

Review Article

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Gastritis and Peptic Ulcer Diseases in Dogs: A Review

Pankaj Kumar Patel¹, Sawita Kumari Patel², S.K. Dixit^{1*} and R.S. Rathore²

¹Division of Medicine, ²Division of Veterinary Public Health, ICAR-Indian Veterinary Research Institute, Izatnagar, UP-243122, India

*Corresponding author

ABSTRACT

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The most common clinical condition reported in dogs is acid related diseases in the stomach like gastric disorders due to a structural and functional defect in gastric mucosa. The most important factor for the development of gastritis, peptic ulcer disease and gastric cancer in human is *Helicobacter pylori*. In the cases of gastric disorder lesions in canine gastric mucosa is closely similar to their human counterparts. Many etiological factors are responsible for oxidative stress due to excessive generation of reactive oxygen species as a cause of gastric mucosal damage. The bacteria exist lifelong in the stomach of the untreated patient. This article reviews the classification, some possible etiopathogenesis, diagnosis and possible differential diagnosis and major strategies of therapy against acid disorders (Fluid therapy, proton pump inhibitors, H-2 blocker, cytoprotective) with an update on the management of oxidative stress with antioxidant therapy (Ascorbic acid, N-acetyl cysteine, Vitamin E) and “Triple therapy” for management of *Helicobacter pylori* induced gastric disorders.

Introduction

Gastric diseases of dogs are usually gastric mucosal inflammation, ulceration, obstruction or neoplasia. Gastritis is the inflammation of gastric mucosa and normally visualized by vomiting. Categorization and gradation of canine gastritis are based on the nature of the predominant cellular infiltrate and the presence of architectural abnormalities (Day *et al.*, 2008). Acute gastritis is clinically characterized by the sudden onset of vomiting (Ettinger and Feldman, 2005) whereas chronic gastritis is clinically defined as intermittent vomiting with duration of more than 1-2 weeks (Day *et al.*, 2008). It

occasionally coupled with the loss of body weight, inappetence, and spells of abdominal pain. In most patients the cause is secondary from the history, such as dietary indiscretion; the diagnosis is rarely confirmed by biopsy, and treatment is symptomatic and supportive. If the hyperplastic polyp (Gencosmanoglu *et al.*, 2003) or foreign body (Papazoglou *et al.*, 2003) obstructs the pyloric region of stomach results onset of acute clinical signs, however if foreign object stays on the body of the stomach may lead to mucosal injury and acute gastritis (Amorim *et al.*, 2016). Fungal infections and spirochetes also lead to gastritis (Helman *et al.*, 1999). Chronic gastritis is defined as the presence of

intermittent vomiting for more than 1-2 weeks (Dowdle *et al.*, 2003).

The peptic ulcer is the imperfection in the mucosal barrier that continues to the muscularis mucosa of the stomach (Stanton and Bright, 1989). The most common clinical symptoms are sudden onset of acute vomiting with or without blood, dehydration, anorexia, weight loss and depression. Peptic ulcer most commonly leads to the condition of GI hemorrhage.

In dogs, non-steroidal anti-inflammatory drugs (NSAIDs), hepatic and renal disease are the most common predisposing factor for the formation of peptic ulceration that leads to anorexia, haematemesis, melena, dehydration, anaemia and abdominal pain. Chronic ulcers have varying size and are larger than normal (Brown *et al.*, 2007).

Chronic gastric ulcers and local ulcerative neoplastic lesions are macroscopically relatively similar; they can be differentiated through histopathological examination (Stanton and Bright, 1989). Based on histological examination (relative control of the reparative processes and the severity of ulceration), the gastric ulcers are classified as acute or chronic.

Microscopically, subacute to chronic ulcers have granulation tissue of uneven thickness and ripeness, infiltrated by a mixed inflammatory cell population and covered by a thin layer of necrotic debris at the bottom and boundaries along with superficial regenerative epithelial hyperplasia (Brown *et al.*, 2007).

Review of literature

Incidences

Gastric disorders are common finding which 35 percent cases look into chronic vomiting

and 26-48 percent of dogs are asymptotically affected (Wiinberg *et al.*, 2005). Although there is a high prevalence of gastritis in dogs, an underlying cause is rarely identified. In Madras veterinary college teaching hospital (two semesters), out of the total reported canine patients, 16.8 % dogs were suffering from gastrointestinal disorders and 0.19 % was reported from duodenal ulcers (Saravanan *et al.*, 2012). In Mekelle veterinary clinic Ethiopia, out of the total 109 reported canine patients, 36 (33.0%) were suffered from gastrointestinal tract disorders and 15 (41.7%) dogs have been shown vomiting (Atsbaha *et al.*, 2014). It is the condition which can be diagnosed on the basis of clinical signs, laboratory findings, and results of imaging techniques such as radiography, ultrasonography, and endoscopy. The most important diagnostic technique for gastritis is the endoscopic examination. In the case of gastritis mostly *Helicobacter* Spp. organisms are isolated from gastric mucosal biopsies of dogs (Wiinberg *et al.*, 2005). Endoscopic reports show that the chances of formation of gastric mucosa ulcer are 48.5 percent in canines (Parrah *et al.*, 2013).

Classification of gastritis

Gastritis in dogs classified into acute or chronic which caused by multiple etiological agencies such as dietary carelessness, ingestion of coarse foreign bodies, plant materials, irritant chemicals, drugs (NSAIDs, glucocorticoids), viral diseases (e.g. canine parvovirus, canine distemper) and bacterial infections e.g. *Helicobacter* spp.). Metabolic disorders frequently present with haematemesis, melena, concurrent diarrhoea and other signs of systemic illness. Acute gastritis is the inflammation of the mucosal layer of the stomach which is characterised by sudden onset of vomiting and suspected to be related to gastric mucosal injury or inflammation (Amorim *et al.*, 2016). Only some reports showed the role of an infectious

agent in acute gastritis (Brown *et al.*, 2007; Simpson, 2013). Chronic gastritis classify based on nature of the leading cellular infiltrates (eosinophilic, lymphoplasmacytic, granulomatous or lymphoid follicular), the presence of architectural abnormalities (atrophy, hypertrophy, fibrosis, oedema, ulceration or metaplasia), severity (mild, moderate or severe) (Wilcock, 2013). It can also be subclassified on the basis of distinct histological classification, Chronic superficial gastritis (CSG) is the most common form of chronic gastritis that no have understandable changes in mucosal thickening always associated with excessive but uneven inflammatory components (Plasma cells, neutrophils, lymphocytes) infiltrate and fibrosis of mucosa and submucosa. Clinical importance of chronic atrophic gastritis (CAG) has occasionally reported (Simpson, 2013) which is characterised by diffuse lesions in fundus and body of the stomach and reduced mucosal layer thickening as well as hypochlorhydria, achlorhydria and proportionally increased of the number of mucus-producing cells within the gland (Wilcock, 2013).

Loss of gastric glands due to atrophy of the gastric mucosa and combines with mononuclear infiltration, glandular atrophy, regenerative glandular nesting and mucosal fibrosis and loss of feedback mechanism leads increased serum gastrin level causes gastric ulceration (Ditchfield *et al.*, 1960; Rugge *et al.*, 2002; Amorim *et al.*, 2016). Lymphoplasmacytic gastritis (LPG) with or without coupled with hyperplasia of lymphoid follicles, infiltration of lymphocytes and other inflammatory cells, including Russell bodies into the lamina propria layer of the stomach and sometimes it may be associated with *Helicobacter* spp. infection (Maxie, 2007; Amorim *et al.*, 2016). Eosinophilic gastritis (EG) rarely reported by widespread Alimentary tract hypersensitivity reaction

(eosinophilic gastroenteritis). Diffuse form of EG has Scirrhus inflammatory thickening on the gastric wall that resembles with gastric neoplasia (Hayden and Fleischman, 1977; Neiger, 2008; Lidbury *et al.*, 2009). Genetic predisposition and diet are noticed for pathogenesis (Sattasathuchana and Steiner, 2014) but some factors like gastric parasitic infestation by *Physaloptera* spp. (Neiger, 2008), *Gnathostoma* spp. (McCarthy *et al.*, 2000), *Heterobilharzia americana* (Rodriguez *et al.*, 2014) and mastocytoma along with infiltration of eosinophils (Ozaki *et al.*, 2002), lesions are rarely observed in *Toxocara canis* infestation (Chira *et al.*, 2005). Focal type chronic hypertrophy occurs as a result of chronic administration of Aspirin. Focal cystic hypertrophic gastropathy is characterised by histopathologically elongated and complexed mucous glands with the recurrent formation of the mucosal cyst. Hypertrophic glandular gastritis is frequently associated with a diffused immune proliferative enteropathy on basenji dogs and this condition also occurs in many dogs due to Hypergastrinemia (Breitschwerdt, 1992). Chronic Giant hypertrophic gastritis (GHG) is rarely found in dogs and characterized by marked thickening on the gastric wall and mucosal hypertrophy gives a cerebriiform look to the rugal folds which protrude into the gastric lumen (Vaughn *et al.*, 2014). Chronic hypertrophic pyloric hypertrophy is hypertrophy of mucosal layer of the antro-pyloric stomach. Lesions are focal/multifocal, polyploidy thickening / regionally generalised rugal enlargement and these lesions are lead to gastric outlet obstruction (Elwood *et al.*, 2010).

Patho-physiology of gastritis and peptic ulcer disease

The gastric mucosal layer acts as a useful protective wall against acidity, bacteria, detergents and alteration in luminal

temperature. The first line of defence of gastric wall is gastric secretion which contains acid, mucus, bicarbonate and antibacterial substances. Epithelial layer on the wall of the gastric glands and gastric mucosal layer prevents from reverse-diffusion of acids and is rapidly repaired by restoration after injury. The quick response showed through gastric mucosa against stimulation of neurohormonal and inflammatory signals to the gastric microvasculature by increasing blood supply for maintenance of gastric mucosal integrity, removal of harmful substances, and restoration of the gastric epithelial layer (Abdel-Salam *et al.*, 2001; Kawano and Tsuji, 2000). Stimulation to the gastric wall by foreign materials, chemical injury, ischemia, infection, or antigens leads to release of inflammatory components and vasoactive substances from neutrophils, mast cells, platelets, endothelial cells and neurons (Wallace and Ma, 2001). Several pro-inflammatory cytokines are released as a response to the pathogenesis of peptic ulcer, like interleukin (IL)-1b, IL-2, IL-6, IL-8 and tumour necrosis factor (TNF)- α . IL-1, lead to reduce the severity of the gastroduodenal injury and increase the resistance to gastric injury (Wallace *et al.*, 1990). These inflammatory components stimulate acid secretion and mucosal breakage increases the permeability of epithelial layer and altered blood flow that continues increase the risk of gastritis, gastric erosion, ulceration, hypoxia, haemorrhage, oedema and necrosis (Jacobson, 1992). Granuloma formation of gastric mucosa is the end result of a response to endogenous substances and foreign objects, such as sewing needles and infectious diseases (Pratt *et al.*, 2014). Transient ulceration commonly noticed due to direct damage of gastric wall and mucosal barrier or generally ingestion of a wide range of foreign materials like coarse foods, chemicals, plants materials, clothes etc. Gastric ulceration is caused by the multi-etiological agent that

includes gastric mucosal damage by physical agent, alterations in the chemical structure and its renovate process (Parrah *et al.*, 2013). Mechanical scratch ulceration is generally superficial and short-lived and superficial lamina propria covered by fibrin, mucus and scattered neutrophils (Wilcock, 2013). Secretion of hydrochloric acid that creates acidity catalyzes pepsinogen to the active proteolytic enzyme pepsin (Chu and Schubert, 2012). Hamper integrity and protective mechanism disturbance in mucosal layer initially, increase rate of reverse diffusion of gastric acid and pepsin lead to GI inflammation and haemorrhages than inflammatory components (e.g. endothelial cells, neutrophils and mast cells) become activated and release inflammatory mediators (e.g. histamine, leukotrienes, platelet-activating factor, proteolytic enzymes, and free radicals) (Henderson and Webster, 2006). Histamine promotes gastric acid secretion; whereas another mediator promotes vascular changes (e.g. vasodilation, vasoconstriction, increased capillary permeability) lead to oedema and translocation of inflammatory cells that plugged the capillary lumen, intensify initial gastric mucosal injury by dropping blood flow, ischemia, disturbed epithelial cell layer restoration, and reduced secretion of mucus and PG-E (Sorjonen *et al.*, 1983; Guilford *et al.*, 1996). Gastric ulcers also have been reported in dogs, having hepatic disease, renal disease, Addison's disease; shock (Parrah *et al.*, 2013). Dogs having the severe head injury, numerous trauma, cerebral injuries and diseases of spinal cord leads to Gastroduodenal ulceration (Neiger and Simpson, 2000; Dowdle *et al.*, 2003).

Etiopathogenesis of gastritis and peptic ulcer diseases

Gastric foreign bodies are the most common cause of gastric disorders in younger dogs

(Sullivan and Yool, 1998). Ingestion of exogenous toxins like a household, cleaning chemical, lead and various plants may directly harm to the gastric mucosal barrier (Sass, 1970). In three dogs experimentally administration of phenol (total dose of 2430 mg of phenol) leads severe oral and gastric ulceration (Gieger *et al.*, 2000). When orally lead salt mixture (Chloride Br, Sulfate, 1:1:2) give orally in nine dogs at diverse doses (range 5-60 mg/kg body weight/day) for 14-152 days gastric ulceration is induced (Hamir *et al.*, 1983). Systemic hypovolemia leads to decrease blood flow to gastric mucosal layer, there is the loss of the tolerable effects of glucocorticoids in mucosal defense mechanism and major electrolyte abnormalities are leads to gastritis (Henderson and Webster, 2006). Dogs with kidney failure have infrequently shown gastric necrosis and ulceration (Peters *et al.*, 2005). Gastric ulcers due to stress less commonly noticed in dogs, regular and severe exercise have a higher risk for occurrence of gastric ulcers in dogs and during sled races mostly gastric disease has known as a causative factor of sudden death in the dog (Chatelain *et al.*, 2014). The diet containing a high amount of fat causes delayed gastric emptying and hyperacidity in the stomach, which in alone or associated with the physiological reaction of stress (increasing the level of serum cortisol level), may influence to GI ulceration in animals (Davis *et al.*, 2003).

The aspirin-induced gastric disorders maximally reported in antropyloric area administrated dogs (Reimer *et al.*, 1999; Ulutas *et al.*, 2006). Administrations of a diversity of NSAID drugs piroxicam including, aspirin, ibuprofen (Godshalk *et al.*, 1992; Lanza *et al.*, 2009) naproxen and flunixin meglumine or ibuprofen (Godshalk *et al.*, 1992; Dow *et al.*, 1990), steroidal anti-inflammatory drugs used for treatment of spinal and vertebral diseases (Neiger, 2000)

are also reported as cause of gastric ulceration (Gralnek *et al.*, 2008). Some drug has been damaged in the gastric mucosal layer of dogs includes glucocorticoids (Valin and Allard, 2012) and various NSAIDs (Mathews *et al.*, 1996). Selective inhibitors of Cyclooxygenase (COX)-2 (e.g. carprofen, etodolac, deracoxib, meloxicam) are used to reducing the ulcerogenic consequence of NSAIDs in the GI tract. Even if they reduce the hazard but they do not fully remove it and in many dogs have reported that formation of gastric ulceration subsequently the given of these safer NSAIDs (Enberg *et al.*, 2006). The NSAIDs inhibits the enzyme COX which is involved in the prostaglandin synthesis, and inhibit the synthesis of prostacyclin and prostaglandin E, resulting in the loss of the gastric protective mechanism (Enberg *et al.*, 2006). If any change on the expression of GKN gene leads to the deficiency of GKN1 & GKN2, results have been reported as gastric inflammation, non-steroidal anti-inflammatory (NSAID) induced mucosal injury and the development of neoplasia of gastric mucosa (Martin *et al.*, 2008; Nardone *et al.*, 2008). Another factor concerned with the pathogenesis of NSAID-induced gastric disorder is peroxidation of lipids of cell membranes and damage to the cellular proteins by the formation of oxidative free radicals and proteases from activated neutrophils (Biswas *et al.*, 2003). NSAIDs acts on mitochondria and uncoupling effect on oxidative phosphorylation, disperse the mitochondrial transmembrane potential and induce mitochondrial permeability transition pore (Yoshida *et al.*, 1992; Tomoda *et al.*, 1994; Mahmud *et al.*, 1996; Mingatto *et al.*, 2000; Davies *et al.*, 2000; Ulutas *et al.*, 2006) leading to the release of cytochrome c from mitochondrial intermembranous space into cytosol. liberated cytochrome c generates reactive oxygen species (ROS) like hydrogen peroxide, thus activation of caspase 9 and caspase 3 pathway and peroxidation of

cellular lipid membrane all resulting into cellular apoptosis (Murphy *et al.*, 2000).

Corticosteroid predisposes the GI tract to damage by diminishing mucus production, changing the biochemical composition of mucus, declining restoration of epithelial cell layer and intensifying acid production (Sorjonen *et al.*, 1983). It has been reported that administration of prednisolone after 1 or 2 weeks of peptic ulcer formation leads to decreased collagen-containing tissue in the ulcer base and delayed healing (Luo *et al.*, 2004). Dexamethasone has been shown inhibitory effects of angiogenesis at the ulcer margins and baseline. Administration of corticosteroids along with NSAIDs leads to the formation of gastric mucosal lesions (Boston *et al.*, 2003). Some studies had been shown that support the theory that corticosteroids alone lead to GI mucosal injury and hemorrhage (Rohrer *et al.*, 1999).

The hepatic disease leads to portal hypertension which causes distorted gastric blood flow, delayed epithelial turnover, gastric hyperacidity, and elevated serum bile acid concentration stimulate to secretion of Gastrin-17, results in apoptosis of gastric epithelial cells (Henderson and Webster, 2006). Animals with mastocytosis may have numerous all over gastric ulcers (Stanton and Bright, 1989; Ozaki *et al.*, 2002). The mast cell tumor produces and releases histamine, which binds to H₂ receptors on gastric parietal cells, gives a powerful stimulant to acid secretion. In humans, peptic ulcer formation as a result of excessive gastrin production and hyperacidity caused by a gastrinoma is known as the Zollinger Ellison syndrome. This is a condition often characterized by the triad of hypergastrinemia, hypertrophic or CAG and GI ulceration. Few cases of a canine homolog of Zollinger Ellison syndrome associated with gastric ulcer formation are reported (Gal *et*

al., 2011). Gastrin directly stimulates to hydrochloric acid secretion from the parietal cells, as well as indirectly stimulating acid production by releasing histamine from fundic enterochromaffin-like cells in response to compromising the protective mechanisms and reducing the epithelial cell turnover of the gastric mucosa (Hughes, 2006). Gross and histological appearances of gastric erosions and ulcers are well documented, erosions involve only surface epithelium with a minimal inflammatory response but ulcers can extend into the muscularis mucosae (Sullivan and Yool, 1998). The chronic liver disease leads to ischemia in GI mucosa that causes portal hypertension and thrombus formation into the gastric vessels (Stanton and Bright, 1989). The renal system has been involved in the elimination of at least 40 % circulating Gastrin-17, with up to 40 percent of circulating Gastrin-17. Hence, in renal disease hampered to clearance of Gastrin-17 lead to hypergastrinemia which induced gastric acid production. It is the principal factor for vomiting and pathogenesis of gastric ulcer formation in renal disease (Schulman and Krawiec, 2000; Peters *et al.*, 2005). Renal failure leading to progressive uremia and urea diffuses from interstitial fluids to stomach, results in damage to epithelial cell layer of gastric wall (Polzin and Osborne, 1995; Guilford and Strombeck, 1996).

The chief gastric pathogenic *Helicobacter spp.* in dogs are *H. felis*, *H. bizzozeronii* and *H. heilmanniisensustricto* (s.s.), while *H. salomonis* is least reported and the prevalence of *H. cynogastricus* and *H. baculiformis* has not yet been studied (Amorim *et al.*, 2016). However, *H. pylori* have been rarely identified in the canine stomach (Chung *et al.*, 2014). There is also evidence of mixed infections of different species (Ekman *et al.*, 2013). *Helicobacter spp.* populations are mostly found in the fundus and body of the stomach (Anacleto *et al.*, 2011). Gastrokines

(GKNs) are bioactive molecules that contain BRICHOS domain and secreted from a specific cell of gastric mucosa (Menheniott *et al.*, 2013). GKN1 connected with decreasing the formation of colonies and proliferation by an atypical glandular cell of gastric mucosa and reducing of cellular viability, proliferation, and colony (Yoon *et al.*, 2013). GKNs and trefoil factors (TFFs) both are together lead to enhance cellular differentiation, cytoprotective role and working on NF- κ B signalling pathways that result anti-inflammatory effects, therefore it promotes restoration of gastric epithelial cells (Rippa *et al.*, 2011). If any change on the expression of GKN gene cause deficiency of GKN1 & GKN2, results from gastric inflammation, non-steroidal anti-inflammatory (NSAID) induced mucosal injury and the development of neoplasia of gastric mucosa (Martin *et al.*, 2008; Nardone *et al.*, 2008).

Gastric disease caused by *H. pylori* suppress to GKNs gene expression by methylation of trefoil factor 2 (Peterson *et al.*, 2010), lead to Gkn1 and Gkn2 deficiency (Menheniott *et al.*, 2013). Progressive loss of expression GKN gene lead to progression of different phases of disease development, started from chronic gastritis to gastric mucosal atrophy followed by a neoplasm of intestine due to complete loss of GKN gene expression (Sharman *et al.*, 2017; Menheniott *et al.*, 2013). Electron microscopic examination of gastric mucosa showed spiral-shaped organisms in the lumen of stomach and canaliculi of parietal cells (Lee *et al.*, 1992). Pathogenic viral infections in dogs include parvovirus; distemper virus, rotavirus, and coronavirus rarely causes gastritis with intestinal or systemic involvement being most responsible for patient morbidity and mortality.

Parasitic infestation is least commonly reported. The larvae of *Spirocerca lupi* pierce

the gastric mucosal barrier than severe mixed inflammatory/neoplastic-like reaction and forms nodular foci, these are generally known as granulomas (van der Merwe *et al.*, 2008). The initial stage of inflammation, larvae encircled by loose connective tissue that are extremely vascularised and containing fibrin-rich fluid, neutrophils, and foci of necrosis. Later stage, these connective tissues are composed mostly of actively dividing fibroblasts which like embryonic appearance, sometimes similar to sarcoma (Bailey, 1963). In *Gnathostoma spinigerum* infestation, adult parasite formed solid nodules in the gastric submucosa and they stick out into the lumen and parasite eggs trapped by connective tissue lead to the formation of center portion granuloma (Maleewong *et al.*, 1992). The Hetero bilharzia mericanais trematode parasite leads to gastric granulomatous inflammation with circumscribing trapped eggs (Rodriguez *et al.*, 2014). Gastric nematode infestation by *Ollulanus tricuspis*, which was commonly observed in cats (Cecchi *et al.*, 2006) also has been reported in dogs with the sign of chronic vomiting and granulomatous gastritis (Kato *et al.*, 2015). Nematodes, *Physaloptera rara*, and *Physaloptera canis*, an uncommon source of gastric ulceration related to chronic vomiting (Burrows, 1983). These parasites are free moving in lumen cause a minimal inflammatory reaction, but mostly they attached with the gastric mucosa lead to inflammation due to the formation of numerous minute hemorrhages (Clark, 1990). Gastric phycomycosis characterized by minute non-specific changes to thickening mucosal folds of gastric wall with outlet hindrance. Granulomatous lesions have typical nodular, circumscribed collections of macrophages along with uneven lymphocytes, eosinophils, multinucleated giant cells, and neutrophils, with or without central necrosis and a peripheral lymphoid cuff (Ectors *et al.*, 1993). Histoplasmosis caused by the fungus

Histoplasma capsulatum infected by spores via inhalation or ingestion route. These spores are phagocytized by macrophages and dispersed through the bloodstream or lymphatic channel to the organ systems and formation of subclinical or clinical granulomatous condition amongst other organs including the GI tract (LinBlache *et al.*, 2011). In young aged, large-breed, male dogs *Pythiuminsidiosum* may produce pyogenic granulomas in mucosa and submucosa of stomach and different places of the GI tract (Grooters and Gee, 2002). *Cryptococcus neoformans* cause granulomatous gastritis mimicking carcinoma which is a factor of gastric outlet obstruction (Van der Gaag *et al.*, 1991).

Different cellular defense mechanisms involve for protection against the free radical damage (Lewin *et al.*, 1997). Enzymes (e.g. catalase, glutathione peroxidase complex and superoxide dismutase) and transition-metal binding proteins (e.g. transferrin, ferritin, and ceruloplasmin) production and action of free radicals. Scavengers (e.g. albumin, bilirubin, ascorbic acid, urates, and thiols, or liposoluble, such as vitamin E and coenzyme Q10) stop and discontinue radical chain by increase peroxidation chain of lipid molecules by a react and neutralize free radicals and convert them into more stable molecules. The peroxidized fatty acids are removed by specific phospholipases, making possible the re-acylation of the damaged molecule by an acetyl-CoA and the respective enzyme lead reconstitution of normal structures. The overproduction of ROS leads to the imbalance between oxidants and antioxidants at cellular as well as systemic level. Reactive oxygen species (ROS) are major molecules of oxidative stress in exceeds the threshold level which is generated as primary part of metabolism that lead to trigger progressive destruction of polyunsaturated fatty acids (PUFA) and membrane destruction

(Halliwell, 1990). In acute events of inflammation free radicals may play a major role in gastric mucosal barrier dysfunction. In humans oxidative stress occurs during exercise leads to decrease gastric and mesenteric blood flow (Qamar *et al.*, 1987; Mastaloudis *et al.*, 1994; Hinchcliff *et al.*, 2000; Otte *et al.*, 2001; Radak *et al.*, 2003) along with mitochondrial electron transport chain inefficiency during respiration leading reperfusion injury mediated by ROS. In the disease condition, exercise has been activated to pro-inflammatory cascades which are able to trigger the leukocytes (Cooper *et al.*, 2007).

Exercise leads to neuroendocrine changes, like increases release of growth hormone may also play a major role in the trigger to the neutrophils (Smith *et al.*, 1996). Neutrophil penetrates into inflammatory sites and then release superoxide anions generated by myeloperoxidase and NADPH oxidase activities. By the help of superoxide dismutase activity and highly reactive hydroxyl radical catalyzed by oxido-reductive active metal ion converts Superoxide to hydrogen peroxide. In rats experimentally feeding of Lipid peroxides lead to change the oxido-reductive mechanism status in gastric mucosal cells and can suppress apoptosis and turnover of epithelial cells (Tsunada *et al.*, 2003). Lipid peroxidation mediated by reactive oxygen species (ROS) is considered as an important cause of oxidative damage and destruction to the cell membrane, changing the structural integrity and biochemical functions of the lipid membrane (Fridovich *et al.*, 1978; Niki *et al.*, 1987). Plasma MDA concentration denotes tissue lipid peroxidation marker (Galunska *et al.*, 2002). Gastrointestinal mucosa detoxifies to the dietary lipid peroxides (Miyamoto *et al.*, 2003) and antioxidant systems may be relatively exhausted by the peroxide intake, consequently changing the cellular redox mechanism. In peripheral tissue, glutathione

peroxidize (GSH) acts as an electron donor in the glutathione peroxidase-catalyzed reduction of organic and hydrogen peroxides. Therefore, the oxidized glutathione formed through this reaction removed from the cell using NADPH-dependent reduction mechanism by glutathione reductase (Meister *et al.*, 1983; Ehrhart *et al.*, 2003).

Diagnosis

History and clinical signs

Gastritis and Peptic Ulcer disease are not depending on breed, age or sex. The disease depends upon history of non-steroidal anti-inflammatory drug (NSAIDs) administration, ingestion of foreign materials, chemicals, poisons, coarse food materials and any other systemic disease like hepatic disease, renal disease, tumour, pregnancy gastric or secondary metastases vomiting frequency and contents of vomitus like bile, food, froth, blood (frank or digested) or evidence of an ingested substance (e.g. grass, bones, foreign material, etc). The most common clinical sign of gastric ulcer is acute or chronic vomiting with or without hematemesis. All animals have gastric ulcer should be vomit, but all animals those are vomit blood should not have gastric ulcers (Otto *et al.*, 1991). The most common clinical sign in gastric disease of animals are underweight, pale mucous membrane, tachycardia from severe anaemia or shock, pain on palpation may be observed if there is widespread of perforated ulcer and spread of contamination into the peritoneum, vomiting, haemoptysis, melena, weight loss, anaemia, abdominal pain, inappetence or anorexia, oedema, septicaemia, liver disease, renal diseases, neurologic diseases. Gastric and duodenal perforated ulcers show sign of extensive pain of abdomen, abdominal distension, high fever, shock and death caused by peritonitis. Only mild signs of abdominal disease with perforated ulcers have presented

by the animals is rarely reported (Cortese *et al.*, 2010). Gastrointestinal lymphosarcoma induced gastric ulceration produces anorexia, vomiting, diarrhoea, progressive loss of body weight, dullness and depression. In NSAIDs induced ulceration has these similar signs with melena and paleness of the tongue has been observed (Shaw *et al.*, 1997).

Laboratory findings

In gastric ulcer disease laboratory findings indicated that clinical abnormalities are how much severe (anemia or septic abdominal fluid sample) and prediction of stimulating cause e.g. (renal failure). The main findings of piroxicam induced gastric ulceration are neutrophilic leucocytosis while the. Phenol poisoning induced gastric ulceration has abnormal hematological changes like neutropenia with toxic neutrophils, thrombocytopenia and increased muscular enzymes (Talbert *et al.*, 2012). The important hormone for the maintenance of normal gastric homeostasis is Gastrin-17 (Fourmy *et al.*, 2011) secreted by G cells of gastric antrum which acts with acetylcholine into receptors of enterochromaffin cells, results in releases of histamine. The secreted histamine binds to receptors on the surface of the parietal cell produces c-AMP whereas Gastrin-17 and acetylcholine open calcium channel leads to stimulating effects on gastric acid secretion from the apical H⁺-K⁺ ATPase (Guarsio *et al.*, 2009). Serum gastrin-17 has become an important biomarker for gastric antrum inflammation (Fourmy *et al.*, 2011). The PGI and PGII are secreted into the gastric lumen and out of the 1 % leaked into circulations (Griti *et al.*, 2000). The Pepsinogen I (PGI) value proportionally decreases with the development of fundic atrophy while Pepsinogen II (PGII) has not shown any pattern with fundic or antral atrophy (Griti *et al.*, 2000). However, the decline in value of PGI to PGII ratio

(PGI/PGII) has been revealed for detection of fundic atrophy and diagnostic biomarkers for atrophic gastritis and patients with high risk of gastric cancer (Vaananen *et al.*, 2003; Graham *et al.*, 2006). The gastric diseases, second-degree dehydration, and the sign of shock have been detected by skin fold test and relative polycythemia. It must be required emergency treatment with different haematological test e.g. complete blood count (Total erythrocyte Count, Total leucocyte Count, Total platelet count, Haemoglobin concentration, Packed cell volume), Blood urea nitrogen [BUN], Serum creatinine level, Blood glucose level, AST (aspartate aminotransferase), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP) level and, if available, lactate, pH, and electrolytes levels also measured. ALT, AST, ALP and BUN, Serum creatinine level are the biochemical marker of hepatic disease and renal diseases which also leads to GI ulceration.

Serum Gastrin-17 is the most important biomarker for gastric antrum inflammation (Fourmy *et al.*, 2011). The reference range of serum Gastrin-17 concentration is 10–40 ng/L (Garcia *et al.*, 2005; Parente *et al.*, 2014). The serum gastrin concentration has been markedly increased in severe gastric disorders (Garcia *et al.*, 2005). Serological biopsy has been reported that serum PG level shows to the morphologic and functional alteration to the gastric environment (Taggart and Samloff, 1987). Serum pepsinogen A level (18 to 129 µg/L) can be used as a diagnostic marker for gastric diseases in the dog (Suchodolski *et al.*, 2002; Suchodolski *et al.*, 2003).

Additional clinico pathological tests are required to detect the liver and renal diseases, hypoadrenocorticism, hypothyroidism, pancreatitis which may lead to gastric mucosal lesions.

Helicobacters organisms produce urease enzyme in gastric mucosa which hydrolyzes urea to ammonia, results increase ammonia concentration in the gastric mucosal layer leads to raises gastric pH in which bacterial populations were survived (Marshall *et al.*, 1990). Rapid urea test (RUT) and modified rapid urease (MRU) test are used for determination of *Helicobacter* infection of gastric mucosa in gastric biopsy samples (Katelaris *et al.*, 1992). These organisms also confirmed by phase microscopic examination. Oxidative stress measurement is difficult to perform directly because unpaired electron makes free radical very unstable and high reactive (hence, short half-life) thus, their measurement needs specific tools like, electron spin resonance that can identify compounds with unpaired electrons. In biological samples products of ROS, reactions are easier to measurable through biological assays e.g. measure the DNA adduct 8-hydroxy-2'-deoxyguanosine, protein carbonylation, and many lipid breakdown products. Sthiobarbituric acid reactive substances (TBARS), Malondialdehyde, 4-hydroxy-2-nonenal, Isoprostane, Ethane, Pentane, and Lipid hydroperoxides are the most Common measurable lipid products. Antioxidants enzymes activity Catalase (CAT) activity (Aebi, 1984) has been determined (U/g Hb) after isolation and lysis of RBCs and glutathione peroxidase (GPx) activity were measured (mU/mg Hb) on whole blood. Healthy dogs have a good defense system against oxidative stress that compensated by balanced redox mechanism by revert the overproduction of free radicals and come again to homeostasis. However, most sick animals unable to show this mechanism and it will promote the occurrence of an extreme oxidative stress. This mechanism is possible by production of the antioxidant agents, which prevents from oxidative stress and lead to regeneration of cells, taking the reduced glutathione (GSH),

superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) enzymes in the frontline (Bae *et al.*, 2011; Naito *et al.*, 2010). It increases the production of H₂O₂ in response to the activity of antioxidant enzymes. CAT and GPx levels are elevated. Catalase enzyme activity is present in all tissues but higher in RBCs, hepatic, renal, adipose tissues and lower in nervous tissue. Catalase converts hydrogen peroxide (H₂O₂) to oxygen and water (Pacheco *et al.*, 2009; Zamocky *et al.*, 2008). GPx enzyme has been used with glutathione as a substrate along with other organic hydroperoxides and catalyzes the H₂O₂ reduction mechanism (Bae *et al.*, 2011). The acute stage of GI haemorrhage leads to normocytic normochromic anaemia while the chronic stage of GI haemorrhage leads to microcytic hypochromic anaemia in iron deficiency anaemia (Waldrop *et al.*, 2003). The acute haemorrhagic diarrhoea with increased haematocrit count and plasma protein concentration indicates haemorrhagic gastroenteritis. The faecal occult blood test should be done in the unclear cases of GI haemorrhage but it gives false positive results due to dietary causes (e.g. vegetables, fruits, red meat, fish meat) or some bacterial population in the alimentary tract so that it suggests that 72 hours before performing this test a meat-free diet should be fed to the patients. It is generally used for coagulation defects that are not the primary cause of GI haemorrhage but noticeable intensifying blood loss e.g. rodenticide toxicity or clotting factor deficiencies. The Total Platelet count is a very useful measure of coagulation defects. In dogs, immune-mediated thrombocytopenia (ITP) is the common factor of GI haemorrhage. If no any cause of ulceration has been found then electrolyte level can be estimated and ACTH stimulation test should be done because it has been reported that hypo adrenocorticism coupled with GI haemorrhage in dogs (Medinger *et al.*, 1993). The dogs have gastric ulceration and

perforation given with IM injection of Pentagastrin, @ 6 micrograms/Kg body weight leads to elevation of the secretion of gastric juice (hyperacidity). The extent of endoscopically detected damage shows a relationship with sucrose permeability. The decrease in the permeability of sucrose is more quickly than gastric ulcer disappearance. Sucrose permeability test is more responsive for widespread mucosal damage than to distinct common ulceration (Meddings *et al.*, 1995).

Diagnostic imaging

The plain and contrast radiographs are useful for determining possible origin of abdominal disturbances (gastric foreign bodies) but may be unsatisfactory in smart verification of gastric ulceration (Guarino *et al.*, 2008). The ultrasonography used for recognizing foreign bodies and masses, identification of GI perforation and used to detect drug-induced gastric mucosal changes and sometimes helpful to suggestion for the need of surgery (Boysen *et al.*, 2003). Ultrasonography of the gastrointestinal tract (GIT) is a valuable diagnostic imaging technique in animals (Penninck *et al.*, 1990). The complete abdominal ultrasonographic evaluation by 5, 7.5 and/or 10 MHz transducers has been performed in all age dogs, gastric lesions are considered by gastric wall thickening, wall layering and contents of gastric lumen. Poor Gastric motility is also considered if the peristaltic movement of the stomach is one or less contraction per minute. Ultrasonography of gastric ulcer can be suspected by the presence of gastric wall thickening associated with a wall defect (crater), gastric fluid accumulation, reduced motility, and constantly accumulation of microbubbles at the crater site (Tomooka *et al.*, 1989; Smithuis *et al.*, 1989). Ultrasonographic findings of the gastric epithelial tumor are gastric wall thickening, pseudolayering,

poorly echogenic wall and regional or distant lymphadenopathy (Penninck *et al.*, 1998). Endoscopy is the most sensitive diagnostic and prognosis of a diversity of gastrointestinal diseases. Endoscopic examination is important for the diagnosis and provides the perfect diagnosis by direct gastric mucosal visualization, biopsy collection, decided to prognosis and therapeutic benefits (Shaheen *et al.*, 2010). For the diagnosis of gastric mucosal lesions endoscopic examination can be protected, non-invasive, exact and without risk of dehiscence or peritonitis for evaluation of the color and gastric mucosal integrity of gastric mucosal layer (Happe *et al.*, 1983; Grooters *et al.*, 1994).

Differential diagnosis

Ingestion of specific foods (mainly protein) induces immune-mediated response leads to the sudden onset of gastrointestinal symptoms due to pruritus of the GIT known as food allergy in dogs (Webb and Twedt, 2003). In the starting phase of the gastric neoplasm no clinical sign appears, thus it can be diagnosed at later stages in most cases, therefore, the higher mortality rate has been reported (Tesensuren *et al.*, 2006). The endoscopic examination of gastric neoplasm reveals cauliflower shape cell mass in the gastric wall and therapy based on clinical signs has not been responded. The biochemical examinations reveal elevation of serum creatinine level, the activity of gastric enzymes and serum arginase activity while the level of the total protein concentration especially albumin level reduces (Meram and Tarakçioğlu, 2000). The male dogs mostly suspected for gastric carcinoma generally originated from pylorus and microscopic examination showed diffused penetration of inadequate differentiated neoplastic cells coupled with scirrhous reaction and gives appearance of typical “signet ring” cells (Brown *et al.*, 2007). Due to obstruction of

the lumen or inflammatory pain in the esophagus reveals star grazing behavior and clinical signs that are the regurgitation of food, excessive salivation, dysphagia, frequent tries to swallow, anorexia, and progressive weight loss (Frank *et al.*, 2012). The anesthesia-induced gastro-esophageal reflex leads to esophagitis which is the most common cause of esophageal pain (Poier *et al.*, 2014). Omeprazole is used for the treatment of the stargazing behavior of dogs due to esophagitis because it enhances gastric pH (Tolbert *et al.*, 2011). The Bravo pH monitoring system calculates Gastro-Esophageal reflux, Nuclear scintigraphy, positive contrast esophagogram and fluoroscopy method (GER) in canines (Tolbert *et al.*, 2011). If the dog is suffering from obsessive-compulsive disorder, reveals signs of excessive licking to foreign objects continuously like floor, wall, furnitures, lead to nauseous sensation and discomforts without GIT disorders (Overall *et al.*, 2002; Bonnet *et al.*, 2012) should be treated with combination of serotonergic drug with behavioral therapy (Overall and Dunham, 2002). If the lipolysis mechanism has been disturbed lead to the generation of an excessive amount of ketone bodies which hampers the blood buffer system and development of acidemia with diabetic ketoacidosis (Kerl, 2001). The disturbed lipolysis mechanism will also lead to GI disturbances and produce polyurea, polydipsia, anorexia, vomiting, progressive weight loss, haematuria, pollakiuria, shock and death of the dogs is generally due to a severe metabolic acidosis or complications to the vital and visceral organs (Hume *et al.*, 2006). If the pH is less than 7.10, bicarbonate and insulin therapy for the treatment of DKA is recommended (Causmaecker *et al.*, 2009). The most important clinical sign of the haemorrhagic gastroenteritis is acute onset of vomiting, profuse bloody diarrhoea, dehydration, and depression. The puppies

having age between six weeks to six months are more susceptible, but more severe in an age of less than six-month young dogs or old dogs (Sutton *et al.*, 2013). In young one GI system and Cardiac system are mostly affected but only GI system is maximally affected in adult dogs. The parvovirus has been identified with the help of ELISA and PCR. In the condition of shock, rapid infusion (over 10-20 minutes) of a bolus of 10-20ml/kg BW of lactated Ringers solution should be administered because lactate has been further converted into bicarbonate in the liver.

Therapy

Principles of therapy

The Principles of therapy of gastritis and peptic ulcer diseases are following (a) Withdrawal of food for prevents stimulation of gastric glands. (b) Removal of the etiological factor that is the hepatic failure, hepatic bacterial infection, NSAIDs or corticosteroid therapy.(c) Ulcer healing supported by- i) stabilization of the cardiovascular system and preserve mucosal perfusion by appropriate fluid therapy ii) diminishing gastric acidity iii) shielding from ulcer by cytoprotective agents (iv) correcting secondary circumstances (dehydration, anemia, weight loss).(d) After the stabilized, the perfusion in the patient than broad-spectrum antibiotics or combination of antibiotic therapy has been started.

Fluid therapy with gastric mucosal therapy

Dehydration, relative polycythemia, Hypokalemia, and hyponatremia are commonly found in dogs after vomiting and diarrhoea. Immediate correction of hypokalemia with antispasmodics is required because hypokalemia leads to hindrance in gastric emptying (Rebar *et al.*, 2001; Bichard

and Sherding, 2005). Reflux of duodenal contents (bile, pancreatic juice etc) into the stomach can damage the gastric mucosal barrier (Rodriguez *et al.*, 1997). In the drug-induced ulcerations, NSAIDs and other steroidal drugs should be stopped; if medication is necessary for therapy of specific disease then it will be considered. GI protectants in combination used for therapy containing H-2 receptor antagonists (cimetidine, ranitidine, famotidine), proton pump inhibitors (omeprazole, pantoprazole), cytoprotectants (sucralfate) and synthetic prostaglandins (misoprostol). Cimetidine is the first H2 receptor antagonist used in dogs and it is administered 3-4 times daily dose of @ 2.5-5 mg/lb body weight for suppressing gastric acid secretion (Ephgrave *et al.*, 1987). Even so, there is only mild to moderate inhibition of acid secretion over a 24 hours period. The fact that it works clinically for ulcer therapy suggests that even partial suppression of gastric acid secretion is beneficial for the healing of most gastroduodenal ulcers. In the GI haemorrhage and vomiting in significantly ill dogs, it must be considered dose and route of drug administration because oral route can the drug absorption. Ranitidine @2mg/kg IV q 12 hr has not been shown a major effect on gastric acid suppression (Bersenas *et al.*, 2005). Proton pump inhibitors are the most potent agents for suppression of gastric acid secretion by the inhibition of the gastric H⁺/K⁺- ATPase enzyme (the proton pump), which leads to failing the gastric secretion and rising the intragastric mucosal pH (Miner *et al.*, 2003; Scott *et al.*, 2002). Mainly clinically available proton pump inhibitors (PPI) are omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole (Miner *et al.*, 2003). Omeprazole is the first PPI that used clinically in 1988 at Losec in Europe, and in 1990 at Prilosec in the United States. Esomeprazole commonly used with omeprazole that is very much effective for

inhibition of gastric acid secretion (Andersson *et al.*, 2000). The esomeprazole (40 mg) is more effective than lansoprazole (30 mg) for healing erosive esophagitis and heartburn condition. For intragastric acid control intravenously once-daily dosing with esomeprazole provides faster and more prominent healing results than intravenously once-daily dosing with pantoprazole (Wilder *et al.*, 2004). In the patients with signs of GERD esomeprazole presents faster and greater acid control results to longer period maintain the intragastric mucosal pH than lansoprazole, omeprazole, pantoprazole, and rabeprazole (Rohss *et al.*, 2004). Famotidine @ 0.5mg/kg IV q12hr, omeprazole @ 1mg/kg orally q24hr) and pantoprazole @ 1mg/kg IV q24hr each have a notable property of the gastric acid secretion in dogs. Omeprazole acts as a Proton pump inhibitor that inhibits the H⁺-K⁺ ATPase pump and the production of hydrochloric acid from gastric parietal cells. Omeprazole enhances regulations of GKNs and produces anti-inflammatory effects, gastric homeostasis and tumor suppression (Kang *et al.*, 2001; Menheniott *et al.*, 2013; Xing *et al.*, 2012). Omeprazole inhibits c-AMP pathway of hydrogen ion generation and leads to prevent ulcer formation and enhance ulcer healing by increasing of gastric mucosal circulation and mucosal epithelial cells migration. The median value of 24-hour intragastric pH on days 2 and 6 were significantly higher when dogs were given famotidine, pantoprazole, or omeprazole than dogs were given ranitidine (Bersenas *et al.*, 2005). Misoprostol is an analog of PGE₂ gives at the doses of 0.5 to 2.3µg/lb body weight twice in a day. In NSAID induced ulceration, misoprostol may provide additional benefit with sucralfate and H₂ antagonist therapy. Prostaglandin E is contraindicated in hypotensive animals because it may lead to increasing of gastric damage. These drugs shield healthy and uncovered mucosa from more harm and

encourage epithelialization of gastric mucosa (Kuwayama *et al.*, 1991). Sucralfate is a non-absorbable aluminum salt of sucrose octasulfate compound that used as an optional extra to H₂ antagonists for treating peptic ulcers, because when ulcerative clinical signs are noticeable It is more effective in NSAID-induced ulceration than other drugs such as sucralfate and H₂ receptor antagonists, so it is choice of drug for NSAIDs producing ulcers (Lanza *et al.*, 2009). Acid-reducing drugs are work on cellular level metabolism to inhibit hydrogen ion secretion (e.g. prostaglandins) (Lanza *et al.*, 2009). Intravenous administration of metoclopramide @ 1-2mg/kg/24hr act as dopamine- antagonists that raise the threshold activity level of chemoreceptor trigger zone in vomiting center and decrease visceral nerve input that prevents vomiting (Sawant *et al.*, 2004). If the GI ulceration is coupled with the acute abdominal pain of unclear etiology, opioid analgesics should be administered for stabilization of GIT motility as well as relieve pain suffering. Antispasmodic drugs (e.g. dicyclomine) can also be administered.

Triple therapy

In considerable GI haemorrhage, broad-spectrum antibiotics should be administered for check the formation of bacterial colonies in the gastric mucosa as well as systemic translocation of the bacterial population. The culture of samples and Antibiotic sensitivity test should be done before started antibiotic therapy. Single Antibiotics does not gives significant effect against *Helicobacter spp.* Because rapidly development of drug resistance “Triple therapy” is effective against *Helicobacter* organism; this contains three antibiotic combinations or a combination of two antibiotics and one acid reducing agent like omeprazole or H₂ receptor antagonist (Bichard and Shreding, 2005). In *H. pylori* induced gastric disease, progressive

diminution of GKNs gene expression is known through disease progression chronic condition to oncogenic transformation (Choi *et al.*, 2013). Removal of *H. pylori* organisms from stomach leads to restoration of normal tissue level for proper expression of GKNs gene (Nardone *et al.*, 2007). Gastric *Helicobacter* infection treated with “Triple therapy” consisting amoxicillin 20 mg/kg BID, metronidazole 10 mg/kg BID and bismuth subcitrate 6 mg/kg BID orally for two to four weeks. Alternative eradication therapy with tetracycline 20 mg/kg BID and omeprazole 0.7 mg/kg OD administered orally for next 10 and 14 days was given after triple therapy for eradication of subsequently persisting helicobacter organism (Happonen *et al.*, 2000). Triple therapy with amoxicillin, metronidazole and famotidine also successfully eradicate gastric *Helicobacter* infection in dog and cat (Simpson *et al.*, 2000).

Antioxidant therapy

It is difficult to prevent the generation of ROS but the proper strategies prevent the gastric mucosal damage and fastening of recovery from oxidative stress. In the diet of sled dog, ROS scavengers such as vitamin E have been used to diminish cellular damage due to exercise (Hinchcliff *et al.*, 2000). Some antioxidants are used to protect gastrointestinal mucosa and apical epithelial membrane. In rats, the Cacao Liquor water-soluble crude polyphenols (CWSP) has been shown radical scavenging ability as well as reduce ethanol-induced gastric lesions (Osakabe *et al.*, 1998). The normal blood level of vitamin-C is 3.2-8.9m/ L in dogs, (Hishiyama *et al.*, 2006). Vitamin -C is necessarily required for absorption of antioxidants like N- acetylcysteine, and alpha-tocopherol in young dogs while in geriatric patient, the oral dosage of Vitamine C gives minor antioxidant and immunological effects

(Hall *et al.*, 2006; Ogawa *et al.*, 2008; Hesta *et al.*, 2009). Ascorbic acid reduces oxidative damage to the gastric mucosal layer by scavenging ROS and attenuating the *H. pylori*-induced inflammatory cascade leads to decreased incidence of gastric carcinoma and bleeding from peptic ulcer disease (Aditi *et al.*, 2012). During scavenging of free oxygen radicals by ascorbic acid produces 2-fold greater amount of ascorbyl radicals in the *H. pylori*-infected gastric mucosa (Drake *et al.*, 1998). Vitamin C is also an important dietary antioxidant because it significantly decreases the adverse effect of reactive oxygen species (ROS) that is a source of oxidative damage to the cell components like, lipids membrane, DNA, and proteins (Maestro *et al.*, 1980; Iheanacho *et al.*, 1993). Vitamin C is the only antioxidant required for complete protection of endogenous lipids from noticeable oxidative damage induced by ROS (Polidori *et al.*, 2004). Before the reaction and oxidation of lipoprotein lipids, Ascorbate seizes the activity of ROS. If serum concentration of Vitamin C has been down, the remaining antioxidants cannot be able to provide complete protection from ROS, leads to oxidative stress and initiate lipid peroxidation (Ulutas *et al.*, 2006).

N- Acetylcysteine works have mucolytic as well as antioxidant effect and reduce colonization of *Helicobacter* organism in gastric mucosa (Huynh *et al.*, 2000). N-acetylcysteine increases liver blood flow and improves liver function and renal function, as well as hepatorenal syndrome, lead to reduce severity of systemic induced gastritis (Holt *et al.*, 1999; Rank *et al.*, 2000). Silymarin significantly affects the serum SGPT, SGOT, Alkaline phosphatase activities, serum urea and creatinine levels and maintains malondialdehyde level (MDA) as an antioxidant in liver and kidney (El-Maddawy *et al.*, 2012).

Others

New synthetic flavonoid derivatives gastroprotectant drugs are also used for the treatment of gastritis and peptic ulcer disease. It was designed by effervescent floating matrix system (EFMS) that float the tablet in gastric fluids and constant release of drug DA-6034 from tablets in acidic media. It acts as solubilizing and alkalizing agent like as sodium bicarbonate has been used as a gas generating agent. DA-6034 EFMS tablets lead to enhancing the gastroprotective effects of gastric ulcer, gastritis and peptic ulcer (Jang *et al.*, 2008). Electron microscopic examination showed abundant osmophilic phospholipids materials are found as a surfactant within the mucosa of gastric and duodenum and administration of phospholipids exogenously may prevent gastric mucosal ulceration (Ethell *et al.*, 1999). If ulcer patient co-existing with motility disorders of delayed gastric emptying also give Cisapride therapy (Natan *et al.*, 1996). Therapy of severe bleeding in acute GI haemorrhage depends on the degree and length of bleeding time and PCV. Whole blood or oxyglobin transfusion is the first protocol of recovery. Blood transfusion in unclearly observed rate and volume of blood loss in patients who do not show sign of shock causes vascular hemodynamic abnormalities, disturbances in haematological parameters, and parallel illness are noticed (Maltz *et al.*, 2000). It may be required if the patient shows clinical signs of hypoxia (e.g. tachycardia, hyper-lactataemia, tachypnoea), or if series of haematological parameters showed failing haematocrit value after the therapy started (Maltz *et al.*, 2000). If the medical therapy fails to respond, surgery should be indicated for pre-existing surgical disease (e.g. perforated ulcer, foreign body or tumours, septic abdomen), Before therapy of GI haemorrhage, it must be considered in hepatic disease (coagulation abnormalities)

and renal diseases (uraemia), otherwise it may lead to intensifying the condition.

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