1. Introduction

The World Health Organization (WHO) has estimated that more than 80% of the world’s population in developing countries depends primarily on herbal medicine for basic healthcare needs (Vines, 2004). In fact, plants are the oldest friends of mankind. They not only provided food and shelter but also served to cure different ailments. Herbal medicine, sometimes called traditional or natural medicine, has always existed in one way or other in different cultures and civilizations, such as Ayurvedic (India), Egyptian, Western, Chinese, Kampo (Japan) and Greco-Arab or Unani-Tibb (South Asia). Traditional medicine all over the world is currently being revalued through extensive research activity on various plant species and their therapeutic properties (Kumar et al., 2012).

Plant products have been used with varying success to cure and prevent diseases throughout history. Written records about medicinal plants date back at least 5000 years to the Sumerians (Swerdlow, 2000) and archeological records suggest even earlier use of medicinal plants. The strong historic bond between plants and human health began to unwind in 1897, when Friedrich Bayer and Co. introduced synthetic acetyl salicylic acid (aspirin) to the world. Aspirin is a safer synthetic analogue of salicylic acid, an active ingredient of willow bark and was discovered independently by residents of both the new and old world as a remedy for ache and fever (Pierpoint, 1994).

In the early nineteenth century, the advent of modern medicine saw a rapid decline in botanical medicinal use. Vaccination, the discovery of antibiotics and improvements in medical technology all contributed to this demise. (Talalay, 2001; Wohlmuth et al., 2002). The interest in nature as a source of potential chemotherapeutic agents continues. Natural products and their derivatives represent more than 50% of all the drugs in clinical use in the world. Higher plants contribute not less than 25% of the total. During the last 40 years, at least a dozen potent drugs have been derived from flowering plants including Dioscorea species derived diosgenin from which all anovulatory contraceptive agents have been derived; reserpine, anti-hypertensive and tranquilizing alkaloids from Rauwolfia species; pilocarpine to treat glaucoma and “dry mouth” derived from a group of South American trees (Pilocarpus species) in the Citrus family; two powerful anti-cancer agents from the Rosy Periwinkle
(Catharanthus roseus); laxative agents from Cassia species and as a cardiotonic agent to treat heart failure from Digitalis species. Although discovered through serendipitous laboratory observation, three of the major sources of anti-cancer drugs on the market or completing clinical trials were derived from North American plants used medicinally by native Americans: the Papaw (Asimina species), the Western Yew Tree (Taxus brevifolia), effective against ovarian cancer and the May apple (Podophyllum peltatum) used to combat leukaemia, lymphoma lung and testicular cancer (Gurib-Fakim, 2006).

Natural products are an excellent source of complex chemicals, possessing a wide variety of biological activities and having great potential therapeutic value (Deng et al., 2006). Therapies developed along the principles of conventional medicine are often limited in efficacy and unaffordable for individuals in many countries. Therefore, treating diseases with plant-derived compounds will be lucrative which may not require extensive preclinical testing unlike in the pharmaceutical synthesis. Furthermore, the awareness and interest in phytomedicine by the medical professionals and public is increasing steadily. Several recent surveys from Europe and the US have demonstrated a sharp rise in the use of botanical drugs within a few years (Kessler et al., 2001).

Plants synthesize a wide array of compounds that play key roles in protecting plants against herbivores and microbial infection and as attractants for pollinators and seed-dispersing animals, allelopathic agents, UV protectants, and signal molecules in the formation of nitrogen fixing root nodules in legumes. Although they have long been ignored from a nutritional perspective, the function of these compounds and their relative importance to human health are gaining significant interest. Phytochemicals are secondary plant metabolites, mainly characterized by having at least one aromatic ring with one or more hydroxyl groups attached. The nature and distribution of these compounds can vary depending on the plant tissue, but they are mainly synthesized from carbohydrates via the shikimate and phenylpropanoid pathways. They range in chemical complexity from simple phenolic acids, such as caffeic acid, to complex high molecular weight compounds, such as the tannins, and they can be classified according to the number and arrangement of their carbon atoms (Cassidy, 2009).
Currently there has been an increased interest globally to identify antioxidant compounds that are pharmacologically potent and have low or no side effects for use in preventive medicine and the food industry. As plants produce significant amount of antioxidants to prevent the oxidative stress caused by photons and oxygen, they represent a potential source of new compounds with antioxidant activity. Traditional herbal medicines form an important part of the healthcare system of India. Ayurveda, supposed to be the oldest medical system in the world, provides potential leads to find active and therapeutically useful compounds from plants (Ali et al., 2008).

Naturally occurring herbal compounds such as phenolic acids, flavonoids, and high molecular weight polyphenols have gained considerable attention as beneficial protective agents against diseases. Phenolics are plant secondary metabolites and they are commonly found in medicinal plants, herbs, fruits, vegetables, grains and are an integral part of human diet. Phenolic compounds are well known as radical scavengers, metal chelators, reducing agents and hydrogen donors. So plants containing high level of polyphenols have a great importance as natural antioxidants (Hajji et al., 2010).

Recently it is widely recognized that human health is influenced by genetic and environmental factors and that nutrition is of fundamental importance. Increasing incidence of “lifestyle related diseases” like obesity, type II diabetes, cardiovascular disease (CVD) or cancer is recognized to be related to Western-style diet. Several reports indicate that a diet rich in vegetables and fruits and low in fat is known to protect against these diseases (Goh et al., 2007).

Plants commonly used in traditional medicine are known to be safe. Traditional medications have been practiced for the treatment of diseases using plant derived compounds that were safe, based on knowledge and understanding that have been accumulated over centuries. However, since the traditional medicinal systems are not scientifically documented, the practices of such systems are facing strong challenges. Recent scientific research has shown that many plants used as food or in traditional medicine are potentially toxic, mutagenic and carcinogenic (Ferrira and Vargas, 1999). Therefore, it is necessary to establish the scientific rationale for and safety of traditional medicine.
Paracetamol is widely used analgesic and antipyretic, but produces acute liver damages at higher dose. The hepatotoxicity of paracetamol has been attributed to the formation of toxic highly reactive metabolite n-acetyl parabenzoinqueimine (NAPQI). Many natural products of herbal origin are in use for the treatment of liver ailments (Mitra et al., 2000).

In India, around 5,55,000 people died of cancer in 2010, according to estimates published in The Lancet (Dikshit et al., 2012). Cancer is the second leading cause of death in the United States (USA) surpassed only by cardiovascular disease (Jemal et al., 2005). Drug discovery from medicinal plants has played an important role in the treatment of cancer and, indeed, most new clinical applications of plant secondary metabolites and their derivatives over the last half century have been applied towards combating cancer (Newman et al., 2003; Butler, 2004). Chemoprevention involving the use of plant chemicals to suppress, block, or reverse the process of carcinogenesis has received considerable attention over several decades. Several types of phytochemicals in vegetables and fruits such as carotenoids, flavonoids, and antioxidative vitamins have been studied as potential chemopreventive agents (Kelloff et al., 1999; Surh, 2003).

One of the major limitations in the currently available treatment modalities for cancer is their side effects. Chemotherapy has been shown to produce severe neutropenia, which can lead to opportunistic infections, which may even lead to death. Hence alternate treatment for cancer is being tested and plants and plant derived products are being tried for the purpose. Information on the ethnopharmacologic use of plants has given important lead in the cancer drug development (Preethi et al., 2006).

_Rhodiola imbricata_ Edgew. (Syn: _Sedum roseum_; _S. imbricata_; _S. rhodiola_) is a perennial herb of the family Crassulaceae, commonly known as golden or arctic root, grows on rocky slopes, common in drier areas of the western Himalaya at an altitude of 4000-5000 m. The genus _Rhodiola_ is known to biosynthesize phytochemicals such as flavonoids, coumarins and phenyl glycosides. The aqueous extract of _R. imbricata_ root was found to contain gallic acid, p-tyrosol, rosavin and rosin (Mishra et al., 2008). _Rhodiola_ root have been used extensively since time immemorial for its medicinal properties in traditional folk medicine in China, Tibet,
Mongolia and former Soviet Republics to increase physical endurance, work productivity, longevity and to treat fatigue, asthma, hemorrhage, impotence and gastrointestinal ailments (Kelly, 2001).

The rhizome is a woody or fleshy elongated stem that usually grows horizontally below the ground, forming leaves above the ground and roots into the ground. A medicated herbal health beverage (tea) has been successfully developed, patented and technology transferred to national vendors which are formulated by using 11 potential high altitude medicinal plants. *R. imbricata* is the major constituent of this herbal tea and rich in antioxidant value. These products are also being introduced in the Indian army as special high altitude rations (Ballabh and Chaurasia, 2007). Recently, rhizome of *R. imbricata*, was found to possess radio protective (Arora *et al*., 2005), cytoprotective and antioxidant (Kanupriya *et al*., 2005), wound healing (Gupta *et al*., 2007), immunomodulatory (Mishra *et al*., 2006), adaptogenic (Spasov *et al*., 2000), anti-fatigue (Darbinyan *et al*., 2000), and neuroprotective (Mook-Jung *et al*., 2002) bioactivities. However, very meager reports exist on hepatoprotective and antiproliferative activity of *R. imbricata*. Hence, the aim of the present study was to investigate the free radical scavenging property, repeated dose oral toxicity study, hepatoprotective activity in animal model and *in vitro* cytotoxicity of *R. imbricata* rhizome in order to add on its phytotherapeutic value. Therefore, the present study has been undertaken with the following objectives;

- To extract the biologically active compounds from *Rhodiola imbricata* rhizome using Soxhlet and maceration techniques
- To determine the total phenolics, tannins, flavonoids and free radical scavenging properties of *R. imbricata* rhizome crude extracts
- To investigate the repeated dose oral toxicity of *R. imbricata* extract in animal model
- To study the hepatoprotective activity against paracetomal induced hepatopathy
- To analyze phytochemical profile in the extract showing better pharmacological activity by GC-MS and qualitative HPLC methods
- To screen the anticancer potential of *Rhodiola* in DAL (Daltons Ascites Lymphoma), EAC (Ehrlich Ascites Carcinoma) cells, HT-29 colon cancer cell line, SNU-C4 colorectal cancer cell line and Splenocyte (normal cells)