1. 1. INTRODUCTION

Peptic ulcer disease is a common disorder that affects millions of people worldwide. The prevalence of peptic ulcer increased with age, with a peak prevalence of 28.8% in the 5th decade of life. It is been suspected that peptic ulcer is widely prevalent in India, more common in south India than North India (Khuroo MS et al., 1989). When complication occurs peptic ulcer disease affects the quality of life and having serious impact on health. Gastric ulcers which happens due to damage of gastric mucosal cells by hydrochloric acid hyper secretion and the imbalance between the hostile factors such as gastric acid, H Pylori, NSAIDs and pepsin and protective factors such as prostaglandins, mucus, bicarbonate, and blood flow to mucosa. Imbalance between the gastric mucosal protective factors and aggressive factor leads to ulceration (Lozano R, 2012).

1.1.1. Normal Structure of Stomach

![Normal Structure of Stomach](https://example.com/structure_of_stomach.png)

Fig-1.1. Normal Structure of Stomach
1.1.2. Ulcerated stomach

![Ulcerated Stomach](image)

**Fig-1.2. Ulcerated Stomach**

1.1.3. Etiology of gastric ulcer

1.1.3.1. Increased gastrin secretion

Luminal amino acids following dietary intake induce production of gastrin. This is cleaved post-translationally into acid-stimulatory peptides including gastrin-17 and gastrin-34. These in combination stimulate gastric acid secretion by promoting synthesis and release of histamine from ECL cells ([Mejia A et al.], 2009). Hyper gastric stimulation increases acid secretion leading to damage of the mucosal layer.

1.1.3.2. *Helicobacter Pylori* infection

*Helicobacter pylorus* is a gram-negative bacterium that colonizes the mucus on the luminal surface of gastric epithelium. Unless treated, it persists and damages the mucosal barrier leading to inflammation, ulceration and sometimes gastric lymphoma and adenocarcinoma ([Kusters JG et al.], 2006; [Tomassetti P et al.], 2003; [Maton P et al.], 1991).
1.1.3.3. NSAIDs

Other than *H. pylori* infection, nonsteroidal anti-inflammatory drug usage is the common cause of peptic ulcer (*Quan C et al., 2002*). In individual patients active gastritis may deteriorate during long-term NSAID therapy. In gastroduodenal mucosa NSAIDs aggravate mucosal injury caused by *H. pylori* (*McCarthey DM et al., 1991; Voutilainen M et al., 2001*).

1.1.3.4. Hypercalcaemia

Development of gastric ulcers in cold-stressed mice was linked to enhancement of calcium/calmodulin-dependent catecholamine synthesis in the brain by Sutoo D *et al.* (1998). During cold stress, serum and brain calcium levels were found to be increased. This was found to enhance dopamine synthesis leading to increased brain dopamine level induced gastric ulcer formation. Pretreatment with verapamil significantly reduced this gastric ulcerative response to cold-restraint stress in the rat. This was attributed to cytoprotection of the gastric mucosa, preservation of gastric mucosal blood flow, or blockade of calcium-mediated ulcerogenic stimuli. This suggested involvement of calcium influx stimuli in the gastric stress ulceration (*Wait RB et al., 1985*).

1.1.3.5. Genetic factors

The familial accumulation of peptic ulcer disease observed in several studies suggested involvement of genetic effects, aggregation of environmental exposure (shared environment), or both. Reports have also suggested the rise of intra familial spread of Helicobacter pylori infection. (*Raiha I et al., 1998*).
1.1.3.6. Alcohol and Smoking

Several studies have suggested that smoking increases both the incidence and rate of peptic ulcer diseases and also delays ulcer healing in humans. The alteration of normal gastric mucosal blood flow and the suppression of cell proliferation largely delay ulcer healing in cigarette smokers (Ko JK et al., 2000). Cigarette smoking has been shown to potentiate ethanol-induced gastric mucosal damage in animal models. Accordingly it is a risk factor for the development, and recurrence of peptic ulcer disease (Eastwood GL et al., 1988; Maity P et al., 2003).

1.1.3.7. Stress

Stress ulceration is diffuse lesions of the mucosal layer of the stomach and sometimes the duodenum. This occurs following stressful events, such as extensive burns, shock, sepsis, major surgery, and severe trauma (Jia et al., 2007; Berndt V et al., 1978). Bleeding from stress ulcer in critical ill patients can result in substantial morbidity and mortality. Under the hypoxic-ischemic condition, reactive oxygen species (ROS) such as superoxide anions (O$_2^-$), hydrogen peroxide (H$_2$O$_2$), and hydroxyl radicals (·OH) are rapidly and continuously produced, and the resulting oxidative stress is crucially responsible for the development and progression of epithelial necrosis and mucosal ulceration.

1.1.4. Management of ulcer

The treatment in peptic ulcers aims to relieve symptoms, heal craters, prevent recurrences and other related complications. This is achieved by reducing levels of hostile factors including gastric acid and H. pylori while augmenting protective factors in the digestive tract. With development of greater insight into the process of acid secretion, many attempts have been made to develop suitable agent with different targets. However,
since development of omeprazole in 1980s as proton pump inhibitor, there has not been any significant achievement in the efforts of developing ideal antiulcer agents. Thus, keeping in view the growing concerns and limited options in ulcer, research in this area to find suitable antiulcer agent is highly desirable.

1.1.5. Design of the present study

Selection of lead
  ↓
Design of amino acid conjugates of lead
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In silico evaluation of drug likeness and toxicity
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Synthesis of conjugates
  ↓
Characterization of synthesized conjugates
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Evaluation of their acute toxicity study
  ↓
Evaluation of antiulcer activity in Shay rat model
  ↓
Selection of two potent conjugates
  ↓
Evaluation in different ulcer model
  ↓
Gastric ATPase inhibition
  ↓
Discussion and rationalization of antiulcer action
  ↓
Conclusion