Introduction
2.0 Introduction

Since time immemorial, man's quest for medicinal agents that alleviate his suffering has remained unquenched. The instinctive behavior of primitive man helped him to realize the beneficial effects of plants in the treatment of various ailments. From about 11th to 18th centuries, a dogma known as the "Doctrine of Signatures" was almost the sole means by which man attributed medicinal value to certain plants. This dogma held that the color, shape, habit, or other physical characteristics of a plant were indicative of its medicinal value. Thus, the worm shaped embryo of Chenopodium (worm seed) suggested it to be an anthelmintic, the yellow color of saffron served to point out its value in liver disorders, the serpentine roots (snake root) indicated that they should be useful in treating snake bite. Quallaria bark is used as detergent due to its soap forming quality and so on. However, as man experimented, he found by trial and error that certain plants are useful for treatment of his myriad illness. Later through conscious rational action, he gained better understanding about the medicinal properties of the plants.

Ayurvedic medicines, as the major remedy in the traditional medical systems, have been used in medical practice for thousands of years and have made great contribution to the health care needs of the people of this sub-continent. Knowledge about the healing property of plants and formulations used in ayurvedic therapeutics and mentioned in classics are a result of astute clinical observations made over centuries. Details about the medicinal plants, their properties and therapeutic applications are available in ancient scriptures like Vedas, Samhitas, and Puranas. Compilations of later period that are Nighantus also contain enormous amount of information. Many drugs used earlier for specific clinical conditions, have been found to be efficacious even today eg. Commiphora mukul in obesity, guggulu in hyperlipidemia, and sarpagandha in psychotic and hypertensive disorders. Prolonged and apparently uneventful use of herbal medicines may offer testimony of their safety and efficacy.

A perfect interpretation of Ayurvedic concepts in modern terms is not yet entirely practicable. It is not that a general idea of different fundamental of Ayurveda can not at all be conveyed to the modern scientifically trained and genuinely curious mind, but the two respective series of concepts, the Ayurvedic and the modern belong
to such different planes of conceptual build up that they cannot fit, in their entirety, into each other in such a way as to become indistinguishable. In spite of the fact that Ayurveda has laid great stress on repeated observation and acceptance of data as reliable only on the basis of their uniform consistency unmarrred by any contradictions, intuitions have played the basic role in the development of Ayurvedic concepts. The concepts of modern science, on the other hand, are based on experimental observations. It is difficult for the two different patterns of concepts based on intuition and experimentaion respectively to become absolutely identical with each other. Therefore, experimental evaluation is required to be carried out to provide scientific basis for traditional use of various medicinal plants and to prove that they are safe and efficacious.

There are two approaches to develop successful drugs from medicinal plants.

(a) Phytochemical approach which emphasizes the development of pure phytochemicals as drugs. Although there are success stories of ancient insights on medicinal plants wading to the discovery of chemical entities as drugs, this type of drug discovery, in general is expensive and time consuming.

(b) Phytotherapeutic approach wherein crude plant preparations (extracts, active fractions, or mixtures) or ayurvedic types of formulations can be used as drugs with modern standards of safety and efficacy. It is cost effective and more relevant to our conditions.

The World Health Organization (WHO) has recognized herbal medicines as essential building blocks for primary health care. It has defined the traditional medicine as “the sum total of all the knowledge and practices, whether explicable or not, used in diagnosis, prevention, and elimination of physical, mental, or social imbalance and relying exclusively on practical experience and observations handed down from generation to generation, whether verbally or in writing (Chitme and Gupta, 2000).

India is the 8th largest country having a total of around 47,000 plant species, out of which more than 7,500 species are cited as medicinal plants. Among these only 800 species are claimed to be in use and around 120 species are used in large quantities, which constituents about 1.6% of the total number of medicinal plants and around 0.25% of the total number of plant species in India. This indicates that there is
Introduction

a huge untapped potential and majority of the medicinal plants are yet to be explored scientifically.

There are two main reasons for interest in natural products. Firstly, the use of medicinal plants as phytomedicines, dietary supplements, food, and beverage ingredients and traditional medicines. This segment is growing rapidly. Secondly, natural products continue to remain an important source of new drug discovery. It is now increasingly accepted worldwide that screening natural products is a more effective strategy for discovering new chemical entities as natural product libraries have a broader distribution of molecular properties such as molecular mass, octanol-water partition coefficient and diversity of ring systems when compared to synthetic and combinatorial counter parts (Feher and Schmidt, 2003). Natural product library can be viewed as a population of ‘privileged structures’ selected by evolutionary pressures to interact with a wide variety of proteins and offer biological target for specific purposes. Another reason for natural compounds to be considered as privileged structures is that they have the diversity space in which chemical scaffolds embody characteristics that promote binding to multiple target proteins.

Since in most cases efficacy of a crude drug could be evaluated as the sum of additive, synergistic, and antagonistic effects of all constituents, the only practical way to ensure uniformity of action of the herb is to prepare an extract, determine its activity by pharmacological and clinical methods, and then prepare a qualitative and quantitative chemical profile of all the significant constituents in it by methods such as High Performance Liquid Chromatography (HPLC), High Performance Thin Layer Chromatography (HPTLC), Gas and Mass Chromatography (GC-MS), or the like. Thus it is not mandatory to go beyond the establishment of chemoprofiling for herbal drugs (Tyler, 1999). Chemical profiling is a versatile technique, which can be made to good use in assessing quality of crude extracts and their fractions. Fingerprinting in essence is chemoprofiling, which means establishing a characteristic pattern for the crude extracts and/or their fractions using various modern methods like HPLC, HPTLC etc.

Gastric ulcers are common and represent a major health problem, both in terms of human suffering and in cost to society in the form of lost productivity and requirement for health care resources. There are some important cornerstones in the
treatment of peptic ulcer disease. Until 1965, almost the only drugs employed in orthodox medicine were simple antacids with a neutralizing effect on gastric acidity and relief from pain, which lasted for about 2 hours. Meanwhile, antimuscarinic agents, such as atropine, have also been used as adjunctive treatment for controlling gastric acid secretion that involves blocking the effect of vagus nerve stimulation. These treatments were supported with bed rest and advice on diet as well as on improving lifestyle of the patient in showing moderation in smoking and alcohol intake. However, the disadvantages and insufficiency of these treatments have demonstrated the need for the development of alternative drugs. Introduction of carbenoxolone, a hemisuccinate sodium salt of gycyrrhetic acid obtained from the roots of G. glabra (licorice), has opened a new era into peptic ulcer treatment in modern medicine after 1965 (Lewis and Hanson, 1991). Glycyrrhetic acid, a triterpenic saponin aglycone, was found as the active principle of the roots and “carbenoxolone” is the hemisuccinate sodium salt of the compound. By the invention of H₂ receptor antagonists, e.g. cimetidine and famotidine, these agents have become important alternatives in the therapy of peptic ulcers in a very short time. Although morbidity and mortality have decreased with the utilization of these agents, adverse reactions like cardiac arrhythmias, impotence, gynaecomastia, and haematopoeitic changes have been reported. Moreover, recurrence rates are high after the termination of the therapy. Other group of recent agents, proton pump inhibitors are also found risky by the researchers. Thus, insufficiency of modern drugs in the treatment of peptic ulcers provoked the researchers for developing more effective and safe agents (Ife et al, 1990). Plants provide an alternative source in the search for new agents. Before the introduction of recent agents into modern medicine, folk remedies had been used effectively for the treatment of peptic ulcers. Decoctions, infusions or oily extracts prepared from various plants have been used worldwide. Some anti-ulcer agents, e.g. carbenoxolone, have already been developed from these sources. Roots of *Glycrrhiza glabra* have been used for this purpose since hundreds of years in Far-East Asian traditional medicine and after 17th century in Europe.

Majority of the currently used drugs in peptic ulcer disease act either by decreasing gastric acid secretion or by providing cytoprotection to gastric mucosa. Besides antisecretory and cytoprotective effect, drugs having antioxidant activity are more effective in healing as well as preventing the ulcer relapse after initial healing. Although H₂ histaminergic receptor blockers and proton pump inhibitors are effective
in the treatment of peptic ulcer disease, search for new drug continues, in an attempt to find agents which may accelerate the healing process and prevent the recurrence of peptic ulcers. The herbal and other indigenous drugs provide safe and effective alternative to modern medicine in the treatment of gastric ulcers.

Diabetes mellitus is a major and growing public health problem throughout the world. With an estimated world wide prevalence 150 million people in 2000, it is expected to increase to 220 million people by 2010 (Zimmet et al, 2001). The human burden of diabetes is a consequence of the devastating chronic complications of the disease. In the US, diabetes remains the leading cause of new blindness in adults, with 24000 individuals becoming blind every year because of diabetes. Diabetes now accounts for 43% of patients of entering dialysis or transplantation, making it by far the leading cause of end-stage renal disease compared to the nondiabetic population. People with diabetes are 2-6 fold more likely to have heart disease and 2-4 fold more likely to have a stroke. Diabetes results in a 15-40 fold increased risk of amputations compared to nondiabetic population.

Diabetes is becoming something of a pandemic and despite the recent surge in new drugs to treat and prevent the condition, its prevalence continues to soar. Perhaps its most worrying aspect is reflected in children. Although several drugs targeted for carbohydrate hydrolyzing enzymes (pseudosaccharides), release of insulin from pancreatic β-cells (sulphonyl ureas), glucose utilization (biguanides) and insulin sensitizers (glitazones) are in clinical practice, the growing diabetes market observes a number of changes. The glitazones are meant to target the problem of insulin resistance and enhance insulin action at the cellular level; however, some of these drugs are linked to liver toxicity (troglitazone), including a number of deaths from hepatic failure and raising the symptoms and risk factors of heart disease leading to heart failure as in case of rosiglitazone. As the long term complications of diabetes related with these drugs are not yet clear, UK Drugs and Therapeutic Bulletin warrants that patients taking glitazones be monitored for signs of heart failure. On the other hand, traditional medicinal plants with various active principles and properties have been used since ancient times by physicians and laymen to treat variety of human diseases such as diabetes, coronary heart disease, and cancer. The beneficial multiple activities like manipulating carbohydrate metabolism by various mechanisms, preventing and restoring integrity and function of β-cells, insulin-releasing activity, improving glucose uptake and utilization and the antioxidant
properties present in medicinal plants offer exciting opportunity to develop them into novel therapeutic entities. The multifactorial pathogenicity of diabetes demands multimodal therapeutic approach. The multiple activities of plant-based medicinal preparations meant for diabetes offer enormous scope for combating the threat of the diabetic epidemic (Tiwari and Rao, 2002).

To achieve a blockbuster status, clear evidence of the advantage over the existing therapy is the most important requirement of the day. The ability of modern medicine and health care systems to adequately manage symptom of chronic and terminal disease is a central theme. The systemic reviews and meta analysis of clinical trials are the foundation of their success. Unfortunately, despite the apparent of herbal medicines, well-organized and rigorous clinical trial evidences are not adequately available in order to advocate their scientific merit and supremacy over the existing drugs. Though the market for herbal medicine is booming and evidence for effectiveness is growing, it is also being simultaneously counterbalanced by adequate regulation. Therefore, the product standardization, efficacy, safety and therapeutic risk/benefit associated with the use of herbal medicines need proper evaluation. A sound basic and rigorous clinical investigation to confirm and advocate the excellence over the existing therapies of traditional medicinal plants, preparations, mechanism of action and therapeutic effects is absolutely required.

Medicinal herbs have been in use in one form or another under indigenous system of medicine like Ayurveda, Sidha, and Unani. India, with its traditional background, needs to increase its share in the world market. But unlike China, India has not been able to capitalize on this herbal wealth by promoting its use in the developed world, despite their renewed interest in herbal medicines. This can be achieved by judicious product identification based on disease prevalent in the developed world for which no medicine or palliative therapy is available. Such herbal medicines will find speedy access into the developed countries.

The plant kingdom still holds many species of plants containing substances of medicinal value, which are yet to be discovered. India is a land of immense biodiversity in which 2 out of 18 hot spots of the world are located. India is also one of the twelve mega biodiversity countries in the world. The total number of plant species of all groups recorded from India is 45,000 (it may even be close to 60,000 as
several parts of India are yet to be botanically explored). The task force appointed by the Planning Commission in June 1999, after studying the export market, suggested targets of Rs. 3000 crores by 2005 and Rs. 10,000 crores by 2010 for the export of medicinal plant based products. This is a challenging task keeping in mind that the present herbal export from India is only Rs. 579 crores. In order to promote Indian herbal drugs, there is an urgent need to evaluate the therapeutic potentials of the drugs as per WHO guidelines. Ironically, not many Indian products are available in standardized form, which is the minimum requirement for introducing a product in the Western market. India is sitting on a gold mine of well recorded and traditionally well-practiced knowledge of herbal medicine. It is perhaps the largest producer of medicinal herbs and is rightly called the botanical garden of the world. There are very few medicinal herbs of commercial importance which are not found in India. It officially recognizes over 3000 plants for their medicinal value. It is generally estimated that over 6000 plants in India are used in traditional, folk, and herbal medicine, representing about 75% of the medicinal needs of the third world countries (Rajshekharan, 2002).

As mentioned above, India with vast experience of use of various medicinal plants and being source of such plants, it can be leader in producing efficacious and safe drugs, which can be made easily available. However, such plants require scientific study for their approval in clinical practice. The present study is an attempt in this direction to approve the establishment of efficacy and safety of *Helicteres isora* Linn with reference to traditional knowledge may possibly add a new remedy to our present therapeutic armamentarium.

*Helicteres isora* Linn. (Sterculiaceae) is a sub-deciduous tree growing throughout India. Its fruits are commonly known as maroorphali (Hindi), Mriga-Shiga (Gujarati), Aavartanee (Sanskrit), Yedamuri (Kannad). The root juice is claimed to be useful in diabetes, empyema, and a reliable cure for snake bite (Singh et al, 1984, Kirtikar and Basu, 1995). The roots and bark are expectorant, demulcent, and are useful in colic, scabies, gastropathy, diabetes, diarrhea, and syphentery (Prajapati et al, 2003). The fruits are astringent, refrigerant, stomachic, vermifugal, and useful in griping of bowels, flatulence in children (Chopra et al, 1956) and antispasmodic (Pohocha and Grampurohit, 2001). Cucurbitacin B and isocucurbitacin B were isolated from root and reported to possess cytotoxic activity (Bean et al, 1985). From
fruits, neolignans, helisterculins A and B and helisorin were isolated. They showed weak inhibitory activity against reverse transcriptase. Several phytochemicals like tannins, cardiac glycosides, sterols, triterpenes, α and β amyrin, lupeol, fridelin, taraxerone, and β-sitosterol were reported to be present in fruits (Deshmukh and Pandit, 1968; Al Yahya, 1986). Isocutellarein and its glucuronides were isolated from the fruits (Kamiya et al, 2001). Isorinic acid, rosmarinic acid, and their derivatives were isolated and reported to possess the superoxide scavenging activity (Satake et al, 1999). The roots are used in the treatment of chronic nephritis and gastric ulcers in China. The fruits are used as anthelmintic against tapeworm and in the treatment of gastrospasm (Kamiya et al, 2001). Pohocha and Grampurohit (2001) reported antispasmodic activity of H. isora induced by acetylcholine, histamine, and BacI₂. H. isora (root) was reported to possess insulin-sensitizing and hypolipidemic activity in different experimental models (Chakrabrati et al, 2002). In another study, the H. isora was reported to possess antihyperglycemic activity in alloxan-induced diabetic rats, while no such effect was observed in normal rats (Venkatesh et al, 2002).

In the light of therapeutic claims in favour of H. isora and on the basis of its traditional uses and experimental evidences, the present study was designed to evaluate the gastroprotective, hepatoprotective, antidiabetic, and antihyperlipidemic activity of this in different animal models. For gastroprotective study, we have studied the involvement of nitric oxide (NO), prostaglandin, and sulphhydryls in ethanol-induced gastric ulcer in rats. We have also studied the antisecretory activity of H. isora in ethanol plus pylorus ligation induced gastric ulcer in rats. As diabetes is associated with several complications, beside the antidiabetic activity of H. isora in alloxan induced diabetic rats we also studied the effects of H. isora on lipid profiles, renal functions, and liver functions. To evaluate the mechanism for its antidiabetic activity, we studied the effects of H. isora on liver glycogen content, glucose-6-phosphatase activity, and glucose uptake by skeletal muscle.

Quality and efficacy of the herbal drugs need to be established throughout systematic pharmacognostic, phytochemical, and pharmacological evaluation. In herbal drug research, it is also essential to authenticate the plant and to establish phytochemical standardization with the help of reliable instruments. So in the present study, we also carried out the phytochemical standardization of H. isora extracts with the help of HPTLC technique.