1. Introduction

Interest in herbal remedies has been revived recently with a new zeal. Around the world, research has been carried out to explore the hidden truths and to utilize the healing property of herbs. Previously, information on the healing power of herbs in traditional systems of medicine was considered as un-codified data. But the recent scientific validation of herbs has changed the view of the scientists on the miraculous effects of natural products. Production of drugs without proper quality control measures would be harmful to both traditional systems of medicine and human welfare. Hence, the World Health Organization (WHO), in 1991, brought out guidelines for the assessment of herbal medicines with the objective of defining basic criteria for the evaluation of quality, safety and efficacy of herbal medicines. The assessment includes evaluating the effect of the crude raw drugs, their preparation, and the finished product; these apart, stability and biological activity studies also form part of the evaluation (Kamboj, 2000). Such studies help the development process and also propagate these traditional systems of medicine.

Plants are the richest resource of drugs used in both the traditional and modern medicinal systems; they are being used in folk medicines, as nutraceuticals, pharmaceutical intermediates, food supplements and also provide chemical entities for semi-synthetic drugs (Hammer et al., 1999). Plants and their products might have been used as medicines right from the beginning of human civilizations. The uses of plants for medicinal purpose have been practiced for centuries in the Indian subcontinent. The “Aushadhisuktha” in the Rigveda, which is said to have been written between 4500 - 1600 B.C., is the oldest document available on medicinal plants (Shwetha et al., 2012). It briefly describes the morphological characteristics of medicinal plants, their habitats and therapeutic classification, and their uses in various ailments.
Medicinal plants are a source of great economic value all over the world. Nature has conferred human a very rich and diverse kinds of plants present throughout the world. In India, herbal medicine is still being used by huge population, where the major portion of traditional therapy utilizes plant extracts and the active constituents present in it (Akerele and Heywood, 1991). Plants have been used in traditional medicines to treat a wide range of diseases in India (Kritikar and Basu, 1993). Approximately 3000 plant species in India are known to have medicinal properties (Prakasha et al., 2010). The traditional Indian systems of medicine viz., Ayurveda, Siddha and Unani, describes the use of plant products for enhancing immunity and healing (Jain et al., 2006).

The Western Ghats (10°10′N 77°04′E), is one of the ‘Hotspots of Biodiversity’ identified in the world (Myers et al., 2000). About 5,000 species of an estimated 17,000 species of flowering plants of India are found in the Western Ghats and almost all have at least one medicinal property (Nayar, 1996). A huge amount of the plant types found here viz., 54 genera, 1720 species and 135 infra-specific taxa are found to be endemic (Shetty and Kaveriappa, 1991).

1.1 Natural Products
By definition, the word ‘natural’ is an adjective referring to something that is present in or produced by nature and not artificial or man-made. Today many natural products are quite commonly understood to refer herbs, herbal concoctions, dietary supplements, traditional or alternative medicines. But the use of herbs as natural-product therapies is different from their use as a platform for drug discovery process. The development of medicinal plants into therapeutic drugs is a process that is time consuming and capital-intensive; the risks are also high with low success rate. Despite all this, natural product drug discovery programs are still in existence all over the world, mainly because of:
• The higher chemical diversity in natural products as compared to synthetics and the largely unexplored potential of these products.
• The large number of terrestrial and marine species yet uninvestigated and the back to nature syndrome.
• Modern technology and advancements made in this field in the last few years that have made such programmes attractive.
• High-throughput screens and sensitive instrumentation for structure elucidation that have greatly reduced the amount of time (and also the amount of sample) required for the first stage of investigation (Lang et al., 2001).

1.2 Sources of Natural Products
Natural products isolated from higher plants and microorganisms have been providing novel and clinically active drugs. Screening of natural products has resulted in a wide array of bioactive agents. For example, there are about 50 commercially available anticancer drugs (excluding endocrines) which have been approved till date by the USFDA; and significantly, one-third of them are based on natural products. The most recent addition is taxol, a natural product derived from the Pacific yew tree, Taxus brevifolia, which is used for the treatment of ovarian and breast cancers (Kharwar et al., 2011).

The sources of natural products vary from plants and animals to microorganisms like bacteria, fungi and algae. Historical evidence indicates that certain Neanderthal remains have been found to contain remnants of medicinal herbs. One of the earliest collections about health sciences dates back to the 13th century B.C. which is called as The Nei Ching. But the use of natural products in medicines recorded dates back to 2600 B.C. which were in cuneiform in Mesopotamia. Interestingly, these agents have still being used one or the other
way in the treatment of influenza, cough, inflammation and parasitic infestations (Holt and Chandra, 2002).

There were several references for the use of the herbs in the medicines, including ayurvedic hymns describing use of various herbs. Theophrastus, a philosopher and natural scientist circa 300 B.C. wrote a History of Plants in which he addressed the medicinal qualities of herbs and the ability to cultivate them. The Greek botanist, Pedanius Dioscorides, circa 100 A.D. produced a work entitled De Materia Medica, a very well-known European document, on the use of herbs in medicine. Monks in monasteries in the Middle Ages copied manuscripts about herbs and their uses. However, Arabs are the ones who maintained most of the documentations of the Roman and Greeks knowledge of medicinal plants and the natural products along with the information of their knowledge of Chinese and Indian herbal medicine (Kroll, 2001). The first semi-synthetic drug based on a natural product, aspirin was introduced by Bayer in 1899.

Peptic ulcer disease (PUD) was recognized through ages and civilizations. In fact, peptic-ulcer has attracted most attention among gastro-intestinal diseases by both the patients and clinicians (Naik and Dhiman, 1993). Dyspepsia in its variable forms has been a companion to human ever since the advent of bad cooking, over-indulgence and anxiety (Goodman and Gilman, 1991). The term “peptic ulcer” is used to refer a group of ulcerative disorders of the upper gastrointestinal tract which appear to have a common role to play in the participation of acid-pepsin in their pathogenesis (Jain and Santani, 1994). There are many causative agents for PUD including stress, hyperacidity, food habits, NSAIDs and the mucosal barriers are to name a few.
Recent information suggests that the prevalence and changing patterns of the disease are mainly due to a Gram-negative bacterium, *Helicobacter pylori*, which colonize the gastric mucosa, particularly the antral region. About 60% of patients with gastric ulcers were reported to have *H. pylori* infection (Jain and Santani, 1994). Allopathic treatment of PUD has undergone a remarkable degree of transformation. The therapeutic management includes antacids, anticholinergic and anti-spasmodic drugs, H₂-receptor antagonists such as cimetidine, ranitidine, famotidine and proton-pump inhibitors viz., omeprazole, lansprazole etc. Previously, since the discovery of the association of *H. pylori* with PUD, many antibiotics have been used in combination including ampicillin, tetracycline, clariothromycin and amoxicillin etc, for killing the bacteria and for histological remedies. Apart from being highly expensive, these 3-4 drug regimes produce many side-effects viz. constipation, osteomalacia, encephalopathy, osteodystrophy and mild diarrhea and CNS depression in case of non-systemic antacids (Romano and Cuomo, 2004).

Systemic antacids results in side-effects such as occasional risk of gastric perforation by sodium bicarbonate, systemic alkalosis and edema due to sodium retention. In case of anti-cholinergic drugs, dry mouth and blurred vision are the main side effects. H₂-receptor blockers mainly cause skin rashes, diarrhea, muscle pain, hepatotoxicity, gynecomastia, sexual impotence, granulocytopenia and reversible confusion (Fisher and Lecouteur, 2001). Proton-pump inhibitors such as omeprazole and lansprezole cause hyper-gastrinaemia due to prolonged achlorhydria. Other miscellaneous agents like bismuth salts, amylpectin sulfate, gafarnate and sucralfate cause constipation. Anti/protozoal drugs like tinidazole and metronidazole produce nausea and a metallic taste; these drugs have also been found to be carcinogenic in rats (Laine et al., 2000).
As many conventional allopathic medicines for treating various ulcer conditions with special reference to peptic ulcer are found to have toxic effects on chronic administration, there is an urgent need for finding alternative herbal remedies for PUD (Goodman and Gilman, 1991).

1.3 Plant Sources
Natural products, once served mankind as source of all drugs, were mostly provided by higher plants. Even today, higher plant-derived natural products represent about 50% of natural products available for clinical use. The WHO estimates that 80% of people in developing countries rely on traditional medicine for their primary healthcare and about 85% of traditional medicine involves the use of plant extracts. This shows that about 3.5-4 billion people depend upon the plants and their products as source of drugs. About 39% of newly approved drugs were of natural origin including original natural products, products derived semi-synthetically from natural products and synthetic products based on natural product models (Jarvis, 2000).

The use of biodiversity as a source of medicine is an ancient and well proven concept. At the start of the 21st century, an estimated 75% of the world’s population continued to depend on traditional plant based medicines for primary healthcare (Mann, 2002), and among the newly developed chemical entities for the cancer treatment from 1940’s, over 70% were obtained from natural products (Johnston, 1998). But the real exploration for the novel natural products has not been seriously initiated since 1960s, where the modern and safe equipments for the diving have been discovered (Kim et al., 1995) along with safe unmanned submerged vehicles a decade later (Bhattaram et al., 2002).
All kinds of animals irrespective of their positions in the phylogenetic tree, their dwelling place can be a good source of natural products. Unicellular organisms like bacteria, yeasts and molds, which are considered as primitive life can produce compounds or provide basic blue print for the production of new compounds which might be potential therapeutic agents. The use of a natural product as a therapeutic agent requires that the particular characteristic of the compound should match with a disease. Developing natural products for therapy needs to have knowledge of the therapeutic target and thorough understanding of the pathophysiology of the disease, where the presence of a particular character in the natural product may suggest the use in the particular condition. Although the choice of the natural products for therapeutics is a trial and error one, the search yielded many natural products at serendipity (Hogg, 1971).

The investigation of micro-organisms as sources of potential therapeutic compounds has much shorter history than compounds from plant as a source of human medicines. Secondary metabolites secreted by micro-organisms are the natural substances which may not have any important role in the growth of the organism which produces it. These metabolites might be secreted because of the interactions between the various organisms present in the environment (Demain, 1983).

Although almost 20,000 microbial metabolites and approximately 100,000 plant products have been described so far, secondary metabolites still appear to be an inexhaustible source of lead structures for new antimicrobials, anti-virals, anti-tumour drugs, agricultural and pharmacological agents. Later various secondary metabolites like benzylpenicillin, erythromycin, strobilurin and cephalosporin etc, were used as lead structures upon which numerous synthetic and semi-
synthetic compounds were derived with improved pharmacological properties (Vicente et al., 2003).

Plant products have been used in different sectors like medical, industrial, veterinary and diagnostic applications. Although several medicinal plant extracts have been used for the treatment for centuries, only 1-10% of the estimated 250,000 to 500,000 species only have been exploited for the purpose (Borris, 1996). Plant products are relatively inexpensive source of biological products which contains a wide spectrum of primary and secondary metabolites. Modern medicine is increasingly expecting plant derivatives for the use of antimicrobial and other drugs, since the traditions antibiotics are becoming ineffective. Moreover the other reason for the growing interest on plant antimicrobials is the extinction of rare plants (Lewis and Lewis, 1995). The scientific discipline, Ethnobotany, utilizes the impressive array of facts gathered by indigenous peoples about the plant and animal products they have used to maintain health (Georges and Pandelai, 1949). Lastly, the emergence of new virus entities such as human immunodeficiency virus (HIV) has spurred intensive investigations into plant derivatives which may be effective, especially for use in developing nations.

Various natural products have been already reported in the literature for the treatment of leukemia, virus infection, thrombosis and coagulopathy, anemia, malaria and bone marrow diseases. Extracts of *Trichothecium roseum* (fungus), *Cucumaria japonica* (the sea cucumber), *Amorpha fruitcosa* (legume), *Magnolia officinalis* (tree), etc. may be highly useful in treatment of Epstein-Barr virus. Extracts from *Mycena pura*, *Nidula candida* and basidiomycetes, are useful in the treatment of leukemia and compounds extracted from *Streptomyces platensis* may be useful in the thrombocytopenia treatment (Miles et al., 1998).
Compounds obtained from the marine sponge, *Aplysina archeri*, have been reported to inhibit the growth of the feline leukemia virus. A number of blood-sucking invertebrates have small, low-molecular-weight proteins in their salivas that interfere with the clotting of blood and therefore might be of value as potential anticoagulants (Zhu *et al*., 1997). *Streptomyces hygroscopicus var ascomyceticus* produces a macrolide that has been reported to have immunosuppressive activity and may prove to be beneficial in preventing transplant rejection in humans. It is quite possible that the plant compounds and the other biological compounds offer a wide range of biological activity, adequate structural diversity and difference in the mechanism of action. Therefore a new, safer and more efficient drugs for the treatment of blood-based disorders could well arise from this family (Sehgal, 2003).

There are several natural products which were claimed to possess the immunosuppressive function, but often it is associated with cytotoxicity (Mann, 2002). Right from the first heart transplant which occurred in late 1960s, modern medicine has travelled to a point where organ transplants have become rather a routine procedure. The survival of the patients with transplants is due to Cyclosporin A, a fungal metabolite discovered in 1970, which is being used for immunosuppression since 1978 (Lechler *et al*., 2005). Apart from immunosuppression, currently cyclosporine A is being investigated for the treatment of Rheumatoid arthritis, Crohn’s disease and systemic lupus erythematosus (Karampetsou *et al*., 2010).

Apart from cyclosporine A, a methyl analog of oligomycin F, which was originally isolated from *Streptomyces ostreogriseus*, was reported to quite efficiently suppress the activation of B-cell and T-cell in the presence of mitogens at treatment concentrations equivalent to that of cyclosporine A.
Concanamycin F which was first isolated from the fungus *Streptomyces diastatochromogenes* in 1992, has been reported to possess a wide spectrum of biological activities, including antiviral and immunosuppressive activities (Mann, 2001). The experimental immunosuppressant (+)-discodermolide, isolated from the marine sponge *Discodermia dissolute*, exhibits relatively nonspecific immunosuppression, causing the cell-cycle to be arrested during the G2 and M phases. Current the compound is being investigated as a potential neoplastic agent since it has been found to stabilize the microtubules and thwarts the depolymerization effectively resulting in the cell cycle arrest in between metaphase to anaphase transition (Goyal *et al.*, 2010). The same mode of activity is seen in taxol (Paclitaxel), epothilones, eleutherobin and sarcodictyins.

The cyclic peptide didemnins, first isolated from a marine tunicate, *Trididemnum solidum* was found to exhibit immunosuppressive activity. It involved the induction of cytotoxicity through inhibition of the cell cycle progression through G1 phase but the mechanism was unknown (Janin, 2003). The trichopolyns I to V produced by *Trichoderma polysporum* (fungus) are lipopeptides which was reported to suppress the lymphocyte proliferation in a murine allogeneic model (Mann, 2001). Triptolide a product from *Tripterygium winfordii* (plant) exhibits immunosuppressive activity through the inhibition of expression of IL-2 receptor and the subsequent signal transduction (Mann, 2002).

Anti-cancer drug discovery is one of the hottest fields of science where natural product based anti-cancer drug remain as an active area of research throughout the world. The tumor incidences, frequency and the type of tumor differ from country to country (Shu, 1998). The most common positions in the body where the frequency to develop cancer more is prostrate, breast, colon, rectum, breast,
cervix, uterus, liver, lung, stomach, esophagus kidney, urinary bladder, oral cavity, blood and ovary (Bostwick and Brawer 1987). A variety of plant and their derivatives based chemicals are used for the chemotherapeutic treatment of the aforesaid cancers. They fall into drug classes like the lignans, taxanes, vinca alkaloids, stilbenes, cephalotaxanes, flavones and camptothecins (Da Rocha et al., 2001).

Although the occurrence of cancer is widespread in the human body in different organs with different functions, yet there remain basic similarities in the pathogenesis of cancer. When more details about the molecular mechanism in cancer get revealed, there is every chance of getting more targets for the possible potential interventions in the growth and development of cancer. A relatively new approach called cancer chemoprevention which either prevents or delays or reverses the carcinogenesis (Mehta and Pezzuto, 2002).

Natural products, besides revealing new therapeutic approach had also played a vital role in the understanding of various biochemical pathways. It also has proved its volubility by acting as a tool in understanding biological chemistry, molecular and cellular biology. Some more natural products which have been used as potential drugs include staurosporine from Streptomyces, huperzine A from moss and manoalide from marine sponge (Grabley and Sattler, 2003).

There is a steep increase in the costs of drug discovery and development whereas there is also a decrease in the number of drugs which comes to the market after all evaluations. Although there is huge amount of success with the natural products in the drug discovery process, yet natural products have waxed and waned in pharmaceutical industries. Since there is a large chemical diversity in natural products, they are most likely to continue to exist and grow to become
even more valuable as sources of new drug leads. This is also because of the novel molecular structures present in natural products that are much greater in number and diversity than the other sources (Dahanukar et al., 2000).

There is a major concern today to improve the tools to develop new drugs and pace by which new products are discovered and developed in the pharmaceutical industries. This can be successfully achieved when the knowledge about the procedures of drug-target elucidation followed by the optimization of the procedures for the lead compound identification and optimization. Human genome analysis will also help in developing innumerable potential targets which may also need to be evaluated (Grabley and Sattler, 2003).

The objective of this study is to evaluate the pharmacologic potential of three Indian medicinal plants viz. *Mimosa pudica*, *Artabotrys hexapetalus* and *Adhatoda vasica* available in the Western Ghats, for their immunomodulatory, hepatoprotective, anti-ulcer, wound healing, antimicrobial and anti-oxidant activities. These three plants chosen are widely distributed, commonly used as a part of herbal medicine and cultivated in gardens throughout India (Kritikar, 1993).