INTRODUCTION

The term "Cytoprotection" is applied to the ability of a sizable and growing number of exogenously administered substances (ranitidine, cimetidine, famotidine, nizatidine as a H₂-receptor blocker, omeprazole, lansoprazole, pantoprazole, rabeprazole as a H⁺-K⁺ ATPase enzyme inhibitor, H⁺ channel blocker or proton pump inhibitor, misoprostol as a prostaglandins stimulator and sucralfate as an acid suppressor) and experimental manipulations (cerebellar-vestibular stimulation and selective sub-diaphragmatic vagotomy) which protect the extent of subsequent mucosal injury by various injurious. These injurious such as non-steroidal anti-inflammatory drugs (NSAIDs; aspirin, indomethacin, ibuprofen), ethanol, hydrochloric acid (HCl), erythromycin, stress and experimental manipulations (cerebellar-vestibular lesion, cerebellar nodular lesion and sub-diaphragmatic cholinergic vagus stimulation) are known as damaging interventions (Jacobson, 1990; Guha and Ghosh, 1995; Sarkar et al., 2006; Debnath and Guha, 2007).

This "Cytoprotection" term has been used before two decades to denote the property of certain substances which protect the stomach from injury. "Cytoprotection" has also been referred to as stimulating natural defense mechanisms (Pilchman et al., 1991). It is a process in which the stomach actively repairs itself. The process does not involve the alteration of gastric acid secretion (Pilchman et al., 1991). Recently, "Cytoprotection" is also applied to the protection from cell damage by reactive oxygen species (ROS) or by oxygen derived free radicals (Das and Banerjee, 1993; Das et al, 1997; Das et al, 1998).

"Peptic ulcer disease" (PUD) is a very common disease, results from an imbalance between luminal injurious factors and mucosal resistance. This disease is caused by a disruption in the balance between acid and mucus, which maintain the normal milieu of gastrointestinal tract (GIT). They affect more than 4 million people in each year. Peptic ulcer disease (PUD) is sum of ulcer disease of two parts of gastrointestinal tract (GIT), one which is usually occur in the stomach called "gastric ulcer disease" (GUD) and another in the duodenum called "duodenal ulcer disease" (DUD), which is the upper region of the small intestine. An equation has been drawn to
understand easily that is $\text{PUD} = \text{GUD} + \text{DUD}$. The stomach and duodenum lining have a number of mechanisms that protects it from digesting itself. These include a coating of mucous (mucus layer) that serves as a barrier against the effects of the acidic digestive juices, the production of substances to neutralize acid and chemicals that protect the cell lining of the stomach and duodenum (Hojgaard et al., 1996). Damage or impairment of the protective features and subsequent exposure to digestive juices can lead to irritation and erosion of the stomach and duodenal lining.

Etiology of peptic ulcer disease (PUD) is not clearly known but clinically ulcers are characterized by abnormal pain, discomfort, cramping and troubles. Pathophysiology of peptic ulcer disease (PUD) is an imbalance between aggressive factors (gastric acid, pepsin, bile secretion, NSAIDs, alcohol, stress, malignancy and $H. pylori$) and defensive factors (endogenous prostaglandins, gastric mucosal barrier, somatostatin, epidermal growth factor and mucosal blood flow). These protective factors act as a defense which is responsible for cytoprotection of the mucosal cells. The development of peptic ulcer disease (PUD) requires excessive acid-peptic activity and break down of mucosal defense mechanisms (Sonnenberg, 1995). Local mechanisms implicate in the mucosal blood flow, mucosal sulfhydryls and increased resistance of gland cells in deep mucosa against acid and peptic activity (Konturek, 1985).

Mucus producing cells of the stomach are found amongst the surface epithelial cells or within gastric glands. Mucus producing cells from the gastric glands are usually most numerous in the region of the neck on the gland, hence giving rise to the term “mucus neck cell”. Mucus neck cells most frequently are localized in the gastric fundus.

Following the release, gastric mucus normally forms a continuous “blanket” over the mucosal epithelial. The “blanket” is composed of random structured fribillar network arranged in layers forming a loose gel; with the complexity and thickness of the meshwork increasing as the volume of secreted mucus increases.

Knowledge of the mechanisms and control of gastric mucus secretion is meager and mostly somewhat circumstantial. It seems, however, unanimously accepted that in healthy animal mucus is secreted continuously even during resting conditions. There is no evidence that usual stimulants of gastric acid output e.g. feeding, gastrin or histamine
exert any appreciable influence on mucus secretion. With respect to the effects of parasympathetic and sympathetic neurotransmitters are difficult to reach in the role of mucus synthesis. Serotonin has been shown to stimulate mucus production in the gastrointestinal tract (GIT) of dogs (Racke et al., 1988). As enterochromaffin (EC) cells produce serotonin (5-hydroxytryptamine; 5-HT) and lie in close vicinity to mucus producing cells, it is tempting to assume that local serotonin (5-HT) production normally influences mucus production by paracrine action (Kaufmann et al., 1979; Konturek et al., 1987; Pesker, 1980). The same is true for endogenous prostaglandins (PGs), as at least E₁ and even more E₂ type prostaglandins (PGs) following oral administrations include both increases in mucosal resistance as well as decrease in aggressive factors mainly acid and pepsin. Both prostaglandins E and I are the prominent prostaglandins (PGs) synthesized by the gastric mucosa and are known to inhibit the secretion of gastric acid and stimulate the secretion of mucus and bicarbonate (HCO₃⁻). Hydrophobic surfactants like phospholipids secretion in the gastric epithelial cells is also stimulated by the prostaglandins (PGs) (Aly, 1987).

The gastro-protective factors combat with the luminal injurious factors to maintain the normal milieu of gastrointestinal tract (GIT). Peptic ulcer disease (PUD) is one of the common diseases affecting mankind. “It kills few but troubles many” (Lawrence and Bennett, 1987) and results from an imbalance between luminal injurious factors and mucosal resistance. The pathogenesis of peptic ulcer disease (PUD) is believed to reflect an imbalance between increased aggressive factors and decreased protective factors (Sarkar et al., 2006).

Damage or impairment of the antioxidant enzymes and excessive generation with subsequent exposure to reactive oxygen species (ROS) or oxygen derived free radicals can lead to irritation and erosion of the stomach and duodenal epithelial lining. Peptic ulcer disease (PUD) is the disruption of balance between antioxidant enzymes system and reactive oxygen species (ROS) or oxygen derived free radicals of gastric and duodenal lining (Das and Banerjee, 1993; Das et al., 1997; Das et al., 1998). The gastric and duodenal mucosal lining cells have a number of mechanisms that protects it from damaging itself. These include a coating of mucous (mucosal layer) cells that serves as an antioxidant against the toxic effects of the reactive oxygen species (ROS) or oxygen
derived free radicals and protects the lining cells of the stomach and duodenum (Das and Banerjee, 1993; Das et al, 1997; Das et al, 1998).

This disease is a disorder of multiple etiologies, characterized by mucosal erosion of gastrointestinal tissues and wide spectrum of pathological and clinical manifestations.

There are number of drugs available to treat peptic ulcer disease (PUD) such as ranitidine, cimetidine, famotidine, nizatidine as a H2-receptor blocker (Hansten, 1994; Bilchik et al., 1989; Havu et al., 1990), omeprazole, lansoprazole, pantoprazole, rabeprazole as an H+–K+ ATPase enzyme inhibitor or H+ channel blocker or proton pump inhibitor (PPI) (Howden and Hunt, 1994; Wolfe and Sachs, 2000; Qi et al., 2009) and misoprostol as a prostaglandin stimulator (Graham et al., 1988), sucralfate as an acid suppressor (Slomiany et al., 1985; Tytgat, 1984) etc but some of them have various side effects.

Therefore, there is a lacunae still existing in the field of proper treatment and appropriate therapy for peptic ulcer disease (PUD). Hence, there is a clear need for alternative source of anti-ulcerogenic medicines, drugs and strategies for peptic ulcer disease (PUD) treatment and appropriate therapy.

Medicinal plants and herbal medicines are part and parcel of human society to combat poverty and diseases from the down civilization (Biswas et al., 2002) and great history of using those plants from time immemorial.

Dietary plants and herbal preparations have been used as traditional medicine in developing countries and obtained a resurgence of use in those countries. Research carried out in last few decades has validated several such claims of use of traditional medicinal plants (Caili. et al., 2006).

Cucurbita pepo Linn. (C. pepo), commonly known as pumpkin or sweet gaurd in English, is a plant under the family-Cucurbitaceae (Paris et al., 2003; Paris, 2009) is available and a rich source of this plant and great history of using this plant from time immemorial throughout India and neighboring countries.
Fruits of *Cucurbita pepo* Linn. are used as vegetable (Sarkar and Guha, 2008; Koike *et al.*, 2005; Mongkolsilp *et al.*, 2004; Sammon *et al.*, 2003; Linskens and Jorde, 1997) and fruit’s pulp is used to treat dyspepsia and enteritis or intestinal inflammation (Orlandelli, 1951), intestinal diseases (Francois *et al.*, 2006) and liver disorder (Sezik *et al.*, 2004). It has been reported that pumpkin is consumed as a diet to increase the pH of fasting gastric sample (Sammon *et al.*, 2003) and the dietetic management of patients undergoing gastric operations is also carried out by supplementation of pumpkin (Loranskaia *et al.*, 1986). Therefore, fruits are used to relieve from inflammation (Caili *et al.*, 2006), cancer (Kune *et al.*, 1992; Heber and Bowerman, 2001), tumor (Fan *et al.*, 2004), mutagenicity (Edenharder *et al.*, 1994). Cytotoxic activity against the human epithelial carcinoma cell line (Wang *et al.*, 2008) has been found. Inhibitory effects of cucurbitacin B from fruit of pumpkin showed on laryngeal squamous cell carcinoma (Liu *et al.*, 2007).

Popularity of pumpkin in various systems of traditional medicine for several ailments such as antidiabetic, antihypertensive, antitumor, immunomodulation, antibacterial, anti-hypercholesterolemia, intestinal antiparasitia, anti-inflammation, antalgic etc focused an attention on this plant. Considerable evidence from several epidemiological studies concerning bioactivities have encouraged or stimulated a number of animal model and clinical trials to test these pharmacological actions (Caili *et al.*, 2006).

So, exploration of anti-ulcerogenic activity of different plants of Indian origin is an emerging area of peptic ulcer research.

**Purpose of the present investigation:** Based on these ethnic reports, the present research programme was designed to undertake detail scientific investigation of the aqueous extract of ripe fruit’s pulp of *Cucurbita pepo* Linn. (*C. pepo*) for its anti-ulcerogenic activity in experimental rat models are following-

1. Aspirin induced ulcerated rat model.
2. Ethanol (Eth-OH) induced ulcerated rat model.
3. Immobilized-cold stress induced ulcerated rat model.
4. Cerebellar nodular lesion (CNL) induced ulcerated rat model.
So, the aim of the present investigation is to elucidate the cytoprotective role of aqueous extract of ripe fruit’s pulp of *Cucurbita pepo* Linn. (*C. pepo*) keeping several objectives for the prevention of different experimental peptic ulcer (drug such as aspirin induced; alcohol such as ethanol induced; stress such as immobilized and cold stress induced; surgery such as cerebellar lesion induced) in rat model.

Assessment of the cytoprotective effects of ripe fruit’s pulp of *Cucurbita pepo* Linn. extract using those ulcer models have been shown at a glance in following chapters-

**Chapter I** deals with a “review of the literature” on some ulcerogenic factors such as acid, monoamines (acetylcholine, histamine), gastrin, NSAIDs, alcohol, stress and cytoprotective factors such as antioxidant enzymes, mucus, PGs, alkaline phosphatase (AP) enzyme, EC cells, serotonin (5-HT), various antiulcer drugs and their side effects. Role of various indigenous antiulcer plant products on gastric secretory functions such acid, mucus and role of *Cucurbita pepo* Linn. in digestive functions have been reviewed.

**Chapter II** describes “aims and objectives” of the present investigation.

**Chapter III** “methodological consideration” describes the experimental designs of different experimental peptic ulcer (by drug such as aspirin induced; by alcohol such as ethanol induced; by stress such as immobilized cold stress induced; by surgery such as cerebellar nodular lesion induced) and chronically prepared indwelling gastric cannulation in conscious rat model for gastric secretion collection. “Methodological consideration” also describes the parameters for studying morphology, biochemistry and histochemical studies of different experimental gastroduodenal tissues of those rat models.

**Chapter IV** describes “Dose dependent antiulcer activity of aqueous extract of ripe fruit’s pulp of *Cucurbita pepo* Linn. and ranitidine against aspirin induced gastric and duodenal ulcer index and mucosal thickness of experimental rat model”.
Chapter V describes “Alteration of alkaline phosphatase enzyme activity, mucosal thickness and ulcer index against aspirin induced gastric and duodenal ulceration following pretreatment with aqueous extract of ripe fruit’s pulp of *Cucurbita pepo* Linn.”

Chapter VI describes “Antioxidant activity of aqueous extract of ripe fruit’s pulp of *Cucurbita pepo* Linn. and ranitidine against aspirin induced gastric and duodenal ulceration of experimental rat model”.

Chapter VII explains “Antiulcer and antioxidant activity of aqueous extract of ripe fruit’s pulp of *Cucurbita pepo* Linn. and ranitidine against ethanol induced gastric and duodenal ulceration of experimental rat model.”

Chapter VIII illustrates “Antiulcer and antioxidant activity of aqueous extract of ripe fruit’s pulp of *Cucurbita pepo* Linn. and ranitidine against immobilized-cold stress induced gastric and duodenal ulceration of experimental rat model.”

Chapter IX describes “Anti-acid secretory and antiulcer role of aqueous extract of ripe fruit’s pulp of *Cucurbita pepo* Linn. and ranitidine against cerebellar nodular lesion induced gastric ulceration by altering pH, volume of secretion, acid secretion and mucus content.”

Chapter X describes “Role of aqueous extract of ripe fruit’s pulp of *Cucurbita pepo* Linn. and ranitidine against ulcer index, mucosal thickness, enterochromaffin cell count and serotonin content in cerebellar nodular lesion induced gastric and duodenal ulceration of experimental rat model.”

In Chapter XI finally, the results of different experiments have been discussed elaborately.

Chapter XII summarizes the whole experimental works and the conclusion of the present investigation has been presented.