Chapter 1

Introduction
1.1. Preamble to the Rationale of the Present Work

Gastric ulcer is a common global disease with increasing incidence and prevalence, despite significant medicinal advances. Worldwide 14.5 million people have ulcers with a mortality of 4.08 million (http://digestive.nidk.nih.gov/statistics/statistics.htm/peptic ulcer prevalence). Infection by *Helicobacter pylori* and excessive use of non-steroidal anti-inflammatory drugs (NSAIDs) (Wallace, 1997) are the two major factors responsible for the disease. The NSAIDs are one of the most commonly used therapeutic drug groups worldwide for addressing a variety of health problems like pain, inflammation, cardiovascular complications, malignancies, stroke, pre-eclampsia, Alzheimer's disease, and many other illnesses. The NSAID-induced gastropathy is widespread accounting for gastric ulcers in 25% of the users. Circumventing the NSAIDs-related ulceration remains an important medical problem, despite pharmaceutical advances. The commercially available synthetic anti-ulcer drugs show various degrees of toxicity and side effects, are inadequate in preventing recurrence of ulceration, and are often very expensive, especially for the common man. In the Indian pharmaceutical industry alone, antacids and antiulcer drugs share 6.2 billion rupees and occupy 4.3% of the market share.

Given the global popularity of the herbal medicines amongst people, extensive works have been carried out with various phytogenic agents to meet the therapeutic goals of developing anti-ulcer drugs that relieve pain, heal the ulcer and delay/prevent its recurrence. A limited number of semi-synthetic natural product congeners have also been used in this end in order to identify the pharmacophore, and address issues such as activity potentiation and toxicity reduction. Excellent reviews on the use of plant/herbal extracts (Borrelli and Izzo, 2000; Yesilada and Gurbuz, 2003) and pure phytochemicals (Maity et al., 2009) against gastric ulceration, caused by various ulcerogens have been published.

Plants have an almost limitless ability to synthesize a large number of organic compounds, and some of these might offer better protection against ulcer. The importance of ethnopharmacolical studies for combating gastro-duodenal ulcers is highlighted by the fact that the first effective drug against gastric ulcer was carbenoxolone from *Glycyrrhiza glabra*. Likewise, gefarnate, which has been employed as an anti-ulcer agent in folk medicine is derived from cabbage (Borrelli and Izzo, 2000). A large number of plant extracts have been studied for their beneficial role against gastric ulceration and some of
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these are also being used for treatment or evaluated at different stages of human clinical trials.

It is now established that amongst others, oxidative stress play a significant role in the pathogenesis of gastric ulceration, including that caused by the NSAIDs. Exploration of a non-toxic, natural antioxidant factor, which is specific in its action and shows antistress property might provide a suitable inexpensive anti-ulcer medications against the NSAID-induced gastropathy. However, given the complexity of the process of ulcer healing, the formulation needs to ensure angiogenesis by augmenting biochemical factors such as synthesis of prostaglandins (PGs), various growth factors and other modulators or enzymes responsible for these as well as modulating Th1/Th2 cytokines. The great Indian biodiversity, especially the edible plants/herbs appear promising in this effort.

1.2. Objectives of the Current Investigation

Against the above backdrop, the primary objectives of the present study can be classified as follows:

1. Formulation of inexpensive and non-toxic plant-based agents with healing property against NSAIDs-induced gastric ulceration.
2. Comparison of their efficacy with that of standard commercial drug, omeprazole (Omez)
3. Quantitative assessment of the ulcer-healing potential of the drugs by histopathology.
4. Mechanistic rationalization of the biochemical and immunological pathways of the action of the drug(s).
5. Critical assessment of the performance of the drug(s) by evaluating the generated data and knowledge base.

To this end, an antioxidant-rich fraction of Picrorrhiza kurroa (K-7) and the phenolic diarylnonanoid, malabaricone C, isolated from Myristica malabarica were assessed their healing capacity against the indomethacin-induced acute gastric ulceration in mice. The methodologies adopted and the results obtained are subsequently discussed and finally the findings of the investigations summarized.