

CHAPTER ONE

GENERAL INTRODUCTION

“Traditional health knowledge extends to an appreciation of both the material and nonmaterial properties of plants, animals, and minerals. In most developing countries like India and China, traditional health systems are firmly rooted in long-standing cultural and spiritual values. In many traditional health systems the fundamental concept found is that of the balance between mind and body, between different dimensions of individual bodily functioning and need, between individual and community, individual/community and environment, and individual and the universe. The breaking of this interconnectedness of life is a fundamental source of *dis-ease*, which can progress to stages of illness and epidemic. Treatments, therefore, are designed not only to address the locus of the disease but also to restore a state of systemic balance to the individual and his or her inner and outer environment. The cosmologies of traditional health systems ascribe life, spiritual value, and interconnectedness among all life forms to the aspects of the natural world used in the processes of promoting human health and well-being” (Bodeker, 2004).

“Herbal, botanical or phytomedicines are medicinal products containing active ingredients of exclusively plant origin. These medicines may be consumed as comminuted powders or as decoctions. Their production may involve concentration or purification processes resulting in the creation of extracts, tinctures, fatty or essential oils, or expressed plant juices. Herbal medicines exclude products that consist primarily of chemically defined constituents. The demand for herbal remedies is rising in many countries. This resurgence in the use of medicinal herbs may be due to various reasons. First, there is much disillusionment of the public with conventional medicine and its cost and inherent nonholistic approach. More important, there exists a perception among consumers that “natural” alternatives are safer than conventional medicine” (Yong et al., 2004).

“The use of herbal medicines presents unique clinical and pharmacological challenges that are not encountered with conventional single-compound medicines. These medicines are usually complex mixtures of many bioactive compounds and conventional “indications and uses” criteria devised for single compound entities may not be applicable to this system in a

significant number of ways. Compared to single-agent pharmaceuticals, phytomedicines may differ in the different mechanisms of action of bioactive constituents, in their dose-response relationships, and in the synergistic/combinatorial effects of the many bioactive compounds found in herbal extracts” (Yong et al., 2004).

Liver is the largest gland in the human body and plays an astonishing array of vital functions in the maintenance and performance of the body. Some of these major functions include carbohydrate, protein, and fat metabolism, detoxification, and secretion of bile (Jones, 1996). Unfortunately the liver is often abused by environmental and biological toxins, poor eating habits, consumption of alcohol, prescription and over-the-counter drug use, and viruses which can damage and weaken the liver. These factors eventually lead to hepatitis, cirrhosis, alcoholic liver disease and hepatocellular carcinoma (Gitlin, 1996).

Pharmacological studies have demonstrated the ability of herbal extracts in protecting liver against damage induced by a variety of chemicals with different pathological symptoms (Achliya et al., 2004; Asha et al., 2004; Kumar et al., 2004; Ohta et al., 2004). Acute liver injury induced by different toxins like acetaminophen, carbon tetrachloride, galactosamine and thioacetamide are experimental models for evaluating the efficacy of herbal extracts (Subramoniam et al., 1999). Toxicity testing in animals is carried out on new drugs to identify potential health hazards before the drugs are given to man, with doses well above the expected therapeutic range. Toxicity studies involve wide range of tests in different species with regular monitoring for physiological or biochemical abnormalities observed in long-term administration of the drug (Rang et al., 1999).

Carbon tetrachloride has proved to be highly useful as an experimental agent for the induction of acute hepatic injury. Cytokines play a major role in the process of acute liver injury and repair (Czaja et al., 1989). The pre-treatment of plant extracts can depending on the dose and time inhibit the overexpression of cytokine levels suggesting that liver cytokine level might be another criterion to be observed while screening new antihepatotoxic drugs (Gao et al., 2004).

Liver fibrosis and cirrhosis developing in response to chronic hepatocellular injury show general features of a wound repair process characterized by specific cellular reactions. These reactions are orchestrated by a set of cytokines and other signaling molecules and finally lead to the excessive deposition of extracellular matrix proteins. As these processes continue, accompanying fibrosis interfere with blood flow through the liver resulting in severe pathophysiological consequences such as portal hypertension, hepatic insufficiency, jaundice and ascites. Although fibrosis and cirrhosis are of high incidence worldwide, therapeutic management of these diseases still remains insufficient. These therapeutic concepts focus mainly on symptoms rather than on blocking central fibrogenic mechanisms. Progress in the understanding of the pathological mechanisms may open new strategies with which to interfere, at early steps, in the development of these diseases (Gebhardt, 2002; Tsukada et al., 2006). Detection of the expression of liver cytokines is useful in exploring the probable mechanisms of anti-fibrotic drugs. Traditional plant drugs have been found to be effective on preventing fibrogenesis and other chronic liver injury and project a more hopeful future in controlling liver fibrosis and cirrhosis (Wu et al., 2003)

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide, which ranks fifth in frequency among human cancers (Semela et al., 2004). Sustained angiogenesis is pathological and characteristic of malignancy, where the formation of a neovasculature is essential for tumor growth and development. Tumor vasculature differs from normal vasculature not only in terms of architecture but also on the level of molecular expression and regulation. The acquisition of the capacity to stimulate angiogenesis by shifting the balance between stimulatory and inhibitory factors of angiogenesis towards proangiogenic factors, the so-called angiogenic switch, is a rate limiting step in tumoral development. Secretion by HCC cells, tumor-infiltrating inflammatory cells and hepatic stellate cells of factors like vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), angiopoietins, platelet derived growth factor (PDGF), transforming growth factor- β (TGF- β)



and others promote the sprouting of new vessels from nearby existing vessels (Semela et al., 2004). The precise mechanism that leads to angiogenesis is not fully understood, but growth factors that cause proliferation of endothelial cells have been shown to play a critical role in this process. Many herbs including curcumin have been evaluated in clinical studies and are currently being investigated phytochemically to understand their tumouricidal actions against various cancers (Aggarwal et al., 2004^a). Traditional Indian medicine with its evolution through centuries has always fascinated practitioners and researchers for its applications in cancer treatment on a scientifically proven research background (Balachandran et al., 2005).

Compounds that block or suppress the proliferation of tumor cells have the potential to function as anticancer agents. Apoptosis is a regulated physiological process leading to cell death characterized by cell shrinkage, membrane blebbing and DNA fragmentation. Apoptosis requires the active inhibition of cell survival, which is accomplished by inhibiting the expression of anti-apoptotic factors as well as promoting the expression of pro-apoptotic factors (Dorai et al., 2004). Nuclear Factor-kappaB (NF- κ B) is a nuclear transcription factor required for the expression of genes involved in cell proliferation, cell invasion, metastasis, angiogenesis, and resistance to chemotherapy. This factor is activated in response to inflammatory stimuli, carcinogens, tumor promoters, and hypoxia, which are frequently encountered in tumor cells (Aggarwal et al., 2004^a). Plant compounds exhibit anticarcinogenic, anti-inflammatory and growth-modulatory effects in cancer cell lines and these effects are mediated through different pathways including suppression of NF- κ B activation (Manna et al., 1999).

“Ethnopharmacology is a multidisciplinary area of research, concerned with the observation, description, and experimental investigation of indigenous drugs and their biological activities and the active substances of plants and animals used in the traditional medicine of past and present cultures”(Rivier et al., 1979). Ethnobotanical and ethnopharmacological studies have

established their growing relevance in search of more dependable herbal drugs free of any side effects (Asha 1996). Herbal medicines derived from plant extracts are being increasingly utilized to treat a wide variety of clinical diseases. Medicinal herbs are currently being investigated phytochemically to better understand their action (Aggarwal et al., 2004^a; Dorai et al., 2004). Many ayurvedic herbs have a long history of traditional use in revitalizing the liver and treating liver dysfunction and disease. A number of herbal preparations (1) *Phyllanthus* (whole plant extract), (2) *Silymarin* (milk thistle), (3) glycyrrhizin (licorice root extract), and (4) Liv-52 (mixture of herbs) are available in the pharmacy for the treatment of liver diseases (Dhiman et al., 2005). Also there are numerous herbal products and polyherbal formulations used in traditional medicines and in tribal medicine to cure liver diseases (Subramoniam et al., 1999). In addition to the known hepatoprotective herbs, there are unexplored group of plants belonging to pteridophytes (ferns) which are also used to cure liver ailments. Hence there is a need to determine the true therapeutic value of medicinal pteridophytes as it may prove valuable for developing new herbal drugs.