Gastric ulcer mechanism, protection and treatment from natural sources

ABSTRACT

Gastric acid secretions are main cause for formation of gastric ulcers that are attributed by *Helicobacter pylori* infection and extensive use of NSAIDs (non-steroidal anti-inflammatory drugs). These contributors facilitate the initiation of cellular and molecular signalling pathways in our body that give rise to formation of gastric ulcer. Generally, gastric ulcer results in minute to deep invading of gastric mucosal linings which may produce harmful symptoms in our body. Non-infectious gastric ulcers are another problem related with gastro-intestinal disorders that mainly caused because of poor daily activities includingalcohol consumption,oxidative stress, mental stress and low consumption in healthy food intake. Stress plays a crucial role in the formation gastric ulceration due to its effect on the generation of ROS (reactive oxygen species) and RNS (reactive nitrogen species).Gastric cancer is found common in severe ulceration and gastric lesions. This type of cancer mainly attributed by untreated gastric ulcer and other related infected and inflammatory conditions. They all increase the worldwide incidence of morbidity and mortality rates. Therefore, a novel approach towards research and development has been must to categorise these complications. Natural agents with adaptogenic and antioxidant properties are useful in this situation. Some of the herbal extracts have been used from ancient times due to their cytoprotective, anti-inflammatory and antioxidant effects. New approaches are still on progress to obtain a potential phytopharmaceutical and natural agent to treat these disorders.It has been reported anti-secretory effects of herbal preparations give rise to protective action in the cure of gastric ulcers.We try to explain mechanisms involve in this complication and important pharmacological activity of natural extracts to counter act these symptoms in our review.

KEYWORDS: Gastric Ulcer, Herbal Extract, ROS, MMPs, SOD, Oxidative Stress, Gastric Inflammation, H+K+- ATPase activity

1. INTRODUCTION

Duodenal ulcers, gastric ulcers and gastric cancer are the commonly occurring disease, *Helicobacter pylori*(*H. pylori*)responsible for infection in the peoples and by fatal in some cases.*H. pylori* infection causes the increased secretion of gastric acids by parietal cell, which can develop duodenal ulcers and in severity of infections the acids secretion may be down regulated due to gastric ulcer or gastric cancer. However, the acid secretions by parietal cells may be unaffected in healthy subjects. Many factors are available that regulate the gastric acid secretion in our body, these includes G cells, histamine H_2receptor antagonists, proton pump inhibitors.Mostly ulcers observed were due to *H. pylori* infection, non-steroidal anti-inflammatory drugs, Crohn's disease, hyper-gastrinaemia idiopathic gastrinoma(Zollinger-Ellison syndrome), cigarette smokingand hyperthparathyroidism [1, 2].Global cases around 85% reported were due to *H. pylori* infection or extensive use of NSAIDs.*H. pylori* are responsible for more than 45% mucosal damage. Another major factor for developing gastric ulcer includes NSAIDs. These drugs when taken internally cause cellular injury to gastric mucosa through increasing cellular permeability that facilitates gastric mucosaldamage [3].Biologically stress is the result which is caused by certain stimuli in response to change in environmental conditions. Since from long time ago it is proved that physiological stress may cause gastric ulcer. One of the scientists suggests that duodenal ulcer can cause severe bleeding and burning sensation in the gastro-intestinal tract[reference]. Stress induced gastric ulcer first presented in 1971. They called it stress-related erosive syndrome. Stress induced ulcer also involves ulcers due to stress, erosions from stress, stress gastritis, erosive gastritis, hemorrhagic gastritis, and mucosal damage related with stress [4, 5, 6]. Restraint-cold stress in rat can be responsible for the release of free radicals i.e. hydroxyl radicals. Stress mainly causes the release of gastric acids secretions which give rise to oxidative stress. By studding the ulcer index of Stress models for long time suggests that there is elevation in the mitochondrial superoxide dismutase activity and a reduction in the peroxidase activity that give rise to severe ulceration[reference]. DMSO(Dimethyl sulfoxide)and PBN(α-phenyl N-tert butyl nitrone) efficiently reduce gastric ulceration; this shows that free radical play major role in ulcer formation.A further study suggests that stress causes a highly increase generation of free radicals. This is proved by ulcer index data. So the oxidative destruction of the gastric mucosa is due to stress induced gastric ulcer. Chronic stress conditions elevated the lymphocytic infiltration and inflammation, which facilitates the up regulation in CD11b (leukocyte integrins αM) and mRNA(messenger ribonucleic acid)expression levels in the stressed mice stomach[reference]. There also seem to increase in the levels of superoxide dismutase, catalase, glutathione peroxidase, IL-1β (interferone? or interleukin?-1β) and TNF-α (tissue necrosis factor-α)[6-9].Rewrite this sentence. You mixed pro-inflammatory cytokines with anti-oxidant enzymes, stating that they both increase, explain this further,under what conditions this occurs and reference.

2. MECHANISM OF GASTRIC INFLAMMATION: Inflammation involves response of living tissues towards harmful stimuli for example damaged cells, allergens, pathogens, irritants [10]. It is a protective action taken by body which involves cells of immunity, bloodvessels, and other molecular regulators. The major anti-inflammatory activity to these stimuli is to protect cells from injury and regulation of protective tissue repair [11, 12, 13].Inflammation is a matrix interaction which can cause cell proliferation, migration, and differentiation. From study on animal and cell cultures the role of MMP-9 (metallo-matrix proteinases-9)has been evaluated in the formation of gastric ulcer/ulcers. Gastric ulcer can be obtained by non-steroidal anti inflammatory drugs, ethanol treatment, stress and by infection of *Helicobacter pylori.* Studies shows MMP-9 and MMP-2 (metallo-matrix proteinases-2) are playing important role in gastric ulceration involving mucosal inflammations which is important factors in facilitating lymphocyte infiltration in gastric tissues [14].

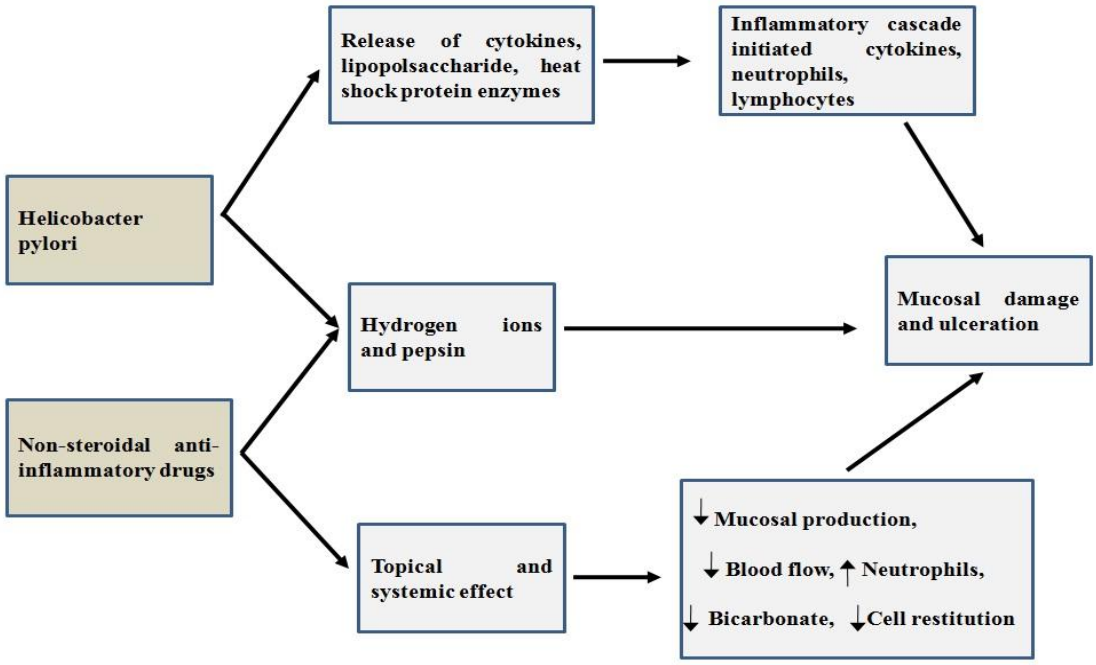

Figure 1. Effects of *H. pylori* and NSAIDs. It has been observed that, *H. pylori* infection can stimulates the release of free radicals, harmful enzymes, and cytokines. Also, excess use of NSAIDs can release the free radicals and systemic effects. It leads to initiation of inflammatory cascade, decreased mucus, decreased blood flow, decrease cell restitution and increased neutrophils [15].

Many proteases are responsible for cellular differentiation, its proliferation, programmed cell death, and angiogenesis. MMPs (metallo-matrix proteinases-9) are significant regulator in tumor growth and inflammation. They are the sub groups of extra-cellular matrix as well as few non-extra cellular matrix components. Gastric ulcer model involves the treatment with anti-inflammatory drugs, ethanol by oral route, induced physical stress and infection by *H. pylori* has been developed. This study shows the importance of MMP-9 and MMP-2 in gastric ulcer formation and inflammation. Studies showed that ulcerated gastric mucosal tissue of human exhibit significant rise of MMP-9 level and moderate reduction of MMP-2 level in comparison with normal tissue[reference].

Table 1:Different types of MMPs and their sub groups are classified.

Sub-groups	**Collagenase**	**Gelatinase**	**Streomelysins**	**Matrilysins**	**Membranetype MMPs**	**OtherMMPs**
MMPs	MMP-1, -8,- 13, -18	MMP-2, -9	MMP-3, -10,-11	MMP-7,-26	MMP-14,- 15, 16,-17, -24, -25	MMP-12,- 19, 20,-21, -23, 27,- 28

Formationof wound its protection and healing are dynamic processes of ECM remodeling which are broadly increased by activities of MMPs and tissue inhibitors of metalloproteinase. Due to various environmental factors molecular changes may occur that are important

issue.Our objective should be to discover novel molecular target and preparation of target based drug entity to control further development of disease [16].

2.1 Role of metallomatrix proteins in the development of gastric and ovarian cancer:???Gastric inflammation and gastric ulcer elevates the chances of gastric cancer, so genomic studies have been started to overcome the further progression of cancer. Link between promoter polymorphism of MMP-1,-3,-9,-7 have found that shows the risk of gastric cancer [14, 17, 18].

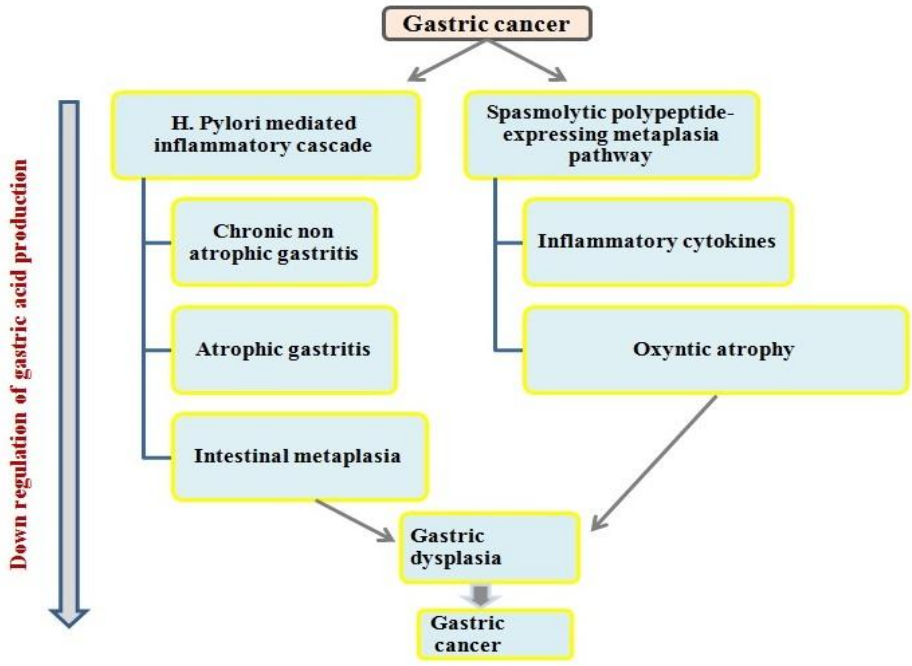

Figure 2. Mechanism of gastric cancer that are triggered by various metabolic pathways [19]

2.2 Role of stress in the formation of ulcer: Oxidative stress describe as the major cause of gastrointestinal disorder like ulcer.The outcomes provide evidences that it generate reactive oxygen species which activate gastric ulcerogenic cascade like release of TNF-αand other inflammatory response including COX(cyclooxygensae)enzymes.These enzymes COX1 and COX2 release arachidonic acid and they also cause osmotic stress with other oxidases. Therefore, this results in up regulation of ROS in oxidative damage. Redox cell signaling reported to be characterizing by involvement of transcriptionfactors namely AP-1(activator protein-1), NFκB (necrosis factor-κB) and NRF-2 (necrosis related factor-2) [20].

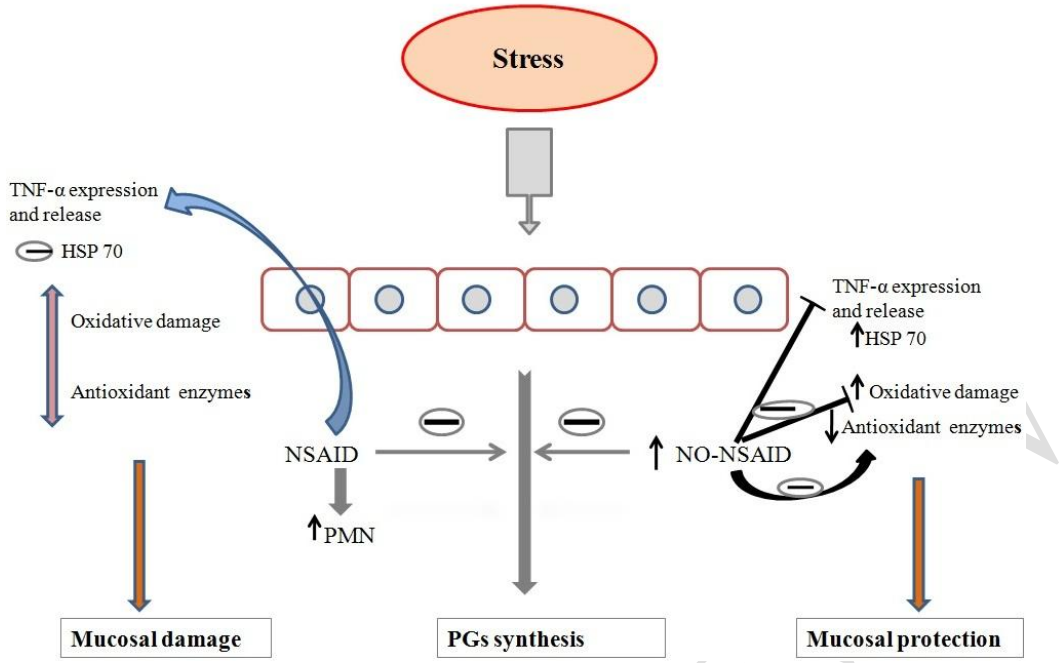

Figure 3. It has been observed from above figure that stress play crucial role in release of TNF-α and causes oxidative damage [21, 22].

Redox cell signallingis effected by stress caused by reactive oxygen species. ROS are also attributed by smoking habit.Mitochondrial matrix governed electron transport chain releases many free radicals like H_2O_2, NO (nitric oxide) and O_2^-.H_2O_2 regulate many changes in protein structure that results in redox reaction and other signalling mechanism [23].

3. NATURAL PRODUCTS IMPORTANCE IN GASTRIC ULCER TREATMENT AND PREVENTION

3.1 Antiulcer Activity of Melatonin: Study of anti-ulcer activity of Melatonin involves the gastric ulcer that was developed by using restraint cold stress and non-steroidal anti-inflammatory drug like Indomethacin. Melatonin shows 90% antiulcer activity on restraint cold stress and Indomethacin induced ulcer/ulcers at a particular dose. Melatonin activity in contrast withother antiulcer drugs such as Ranitidine and Omeprazole shows potent activity as compare to Ranitidine and less active than Omeprazole in preventing stress ulcer. Melatonin is more effective than antioxidants like glutathione and equally effective as compared to α-tocopherolin inhibiting stress induced gastric ulcer. As we know stress induced gastric ulcers are because of oxidative damage caused by •OH, Melatonin are very effective in decreasing levels offree radicals. Melatonin is effective in the range from 88-90% [24]. Therefore melatonin reported potential activity to lower free radical when compared with Benzoate. From this study it is clear that the Melatonin shows gastro-protective action against the acute gastric ulcers. Melatonin also showed in healing and protective activity in model of chronic gastric ulcers[reference]. Melatonin act by increasing the nitric oxide synthase and cyclo-oxygenase-prostaglandin E2 activity. Melatonin released from pineal gland. Melatonin is an indole generates from L-tryptophan, an amino acid precursor. Melatonin is having potential to inhibit the reactive oxygen species. It shows potent protective action against the various ROS [25-27].Melatonin, Famotodine, and nano-capsulated Quercetin inhibits gastric ulcer by MMP-9 mediated pathway [28]. Melatonin act by tightly binding with the active site and reduce the catalytic activity of MMP-9 [29]. Chronic ulceration also leads to regulated expression of MMP-9 and MMP-3 (metallo-matrix proteionase-3)which attributed by inflammatory responsesresults in generation of NF-κβ and AP-1 signalling. Melatonin managed to down regulate these inflammatory responses and treat the chronic ulcers [30].

3.2 Antiulcer Activity of Neem: Water extract of Neem bark have the potential to inhibit the gastric ulcer on animals with out exerting any side effects. The same experiment was carried out on humans who are suffering from gastric ulcers in the dose of 30 mg two times a day of Neem bark aqueous extract. The doses are given by oral route. For this experiment the Neem bark extract was lyophilized and given for ten days. It shows 77 percent decrease in gastric secretions. Also the aqueous bark extract from Neem tree in the dosage of up to 60 mg two times a day for ten weeks completely heals the ulcers. So it is clear that Neem bark extract have very potent effect on gastric ulcers [31]. Neem stem bark when tested on rats results in potent anti gastric activity induced by Indomethacin. The dose of the extract in the range of 100-800 mg/kg b.w. significantly inhibits gastric ulceration. Also the Neem stem bark aqueous extract protect gastric lines by reducing the gastric acid secretion induced by histamine. In combination with Cimetidine Neem bark extract inhibits the gastric acid secretion. This shows that it acts via Histamine H2 receptor. Neem is used as anti-malarial, insecticidal, antibacterial, hypotensive, anti fertility action. Intra-peritoneal and orally administration of extract in the increasing doses produces acute toxicity. An Intrapritoneally extract dose does not produce any toxicity but high doses when given orally can produce death [32]. Ulcer protective action of aqueous Neem leaves extract on stomach ulcer and ulcer in diabetic rats shows potent effects. For this study the offensive acid secretion in 4 hours pylorus ligation by stimulation of acid secretion and defensive mucin secretion were done. This shows that aqueous extract of Neem leaves inhibit the acid pepsin secretion in chemically stimulated acid secretion models. The Neem leaves extract shows ulcer healing effect both in acute as well as in chronic models [33].Neem is referred as very potent herbal medicine from ancient times. A natural chemical compound obtained from ethanolic Neemseeds extract that is known as Azadiradione have shown very potent antiulcer activity. Azadiradione shows its activity by reduction of H+K+-ATPase activity. These were due to its cytoprotective and anti-secretory effect. This shows that Azadiradione are very important compound for treating peptic ulcer. Study was proved on gastric ulcer in rats. Azadiradione has been tested on various gastric ulcers caused by cold stress, Aspirin, Alcohol, pyloric ligation induced models. This isolated Azadiradione (20 mg/kg) are given orally before ulcer induction in all models. Omeprazole are considered as reference drug(10 mg/kg) given forty five minute before the formation of gastric ulcer. It has been induced by cold restraint stress, the pyloric ligation ulceration and the aspirin induced gastric ulcer model. Gastric ulcer induced by using alcohol followed the administration of sucralfate (500 mg/kg) before initiation of the experiment. In the cold restraint and aspirin models, it has been showed to inhibit gastric acid secretion in the alcohol model of gastric ulcer. The potential effect of Azadiradione involves the protection of gastric mucosal [34]. The alcoholic Neem leaf extract were when experimentally introduced with gastric cancer cell lines successfully reduced the cell viability and cell proliferation.This crude extract has been protecting the gastric mucosal lines from Indomethacin induced ulceration in Sprague-Dawley rats. Although, the extract prepared from TLC ?technique were decreases the intensity of ulcerationwhich was maximum at a dose of 75mg/kg body weight.These effects were almost similar to the effect produced by Omeprazole in Bulb C mice [35].

3.3 Gastro-protectiveaction ofCurcumin: Curcumin an active constituents from turmeric inhibits MMP-9 and MMP-3. It prevents gastric ulcer caused by *Helicobactor pylori* and non-steroidal anti-inflammatory drugs. Antiulcermechanism of action of Curcumin constitutes the two steps: (1) blockage of MMP-9 derived inflammatory response and (2) initiation of activity of MMP-2 to facilitate angiogenesis during healing mechanism of gastric ulcer [36].It has been reported that *Helicobacter pylori* infected mice when treated with lipidic solution ofcurcumin(500 mg/kg)for 6 weeks to 18 weeks, observedno damage and tissue injuries to gastric mucosal linings. In genomic analysis curcumin managed to down regulate the expressions of up regulated genes in infected genes also. These contribute the down regulation of inflammatory responses. Therefore, curcumin successfully reduced the chronic inflammation caused by *Helicobactor pylori,* suggests its important activity to control gastric damage [37]. Curcumin capsules (500mg) when given alone and as anadjuvant with

Clarithromycin tablets, amoxicillin capsules and esomeprazole tablets,3 times a day for around 2-6 weeksexperimental protocol to human subjects that were diagnosed with peptic ulcer diseasereported to cure the peptic ulcer from 55-58%(curcumin capsules) and 88-90% (Curcumin capsules+ standard triple therapy) respectively [38].Encapsulated formulation of curcumin at a dose concentration of 20 mM inhibits the bacterial strains of *Helicobactor pylori*because of enhanced bioavailability of this compound which further inhibits Cag A (Bacterial protein), its translocation and phosphorylation prevent conversion into infected epithelial cells.Significantly, biological activity of enhanced curcumin formulation prevents inflammation caused by *Helicobactor pylori* infection; this lowers the risk of gastric cancer respectively [39, 40].

3.4 Ameliorating activity of*Spondias mombin* and *Ficus exasperate*

Wister albino rats of uniform weight were induced with Indomethacin to develop gastric ulcers, esomeprazole act as reference drug and the aq. leaves extract of individual plant *Spondias mombin* as well as *Ficus exasperate*given through oral route. The inhibitory role of these extracts was observed in dose dependant manner and maximum protective to antioxidative effects was at the dose of 200mg/kg body weight. The cumulative activity of these extracts results in lowering the number of ulcers, maintaining pH and mucin level, malondialdehyde content. This has been also results in recovering the gastric volume and regulation in superoxide dismutase activity that were lowered on treatment with Indomethacin [41].

3.5 Therapeutic efficacy of Manuka Honey

The formulation were prepared by mixing Royal Bee 20 with active manuka honey at the dose of 0.1gm/kg, 1gm/kg and 2.5gm/kg, following oral route for administration in rats that had gastric ulcerogens induced with the help of ethanol. The preparation at the dose of 2.5gm/kg b.w. significantly showed maximum anti-inflammatory, antioxidant activity and gastric mucosal protective action against induced ulcers. When compared with Omeprazole, manuka honeyalmost in similar manner lower all the parameters associated with this disorder. The mechanism involvesbalancing level of nitric oxide, glutathione, and superoxide dismutase and glutathione peroxidase in gastric mucosal linings. Furthermore, manuka honey decrease the lipid peroxidation levels and reduces the inflammatory cytokines to maintain gastric mucous proteins[42].

CONCLUSION

A major role of natural products and bioactive compounds has been reported from previous as well as current studies regarding their role in the treatment and management of many types of ailments. As, it is also confined from these researches that they are also eco-friendly with few side effects to the biological system if taken in prescribed dosage. Since these are the wide facts related to our current approach for novel drug discovery over the last century from natural sources. It has involved utilization of naturally occurring entities as a chemically diverse starting building block for the preparation of synthetic, semi-synthetic and organic drugs. It has been discovered from ancient times the natural products importance covered a broad spectrum in the cure of fatal diseases. Because they have many protective and prevent action on living system are noticed from traditional knowledge as well. Our review focuses on the increasing interest related to gastro-intestinal antiulcer effects of plant driven extracts and their main components. The protective nature of these, such as antibacterial, anti-oxidative, and anti-inflammatory actions are already well established. However the antiulcer role of Neem leaves extract, Melatonin, Curcumin are studied in limited manners. So, antiulcer activity of Melatonin on induced gastric ulcer by using restraint cold stress and anti-inflammatory drug i.e. Indomethacin proved to be very potent in scavenging the free radicals. Results showed that Melatonin is very much effective as compared to benzoate to overcome oxidative damage benzoate are well known for its scavenging effects on hydroxyl radicals. The mechanism of action Melatonin, Famotodine, and nano-capsulated quercetin to

inhibit gastric ulcers reported are through MMP9 mediated pathway. Melatonin activity is due to its tight binding with the active site and that reduce the catalytic activity of MMP9. Neem stem barkaqueous extract have the potential to inhibit the gastric ulcer on animals without exerting any side effects. This showed that aqueous bark extract are very potent when given to human in a particular dose i.e. 30 mg twice a day. Oral route preferred for this study surprisingly protect the subject from gastric ulcer. In another study it has been reported that it decrease in gastric secretions to many folds. This Neem extract completely treat the gastric ulcer in the dose of up to 60 mg two times a day for ten weeks. These findings suggest that neem leaves extract are having potent antiulcer activities. Curcumin a well known active bio-molecule obtained from *Curcuma longa* inhibits MMP9 and MMP3. It has been reported to prevent gastric ulcers that were caused by *Helicobactor pylori* and non-steroidal anti-inflammatory drugs.

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