Peptic ulcer disease (PUD), a most common disease and global health problem, has been widely studied from time immemorial. Most of the early works have been widely focused around management of the vagus and acid index of the gastrointestinal tract (GIT) by various antacids as H$_2$-receptor blockers, proton pump inhibitors (PPIs), sucralfate giving little attention to mucus secretion and protection of antioxidant enzymatic defense system by herbal remedies. It is well known to peptic ulcer researchers that a balance between acid and mucus as well as reactive oxygen species (ROS) or oxygen derived free radicals and antioxidant enzymatic system management by herbal remedies are being used to maintain the internal normal milieu of the gastrointestinal tract (GIT). Changes in the functions of the mucus, antioxidant enzymatic defense system and alteration in its composition, quantity, functional activities are closely associated with gastric and duodenal ulceration. The increased acidity and reactive oxygen species (ROS) or oxygen derived free radicals alter composition, quantity, functional activities of mucus and antioxidant enzymatic defense system respectively. Similarly, the amount of mucus degraded appears to be related to the total quantity of acid. Thus beside this acid secretion and generation of reactive oxygen species (ROS) or oxygen derived free radicals alter composition, many condition, which upsets the equilibrium or imbalances the normal functions and impairs the integrity of mucus layer of gastric and duodenal tissues are closely related to ulceration.

Peptic ulcer is also induced through generation of ROS, by alteration of antioxidant systems of the gastric (Levi et al., 1990; Vaananen et al., 1991; Yoshikawa et al., 1993) and duodenal (Phull et al., 1995) mucosa.

Medicinal plants and herbal medicine are part and parcel of human society to combat poverty and diseases from the down civilization like Bangladesh (Ahmed et al., 2003), Zegie Peninsula and Northwestern Ethiopia (Teklehaimanot and Giday, 2007), Pakistan (Iqbal et al., 2005) as well as India (Dharmani and Palit, 2006) where is a rich source of medicinal plants and great history of using those plants from time immemorial.
Some of the herbal extracts (Yesilada et al., 1997; Goel and Bhattacharya, 1991), herbal composites (Garg et al., 1993; Yang et al., 2007), herbal preparations and formulations (Manonmani et al., 1995; Zhu et al., 2002) are still used as herbal drugs to treat the gastric disorders and these have been documented in the ancient medicinal literature of various countries from time immemorial.

A deleterious effect of ulcerogens such as non-steroidal anti-inflammatory drugs (NSAIDs; aspirin, indomethacin, ibuprofen) (Pihan et al., 1987; Miura et al., 2002; Yoshikawa et al., 1993; Vaananen et al., 1991; Salim, 1992), ethanol (Peskar et al., 1986; Pihan et al., 1987; Szelenyi and Brune, 1988) and stress (Das and Banerjee, 1993; Das et al., 1997; Das et al., 1998; Bandyopadhyay et al., 2002) is the production of reactive oxygen species (ROS) which results in damage to bio-molecules (e.g., lipids, proteins, amino acids and DNAs) (Fang et al., 2002). Understanding free radical biology is necessary for designing an optimal nutritional countermeasure against peptic ulcer disease (PUD). Free radicals (e.g., superoxide anion and hydroxyl radicals) and other reactive species (e.g., hydrogen peroxide, peroxynitrite and hypochlorous acid) are produced in the body, primarily as a result of aerobic metabolism. Antioxidants (e.g., glutathione, arginine, citrulline, taurine, creatine, selenium (Se), zinc (Zn), vitamin A, vitamin C, vitamin E, catechin, epigallocatechin gallate and tea polyphenols) and antioxidant enzymes (e.g., superoxide dismutase, catalase, glutathione reductase and glutathione peroxidases) exert synergistic actions in scavenging free radicals. There has been growing evidence over the past three decades showing that malnutrition (e.g., dietary deficiencies of proteins, selenium and zinc) gives rise to the oxidation of biomolecules and cell injury. A large body of the literature supports the notion that dietary antioxidants are useful as stress protectors and play an important role in preventing many human diseases (Fang et al., 2002; Granger et al., 1986). Amino acids such as tyrosine (Mahajan et al., 1985), cysteine (Loguercio et al., 1991), methionine (Galey et al., 2007; Bourdon et al., 2005; Panasenko et al., 2005; Erdmann et al., 2005; Slyshenkov et al., 2002; Selvam and Ravichandran, 1991; Levine et al., 2000; Levine et al., 1996; Stadtman et al., 2002; Kroger et al., 1997; Patra et al., 2001; Devasagayam et al., 1991) and act as antioxidant (Fang et al., 2002) exhibit phenolic activity scavenging free radicals. Cadmium (Cd) also exerts synergistic actions in scavenging free radicals (Izgut-Uysal et al., 1993; Jamal and Sprowls, 1987).
From the results of present experiment it is evident that cerebellar nodular lesion (CNL) produced an increase in volume of secretion, excessive gastric acid secretion and decrease in pH, mucus (carbohydrate: protein; CHO: P) content of gastric juice in rat model. The increase in gastric acid secretion (Wolf and Soll., 1988), volume of secretion, acid-peptic activity and decrease of pH, mucus content (CHO: P) of gastric juice are related to gastric ulcer pathogenesis (Debnath and Guha, 2007; Sarkar et al., 2006; Guha et al., 2002; Sarkar and Guha, 1999; Guha et al., 1995; Guha and Ghosh, 1995; Guha and Maiti, 1990; Maiti and Guha, 1978; Wolf, 1969; Brooks, 1967).

The anti-acid secretory and antiulcerogenic plant extracts, composites, preparations, formulations of licorice root (Goso et al., 1996), calendula, chamomile (Beil et al., 1995), garlic (Sivam et al., 1997), thyme (Ernst, 1999), cinnamon (Graham et al., 1999), corydalis (Chang et al., 1986), comfrey (Graham, 1999), Azadirachta indica (Garg et al., 1993), Stachytarpheta cayennensis (Vela et al., 1997), Cistus laurifolias L (Yasilada et al., 1997), Musa paradisiacal (Goel and Bhattacharya, 1991) and phytochemicals which are currently used as herbal remedies that can effectively control these conditions.

Origin of several antiulcer compounds from some medicinal plants (Lewis and Hanson, 1991) and antioxidative dietary fruits (Chun et al., 2005) has been reported. These antiulcer compounds are classified as terpenoids (Rao et al., 2004), diterpenoids (Feliciano et al., 1993; Maciel et al., 2000; Schmeda-Hirschmann et al., 2003), triterpenoids (Siqueira et al., 2007), flavonoid (Zayachkivska et al., 2005; Repetto and Llesuy, 2002; Beil et al., 1995; Alarcon de la Lastra et al., 1994; Reyes-Ruiz et al., 1998; Suzgec, 2005), flavonone-glycosides (Naseri-Mansour, 2007), flavonoid-glycosides (Dharmani and Palit, 2006; Yasilada et al., 2000; Lewis and Hanson, 1991), cucurbitacin glucosides (Tannin-Spitz et al., 2007) cucurbitane glycoside (Ukiya et al., 2002a; 2002b), sulfhydrlys (Loguercio et al., 1991; Szabo et al., 1981) such as glutathione (Kimura et al., 2001; Loguercio et al., 1993; Boyd et al., 1981) and cysteine (Loguercio et al., 1991), methionine (Galey et al., 2007; Bourdon et al., 2005; Panasenko et al., 2005; Erdmann et al., 2005; Slyshenkov et al., 2002; Selvam and Ravichandran, 1991; Levine et al., 2000; Levine et al., 1996; Stadtman et al., 2002; Kroger et al., 1997; Patra et al., 2001; Devasagayam et al., 1991). Amino acids also function as antioxidants (Fang et al., 2007).
2002), vitamin A (Kasper et al., 1975; Mozsic et al., 1989), vitamin C (Smirnoff et al., 2001; Brzozowski et al., 2001; Davey et al., 2000; Kitano et al., 1997) and vitamin E (Wu et al., 2007; Azlina et al., 2005; Ichikawa et al., 2003; Saad et al., 2002; Nafeezza et al., 1999; Guzel et al., 1998, O’brien, 1992; Zaror-Behrens et al., 1992; Yoshikawa et al., 1991; Armario et al., 1990; Granger et al., 1986; Brady et al., 1979; Young et al., 1976; Toshikazu et al., 1991; Okuma et al., 1980; Nakamoto et al., 1997) phenols such as tannin (Banerjee et al., 2008; Souza et al., 2006; Ramirez and Roa, 2003; Repetto and Llesuy, 2002; Czinner et al., 2001; Ezaki et al., 1985), syringic acid (Aberoumand and Deokule, 2008; Li et al., 2007; Zhao et al., 2006; Fecht-Christoffers et al., 2006; Que et al., 2006; Chen et al., 2005; Wang et al., 2004; Yrjonen et al., 2003; Baublis et al., 2000; Pecur et al., 2000; Hirota et al., 2000; Masaki et al., 1995), tea polyphenols such as catechin and epigallocatechin gallate (Graziani et al., 2005, Euaelhardt et al., 2001), polyamines (Cheng et al., 2004; Ma et al., 2000; Brzozowski et al., 1993), selenium (Fang et al., 2002; Combs, 2001; Combs, 1999; O’brien, 1992; Jamal and Sprowls, 1987; Brady et al., 1979; Young et al., 1976), cadmium (Cd) (Izgut-Uysal et al., 1993; Jamal and Sprowls, 1987), Zinc (Zn) (Fang et al., 2002) and compounds of other chemical nature are also evident.

Different parts of the plant have been used as traditional medicine in Ayurveda (Caili et al., 2006). This plant is used to treat cuts, injuries and swellings (Lans, 2007). Plant is also used as anthelmintics (Al-Qura’n, 2008; Lans et al., 2007), diuretic (Al-Qura’n, 2008) and used to expel tape worms from intestine (Lans et al., 2006).

Fruits of Cucurbita pepo Linn. are used to relieve inflammation (Caili et al., 2006). Fruits are used as vegetable (Sunilson et al., 2009; Linskens and Jorde, 1997) and fruit’s pulp is used in dyspepsia and enteritis or intestinal inflammation (Orlandelli, 1951), intestinal diseases (Francois et al., 2006) and use to treat 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). Fruits are also used to treat 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 showed on laryngeal squamous cell carcinoma (Liu et al., 2007).

Multi-trace elements are such as K, Ca, Mg, Na, Zn, Cu, Mn, Fe, Co and Cr in different parts and different growth periods of pumpkin. Some elements are essential to human such as K, Ca, Mg, Zn, Cr and Mn in pumpkin are abundant, implying that the nutritive value of pumpkin is high (Fan et al., 2006). Furthermore, some antioxidant-type elements such as selenium (Se) (Yoshida et al., 2005; Stibilj et al., 2004), cadmium (Qadir et al., 2000) has been found in C. pepo fruit.

Several anti-ulcer compounds such as triterpenoids (Wang et al., 2008), glycosides such as cucurbitacin B, cucurbitacin D, cucurbitacin E, cucurbitacin F (Feng et al., 2007), cucurbitacin L and cucurbitacin K (Wang et al., 2007), sulfhydryls like glutathione (Alosi et al., 1988), cysteine (Cys or C) (Fahmy et al., 2008; Pham et al., 1985; Allen, 1979; Kleinig et al., 1975; Ogura et al., 1972; Walker, 1972; Kataoka et al., 1998), S-adenosyl methionine (SAM) (Huang et al., 1991), methionine (Met or M) (Yoshida et al., 2005), phenolic compounds such as tannin (Ojiako and Igwe, 2008; Silveira et al., 1996), syringic acid (Dragovic-Uzelac et al., 2005), phenolic phytochemicals (Kwon et al., 2007), polyphenol and phenolic contents (Mongkolsilp et al., 2004), polyamines (Nishimura et al., 2006; Martinez-Tellez et al., 2002), beta-carotene (Veda et al., 2006), pro-vitamin A carotenoids (Azevedo-Meleiro et al., 2007; Priyadarshani and Chandrika, 2007; Seo et al., 2005; Mongkolsilp et al., 2004; Manzi et al., 2002; Gonzalez, 2001; Rodriguez-Amaya, 1999; Kune et al., 1992; Arima and Rodriguez-Amaya, 1990; Arima and Rodriguez-Amaya, 1988), vitamin A (Lans et al., 2007; Ahmed et al., 2003; Ribaya-Mercado et al, 1999), vitamin C (Hancock et al., 2008; Mongkolsilp et al., 2004; Hancock et al, 2003) and vitamin E (Franke et al., 2007; Tadmor et al, 2005; Imaeda et al., 1999; Sedghi et al., 2008) are present in Cucurbita pepo Linn. fruit have been reported.

Some proteins such as pepocin, a type-1 ribosome-inactivating protein (RIP) (Yoshinari et al., 1996), carbohydrate binding protein such as lectin (Allen, 1979), mavicycyanin (Xie et al., 2005; Xie et al., 2003; Marchesini et al., 1979; Kataoka et al., 1998), CpNIP 1, a Nod 16-like protein, patellin 1, a novel sec14-related protein (Peterman et al., 2006), sieve tube proteins (Kleinig et al., 1975; Walker, 1972), aspartic
proteinase inhibitor (Christeller et al., 1998), trypsin inhibitor (Pham et al., 1985) and some enzymes such as ascorbic oxidase (Altmann, 1998; Pitari et al., 1998; Kisu et al., 1997; Esaka et al., 1992; Lin et al., 1991; Esaka et al., 1990; Esaka et al., 1989; Chichiricco et al., 1989; D'Andrea et al., 1989; Casella et al., 1988; Esaka et al., 1988; Avigliano et al., 1983; Marchesini et al., 1979; Marchesini and Kroneck, 1979; Marchesini et al., 1977; Porat et al., 1967), catecholoxidase (Marchesini et al., 1977), multi-copper oxidase (Marchesini and Kroneck, 1979), glutathione reductase (Alosi et al., 1988), esterase (Fahmy et al., 2008), peroxidase (Lupetti et al., 2005) CpCPK1, a Ca-dependent protein kinase (Ellard-Ivey et al., 1999), geranylgeranyl pyrophosphate synthetase and farnesyl pyrophosphate synthetase (Ogura et al., 1972), serine palmitoyltransferase (Lynch and Fairfield, 1993), 1-aminocyclopropane-1-carboxylate synthase and S-adenosyl-L methionine methylthioadenosine-lyase (Huang et al., 1991), isocitrate lyase (ICL), malate synthase (MLS) (Pracharoenwattana and Smith, 2008) have been isolated from the fruit of pumpkin.

Some tryptophan (Trp or W) amino acid containing proteins such as lectin (Allen, 1979), mavi cyanin (Xie et al., 2005; Xie et al., 2003; Marchesini et al., 1979; Kataoka et al., 1998), aspartic proteinase inhibitor (Christeller, et al., 1998) and pepocin or ribosome-inactivating protein (RIP) (Yoshinari et al., 1996) and enzymes such as 1-aminocyclopropane-1-carboxylate synthase and S-adenosyl-L methionine methylthioadenosine-lyase (Huang et al., 1991) have been isolated from the fruit of pumpkin.

Pepocin is a type-1 ribosome inactivating protein (RIP) isolated from the sarcocarp of Cucurbita pepo Linn. having single A-chain (Yoshinari et al., 1996). It has been reported that A-chain from ricin, the ribosome inactivating protein (RIP), is similar amino acid sequence to A-chain of pepocin isolated from the rice that contains tryptophan (Trp or W) residue at position 211 (Ding et al., 2002).

This tryptophan (Trp or W) containing pepocin and others proteins consumption from the fruit of Cucurbita pepo Linn. may be a dietary source of tryptophan (Trp or W) and precursor of serotonin in the EC cells.
Pepocin is a type-1 ribosome inactivating protein (RIP) isolated from the sarcocarp of *Cucurbita pepo* Linn. (Yoshinari *et al.*, 1996) having single A-chain and others. It has been reported that type-1 ribosome inactivating protein (RIP) isolated from the bulbs of *Iris hollandica* named IRIP that contains cysteine (Cys or C) residue(s) in their primary sequence. IRIP contains a single cysteine (Cys or C) residue at position 242 (Hao *et al.*, 2000). Therefore, cysteine residue(s) have been found in fruit of *C. pepo* esterase (Fahmy *et al.*, 2008), geranylgeranyl pyrophosphate synthetase (Ogura *et al.*, 1972) and trypsin inhibitor (Pham *et al.*, 1985). Methionine (Met or M) is also present in aspartic proteinase inhibitor of squash phloem exudate (Christeller. *et al.*, 1998), selenomethionine (Yoshida *et al.*, 2005) and in 1-aminocyclopropane-1-carboxylate synthase and S-adenosyl-L methionine methylthioadenosine-lyase (Huang *et al.*, 1991).

This cysteine (Cys or C) and methionine (Met or M) containing protein consumption from the fruit of *Cucurbita pepo* Linn. may be a dietary source of sulfhydryls which act as an antioxidant in the gastric and duodenal tissues.

Considering the role of mucus and antioxidant enzymatic defense system on gastric and duodenal functions, through modulating the acid and reactive oxygen species (ROS) or oxygen derived free radicals respectively by herbal product, we set up different 4 (four) experimental designs to study the role of aqueous extract of ripe fruit’s pulp of *Cucurbita pepo* Linn. during ulceration produced by following rat models:-

1. Drug such as aspirin induced ulcerated rat model.
2. Alcohol such as ethanol (Eth-OH) induced ulcerated rat model.
3. Stress such as immobilized-cold stress induced ulcerated rat model.
4. Higher brain surgery such as cerebellar nodular lesion (CNL) induced ulcerated rat model.

Inbred Holtzman strain adult albino rats (180-200g) of both sexes were used in these investigations.

In aspirin induced ulcer model, previously, rats were fasted for 24 hours and given a single dose of aspirin (500 mg/kg body weight) (Szabo *et al.*, 1985; Bose *et al.*, 2003) dissolved in double distilled water and was administered orally by orogastric
cannula (Cho and Ogle, 1979). After 4 hours, the rats were anesthetized by ether and then they were sacrificed and their stomach and duodenum were collected.

In ethanol (Eth-OH) induced ulcer model, rats were deprived of food for 24 hours prior to the experiments but they were allowed free access to water. The rats were administered a single dose of 70% 1 ml of ethanol intragastrically (i.g) by orogastric cannula and waited for 1 hour. After 1 hour, the rats were euthanized with ether and the stomach and duodenum were collected.

In immobilized-cold stress induced ulcer model, rats were suspended horizontally in restraint cage at dark condition and subjected to immobilized-cold stress by placing them in the refrigerator compartment at 4°C temperature for 3 hours daily and repeated consecutively for 7 days as per procedure followed by Senay and Levine (1967). After 7 days, they were sacrificed under anesthesia and their stomach and duodenum were collected.

In cerebellar nodular lesion (CNL) induced ulcer model, rats were anaesthetized with intraperitoneal sodium pentobarbital (40 mg/kg body weight; Abbott India Ltd). Each rat was placed in a stereotaxic instrument. A burr hole was made on the posterior aspect of the skull as per stereotaxic co-ordinates (AP=12.8, L=0.4, D=6.) (Pellegrino and Cushman, 1967). Electrolytic lesions were made in the nodular cerebellum by conventional bipolar electrode (insulated by epoxylite with 0.5 mm tip exposed) using 1.5 mA DC (milli ampere direct current) for 20 seconds.

After post operative period of 7 days from the day of implantation of gastric cannula, rats were placed in perplexed glass made restraining cages and gastric secretion was collected at particular time interval under fasting condition through sialistic tube firmly attached with the cannula by opening the screw. Prior to gastric juice collection, stomach was washed with 0.9% saline.

A preliminary experiment was conducted to study the effective dose (ED) of aqueous extract of ripe fruit's pulp of Cucurbita pepo Linn. against a single dose of aspirin (500 mg/kg body weight) induced gastric and duodenal ulcer in rats model and using graded doses of aqueous extract of ripe fruit's pulp of Cucurbita pepo Linn. i.e.,
200 mg/kg, 300 mg/kg, 350 mg/kg, 400 mg/kg, 450 mg/kg, 500 mg/kg body weight. Results showed that aqueous extract of ripe fruit’s pulp of *Cucurbita pepo* Linn. at a dose of 400 mg/kg body weight exhibited significant protection and hence this effective dose (ED) of *Cucurbita pepo* Linn. (400 mg/kg body weight) was used throughout the experiments (Sarkar and Guha, 2008).

Analysis from present experimental study, it is evident that severity of ulcerations, (Ulcer index; UI) and lipid peroxidation (LPO) were increased along with decrease in mucosal thickness (MT) as well as decreased antioxidant enzymes activity of superoxide dismutase (SOD), catalase (CAT) and reduced glutathione (GSH) level in gastric and duodenal tissues of different ulcer models (aspirin induced, ethanol induced and immobilized-cold stressed) in albino rat of both sexes. Increased lipid peroxidation (LPO) (as reflected by increased level of lipid peroxidation), ulcer index (UI) and decreased mucosal thickness (MT) were observed in those different ulcer models indicating the involvement of oxidative damage mechanism by causing erosions of gastro-duodenal mucosa which lead to generation of ulcer formation. Therefore, an increase in volume of secretion, acidity and decrease amount of mucus content (carbohydrate protein ratio; CHO: P), pH of gastric secretion, EC cell count, serotonin (5-HT) level and mucosal thickness (MT) of gastric and duodenal tissues were observed in cerebellar nodular lesioned (CNL) ulcer model. However, pretreatment with aqueous extract of ripe fruit’s pulp of *Cucurbita pepo* Linn. (400 mg/kg body weight) showed protective effect and antiulcer activity by decreasing ulcerations (evidenced by ulcer index; UI) and increasing mucosal thickness (MT) and alkaline phosphatase (AP) enzyme activity intact in gastric and duodenal tissues which cumulatively increased mucosal defense activity of gastric and duodenal tissues in all rats (evidenced by histological evaluation of AP enzyme staining) against aspirin induced ulcer model (Sarkar and Guha, 2008). Therefore, aqueous extract of ripe fruit’s pulp of *C. pepo* showed antioxidant enzymes activity by increasing SOD, CAT activity along with increased level of reduced glutathione (GSH) and decreasing lipid peroxidation (LPO) against aspirin induced ulceration. Ripe fruit’s pulp of *C. pepo* showed an antiulcer and antioxidant activity decreasing ulcer index (UI), lipid peroxidation (LPO) and increasing mucosal thickness (MT), antioxidant enzymes activity of SOD, CAT activity along with increasing the level of reduced glutathione (GSH) against ethanol induced and
immobilized-cold stressed ulcer models. Therefore, ripe fruit's pulp of *C. pepo* also showed anti-secretory and antiulcer activity by decreasing volume of secretion, acidity and increasing pH, amount of mucus content (CHO: P) (evidenced by histological evaluation of PAS staining) of gastric secretion in cerebellar nodular lesioned (CNL) ulcer model. Furthermore, ripe fruit's pulp of *C. pepo* showed an antiulcer activity increasing mucosal thickness (MT), EC cell count (evidenced by histological evaluation of EC cell staining), level of serotonin (5-HT) and decreasing ulcer index (UI) of gastric and duodenal tissues against cerebellar nodular lesioned (CNL) ulcer model. Serotonin, produced by EC cells, inhibits gastric acidity by modulating gastric mucus secretion (Guha and Ghosh, 1995; Fink *et al.*, 2006; Tack and Sarnelli, 2002).

The pathophysiology of experimental peptic ulcer formation is not clearly known (Dhikav *et al.*, 2003). A number of mechanisms are involved in gastric and duodenal damage caused by stress, NSAIDs (aspirin, indomethacin and ibuprofen) and alcohol (ethanol). Although an unified concept for development of gastro-duodenal lesions by various factors has not yet developed but it is multifactorial process (Guzel *et al.*, 1998) and generally agreed among the multimechanisms (Goodwin *et al.*, 1986; Konturek *et al.*, 1999) of oxidative damage by reactive oxygen species (ROS) and oxygen derived free radicals are the major causative factors for gastro-duodenal ulceration (Pihan *et al.*, 1987; Miura *et al.*, 2002) and reduction of mucosal thickness (MT) induced by stress, ethanol, aspirin (NSAIDs) (Sarkar and Guha, 2008) hemorrhagic shock (Chang *et al.*, 2005). Recently role of reactive oxygen species (ROS) in gastric pathology has attracted the attention of scientific community and much attention has been focused on oxygen derived free radicals (Ray *et al.*, 2002; Jainu *et al.*, 2006; Kath and Gupta, 2006). In various stress conditions, ulcer is developed mainly due to oxidative damage as indicated by derangement or by the imbalance of antioxidant enzymes such as SOD and catalase (Jainu and Devi, 2004). Glutathione, a major non protein thiol in living organisms, also plays central role in coordination of antioxidant defense process. Reduced thiols have been reported to be essential for recycling of antioxidants like vitamin C and vitamin E (Ray *et al.*, 2002). So decrease in the level of antioxidant defense enzymes along with reduced glutathione in gastro-duodenal tissues suggesting the involvement of free radical induced damaging mechanism for etiology of ulcer genesis.
Ulceration is thought to be produced due to imbalances in gastric offensive and defensive factors. While stress, gastric acid, exogenous NSAIDs and ethanol act as offensive factors and mucus, bicarbonate, epithelial cell proliferation (Mahendran et al., 2002) and serotonin (Guha and Ghosh, 1995) etc are the defensive factors. In our present investigation, different ulcer models (aspirin induced, ethanol induced, immobilized-cold stressed) produce ulceration either by over activity of offensive factors (aspirin, ethanol and immobilized- cold stressed) or diminished activity of defensive factors (cerebellar nodular lesion; CNL). Aspirin causes breakage in the mucosal barrier by disruption of mucosal epithelial cells (Brzozowski et al., 2000), ethanol induces ulceration by decreasing glutathione level (Szabo et al., 1981) while cold stress induces ulceration by decreasing blood flow in gastro-duodenal mucosa thus hampering nourishment of tissue and make vulnerable to oxidative damage (Salim, 1989; Filaretova et al., 1998). Normally cerebellum plays a vital role in mucus (defensive factor) secreting process. It has been already observed that stomach of cerebellar lesioned rats showed greater amount of gastric erosions when lesions were produced in the nodule (Guha and Ghosh, 1995) and nucleus fastigii of cerebellum (Maiti and Guha, 1978). Gastric erosions seemed to be initiated by a localized congestion at the mucosal surface due to decreased mucosal resistance (Maiti and Guha, 1978).

In our present investigation, decreased mucus content (carbohydrate protein ratio; CHO: P) was noticed in cerebellar nodular lesion induced ulcer models while C. pepo pretreatment showed an increase in mucus content (carbohydrate protein ratio; CHO: P). A decrease in the synthesis of mucosal glycoprotein has been implicated in the etiology of gastric ulcer (Jainu et al., 2006). The increase in mucus content (total carbohydrate protein ratio; CHO: P) has been regarded as direct reflection of mucin activity, which is indicated by enhanced level of individual mucopolysaccharides like hexose, hexosamine, fucose and sialic acid (Jainu et al., 2006). Thus biochemical studies of gastric juice of cerebellar nodular lesion induced ulcer models also confer the significance of mucus as a defensive factor in cytoprotection of gastric mucosa.

Informations from the literature have suggested that the fruits of Cucurbita pepo Linn. are used as vegetable (Sunilson et al., 2009; Linskens and Jorde, 1997) and fruit’s pulp are used to treat dyspepsia and enteritis (Orlandelli, 1951), intestinal diseases...
(Francois et al., 2006) and liver disorder (Sezik et al., 2004). It has been reported that pumpkin increases 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). These properties may be responsible for the increase in pH, mucus and decrease in volume and acidity of gastric secretion in cerebellar nodular lesion (CNL) induced ulceration possibly by synthesizing of mucus.

Recently, several antiulcer compounds from herbal plant origin have been reported to possess cytoprotective, antioxidant and antiulcer properties (Lewis and Hanson, 1991; Ray et al., 2002; Jainu et al., 2006; Jainu and Devi, 2004). Fruit’s pulp of C. pepo is used to relieve inflammation (Caili et al., 2006). Antiulcer property of ripe fruit’s pulp of C. pepo has already been established (Sarkar and Guha, 2008). The chemical constituents of ripe fruit’s pulp of C. pepo responsible for its antiulcer and antioxidant activities are not known. However, pharmacological investigations have suggested the presence of several major groups of active compounds in C. pepo pulp such as tannin (Ojiako and Igwe, 2008; Silveira et al., 1996), triterpenoids (Wang et al., 2008), glycosides such as cucurbitacin B, D, E, F (Feng et al., 2007), cucurbitacin L and cucurbitacin K (Wang et al., 2007), sulphhydrils like glutathione (Alosi et al., 1988), cysteine (Cys or C) (Fahmy et al., 2008; Pham et al., 1985; Allen, 1979; Kleinig et al., 1975; Ogura et al., 1972; Walker, 1972; Kataoka et al., 1998), S-adenosyl methionine (SAM) (Huang et al., 1991), methionine (Met or M) (Yoshida et al., 2005), phenolic compounds such as tannin (Ojiako and Igwe, 2008; Silveira et al., 1996), syringic acid (Dragovic-Uzelac et al., 2005), phenolic phytochemicals (Kwon et al., 2007), polyphenol and phenolic contents (Mongkolsilp et al., 2004), polyamines (Nishimura et al., 2006; Martinez-Tellez et al., 2002), beta-carotene (Veda et al., 2006), pro-vitamin A carotenoids (Azevedo-Meleiro et al., 2007; Priyadarshani and Chandrika, 2007; Seo et al., 2005; Mongkolsilp et al., 2004; Manzi et al., 2002; Gonzalez, 2001; Rodriguez-Amaya, 1999; Kune et al., 1992; Arima and Rodriguez-Amaya, 1990; Arima and Rodriguez-Amaya, 1988), vitamins A (Ahmed et al., 2003; Lans et al., 2007; Ribaya-Mercado et al., 1999), vitamin C (Mongkolsilp et al., 2004; Hancock et al., 2003; Hancock et al., 2008) and vitamin E (Franke et al., 2007; Tadmor et al., 2005; Imaeda et al., 1999; Sedghi et al., 2008) are present in C. pepo fruit. Some of these components
including vitamin A (Kasper et al., 1975; Mozsik et al., 1989), Vitamin C (Smirnoff et al., 2001; Brzozowski et al., 2001; Kitano et al., 1997), vitamin E (Guzel et al., 1998), triterpenes (Siqueira et al., 2007) and glycosides (Yesilada et al., 2000; Naseri and Mard, 2007) have been reported to have a role in protection against gastric mucosal damage.

Both clinical observations on humans and experimental studies on animals suggest a protective action of vitamin A against gastric ulcer induced either by stress (Kasper et al., 1975) or by well-known gastric-offensive agents like non-steroidal anti-inflammatory drugs (NSAIDs) (Mozsik et al., 1989) and ethanol (Ligumsky et al., 1995). The ability of vitamin A in C. pepo to protect the mucosa against lesions induced by stress, aspirin (NSAIDs) and ethanol as seen by the decreased in UI and increased mucosal thickness (MT) are likely by maintaining the structural integrity of gastric and duodenal epithelium and balance of aggressive factors and inherent protective mechanism. Further, the mucus gel and its bicarbonate gradient together with the alkaline environment maintained by AP activity seem to be an important first line defense against harmful stimuli.

Vitamin C (Smirnoff et al., 2001; Brzozowski et al., 2001; Kitano et al., 1997) and vitamin E play an important role in the reduction of pathogenesis of ulcer formation by probably reducing the ischemia (Brady et al., 1979; Young et al., 1976; Yoshikawa et al., 1991; Nakamoto et al., 1997). The deficiency of dietary vitamin E reduces the synthesis of arterial prostaglandins (PGs) significantly (Okuma et al., 1980) which may trigger ulcer formation. Thus, it may be suggested that pre-treatment of C. pepo may prevent the gastric mucosal damage by aspirin increasing PGE$_2$ level or by reducing the ischemia (Guzel et al., 1998) which may be due to the presence of vitamin C and E in the pulp of C. pepo.

However, various antioxidant phenolic compounds such as tannin (Souza et al., 2006; Ramirez and Roa, 2003; Czinner et al., 2001; Ezaki et al., 1985), vitamin C (Kitano et al., 1997) and vitamin E (Nakamoto et al., 1997), triterpenes (Siqueira et al., 2007), glycosides (Yesilada et al., 2000; Naseri and Mard, 2007) sulfhydryls like glutathione (Alosi et al., 1988), cysteine (Cys or C) (Fahmy et al., 2008; Pham et al., 1985; Allen, 1979; Kleinig et al., 1975; Ogura et al., 1972; Walker, 1972; Kataoka et al., 1998), S-adenosyl methionine (SAM) (Huang et al., 1991), methionine (Met or M)
(Yoshida et al., 2005), phenolic compounds such as tannin (Ojiako and Igwe, 2008; Silveira et al., 1996), syringic acid (Dragovic-Uzelac et al., 2005), phenolic phytochemicals (Kwon et al., 2007), polyphenol and phenolic contents (Mongkolsilp et al., 2004), polyamines (Nishimura et al., 2006; Martinez-Tellez et al., 2002), betacarotene (Veda et al., 2006), pro-vitamin A carotenoids (Azevedo-Meleiro et al., 2007; Priyadarshani and Chandrika, 2007; Seo et al., 2005; Mongkolsilp et al., 2004; Manzi et al., 2002; Gonzalez, 2001; Rodriguez-Amaya, 1999; Kune et al., 1992; Arima and Rodriguez-Amaya, 1990; Arima and Rodriguez-Amaya, 1988) have been identified as oxygen derived free radicals or reactive oxygen species (ROS) scavengers present in fruit’s pulp of C. pepo which may be responsible for reduced ulcer index (UI), LPO, acidity and increased antioxidant enzymes activity of SOD, CAT and GSH level, pH, mucus and mucosal thickness (MT) possibly by scavenging of oxygen derived free radicals or reactive oxygen species (ROS).

Some tryptophan (Trp or W) amino acid containing proteins such as lectin (Allen, 1979), mavicyanin (Xie et al., 2005; Xie et al., 2003; Marchesini et al., 1979; Kataoka et al., 1998), aspartic proteinase inhibitor (Christeller, et al., 1998), and pepocin or ribosome-inactivating protein (RIP) (Yoshinari et al., 1996) and enzymes such as 1-aminocyclopropane-1-carboxylate synthase and S-adenosyl L-methionine methylthioadenosine-lyase (Huang et al., 1991) have been isolated from the fruit of pumpkin. Pepocin is a type-1 ribosome inactivating protein (RIP) isolated from the sarcocarp of Cucurbita pepo having single A-chain (Yoshinari et al., 1996). It has been reported that A-chain from ricin, the ribosome inactivating protein (RIP), is similar amino acid sequence to A-chain of pepocin isolated from the rice that contains tryptophan (W) residue at position 211 (Ding et al., 2002).

Dietary supplementations of tryptophan containing proteins are the major source of serotonin (5-HT) precursor especially in the enterochromaffin (EC) cells of the gastrointestinal tract (GIT) (Wheeler and Challacombe, 1984). 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 or proximity to mucus producing cells, it is tempting to assume that local serotonin (5-HT) production might normally influence mucus production by
paracrine action (Kaufmann et al., 1979; Konturek et al., 1987; Pesker, 1980). Orally administration of tryptophan containing proteins from aqueous extract of fruit’s pulp of C. pepo may be precursor of serotonin (5-HT) in the EC cells of the gastrointestinal tract (GIT) which may protect gastro-duodenal ulceration by synthesizing mucus (Guha and Ghosh, 1995; Fink et al., 2006; Tack and Sarnelli, 2002).

So, the tryptophan containing proteins such as mavicyanin, lectin, pepocin, aspartic proteinase inhibitor etc, consumption of tryptophan from aqueous extract of the medullosa, sarcocarp of Cucurbita pepo fruit may be a dietary source of tryptophan and precursor of serotonin (5-HT) in the EC cells.

Thus, it may be suggested that pretreatment of C. pepo may be a source of tryptophan as well as serotonin (5-HT) of the EC cells which is present in various proteins of C. pepo (Allen, 1979; Xie et al., 2005; Xie et al., 2003; Marchesini et al., 1979; Kataoka et al., 1998; Christeller et al., 1998, Yoshinari et al., 1996, Huang et al., 1991) and may be responsible for increased 5-HT levels and EC cells counts of the gastro-duodenal tissues. Thus from the present investigation it can be concluded that C. pepo protects gastric and duodenal ulceration by modulating 5-HT and EC cell.

Our findings reveal that pretreatment with aqueous extract of ripe fruit’s pulp of C. pepo exerts cytoprotective, antiulcer, anti-secretory and antioxidant activity by decreasing the severity of ulcerations and increasing mucosal protection in different experimental peptic ulcer models (aspirin induced, ethanol induced, immobilized-cold stress induced and cerebellar nodular lesioned) by modulating antioxidant enzymes activity, GSH level, serotonin level and mucus secretion.