people have chronic HBV. HCV is also quite frequent, about 170 million people suffer from HCV in the world, and it is currently estimated that four million persons in the US have HCV infection, 2.7 million of whom are chronically infected. Fortunately, vaccination is provided for HBV, but no vaccine is yet formulated for HCV. For HCV the treatment of choice is interferon together with ribavirin with 40% efficiency. When interferon is attached chemically to polyethylene glycol, its efficiency is increasing to 60% by
administering it together with ribavirin [Davis & Rodriguez, 2001; Okamoto et al., 2001].

**Silymarin**

Recent pharmacological and clinical experiments have shown that herbal medicines are beneficial against liver disorders, as measured by standard liver function tests. They support or promote the process of healing or regeneration of liver cells with fewer side effects. The majority of plants described as being used for liver disorders increase the bile flow and reverse cholestasis [Farnsworth et al., 1985]. Various categories of compounds isolated from natural sources have been evaluated for the treatment of hepatocellular injury [Chang et al., 1985]. Modern science has examined numerous plant extracts for this purpose and has confirmed the traditional experience and wisdom by discovering the mechanisms and modes of action of these plants as well as reaffirming the therapeutic effectiveness of certain plants or plant extracts in clinical studies [Luper, 1998; Schuppan et al., 1999].

The most successful liver protective natural product is silymarin, an extract of the milk thistle *Silibum marianum*. Silymarin treats almost all types of liver diseases, as it protects liver cells from a wide variety of toxins, from ischemic injury, radiation and viral hepatitis. Silymarin mechanism includes antioxidant, anti-lipidperoxidant, antiinflammatory and antifibrotic effects [Li & Friedman, 1999; Kiso et al., 1987]. Silymarin has drawn increasing attention because of its antifibrogenic properties; it reduces collagen accumulation by 30% in secondary biliary fibrosis in rats. Due to its antioxidant activity it decreases hepatic injury by both cytoprotection and inhibition of Kupffer cells activation. A clinical trial involving patients with alcoholic liver cirrhosis indicated a slight survival advantage of treated compared with untreated
controls. Silymarin is intensively used in vitro on various liver cell lines such as primary hepatocytes and HepG2 [Thabrew et al., 1997; Oh et al., 2002].

Aim of the work

Antioxidants are micro constituents of diet that are involved in the structural maintenance of DNA and cell and their repair. They protect DNA and cell membranes against oxidative damage, including that induced by xenobiotics or carcinogenic agents. It is therefore biologically possible that diets rich in antioxidants protect against liver damage and cancer. Individual and population requirements for antioxidants are determined by the level of exposure to oxidative stress. Diets rich in vegetables and fruits protect against oxidative damage. In view of the importance of pharmacological activity attributed to the plants of the family Myrsinaceae and non availability of work pertaining to the hepatoprotective effect of Embelia basaal in particular, the present study has been initiated with following objectives:

1. Phytochemical studies of E. basaal and
2. Hepatoprotective screening including antioxidant potential of E. basaal.