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# PEPTIC ULCER - Its Pathogenesis and Recent Approaches for the Treatment

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**ABSTRACT:**

Gastric ulcer usually develops due to a break in the tissue lining of the stomach. Formation of gastric ulcer is a complex mechanism. Several factors are responsible for the pathogenesis of gastric ulcer. The present article provides all information regarding causal factors that help in understanding of pathogenesis of ulcer. It includes gastric acid, histamine, NSAIDs, H. pylori infection, oxidative stress and bile acids. It also includes various recent approaches for the treatment of the ulcers like- role of nitric oxide, role of copper complex, probiotics, role of growth hormones and herbal drugs like curcuminoids.

**KEY WORDS:** - H. pylori, Apoptosis, Copper complex, Probiotics.

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## INTRODUCTION:

A peptic ulcer is an excoriated area of stomach or intestinal mucosa caused principally by the digestive action of gastric juice or upper small intestinal secretions. Peptic ulcer is a conglomerate of heterogeneous disorders, which manifests itself as a lesion in the lining of the gastrointestinal mucosa bathed by acid and/or pepsin. Peptic ulcers frequently occur along the lesser curvature of the antral end of the stomach or, more rarely, in the lower end of the esophagus where stomach juices frequently reflux. [(1)]

There are three common forms of peptic ulcers: *Helicobacter pylori* (HP)–associated, nonsteroidal anti-inflammatory drug (NSAID)–induced, and stress ulcers. Non Steroidal anti-inflammatory drugs (NSAID) ingesion is associated with erosions, type C gastritis, ulceration, interference with ulcer healing, complications and injury to the small and large intestine. [(2)]

The term “stress-related mucosal damage” (SRMD) is preferred to stress ulcer or stress gastritis, because the mucosal lesions range from superficial gastritis and erosions to deep ulcers.

The usual cause of peptic ulceration is an imbalance between the rate of secretion of gastric juice and the degree of protection afforded by (1) the gastro-duodenal mucosal barrier and (2) the neutralization of the gastric acid by duodenal juices. [(3)]

The defect in defensive protectors like bicarbonate, mucus is first step towards the ulcer formation than other causative factors like acid, pepsin. [(4)]

After discovery of H.pylori infection as a causal factor, the management of the patient with peptic ulcer is changed and it had major clinical impact. (kuiper et al from webmed) However, none of the factor could clearly explain the pathogenic effectors of the disease due to recurrence after cessation of the treatment.

In conventional therapy, many antiulcer drugs are there, such as $H_2$ receptor antagonists, proton pump inhibitors and cytoprotectants but all these drugs have side effects and limitations. [(2)]

For H. pylori infection, now a days, the most effective proven treatment comprises of a 2-weeks course called "triple therapy" involves taking two antibiotics to kill the bacteria and either an acid suppressant or gastric epithelial lining shield. [Lansoprazol (30mg), amoxicillin (1g), clarithromycin (500mg) b.d.]. [(5)]

Ulcer associated with the NSAIDs remains a major problem which has not been resolved through introduction of selective inhibitors of COX2. [(6)]

Many new approaches are there for treatment of peptic ulcer including herbal treatment, role of cytokines, role of copper complexes, nitric oxide and growth factors but very scant data are available on these.

**VARIOUS CAUSATIVE FACTORS FOR PEPTIC ULCER:-**

Peptic ulcers appear to be produced by an imbalance between gastro duodenal mucosal defence mechanisms and the damaging forces. Gastric and pepsin are requisite for all peptic ulcerations. Gastric ulceration can readily occur when mucosal defenses fall. [(1)]

Defensive factors mainly involve mucus-bicarbonate secretion and prostaglandins. Stress, smoking, nutritional deficiencies and ingestion of nonsteroidal-anti-inflammatory drugs (NSAIDs) are all factors, which increase the incidence of gastric ulcer. [(7)]

**A) Gastric acid Secretions**

The stomach mucosa has two important types of tubular glands: *oxyntic glands* (also called *gastric* glands) and *pyloric glands*. The oxyntic (acid-forming) glands secrete *hydrochloric acid*, *pepsinogen*, *intrinsic factor*, and *mucus*. The pyloric glands secrete mainly *mucus* for protection of the pyloric mucosa from the stomach acid. They also secrete the hormone *gastrin*.

A typical stomach oxyntic gland is composed of three types of cells: (1) *mucous neck cells*, which secrete mainly *mucus;* (2) *peptic* (or *chief*) cells, which secrete large quantities of *pepsinogen*; and (3) *parietal* (or *oxyntic*) *cells*, which secrete *hydrochloric acid* and *intrinsic factor*. [(1)]

Gastric parietal (oxyntic) cells secrete isotonic hydrochloric acid. The parietal cells secretion is an isotonic solution of essentially pure HCl. The $P^H$ of this solution is as low as 0.8, the concentration of $H^+$ being a million times higher than that of plasma. Carbonic anhydrase enzyme has been found to be abundantly present in the gastric parietal cell which combines carbon dioxide and water forming carbonic acid, from where bicarbonate ion ($HCO_3^-$) is exchanged with plasma $Cl^-$. Hydrogen ion is pumped out against the concentration gradient into the gastric lumen by $H^+K^+$ ATPase that is located in the apical membrane of the parietal cells. This pump generates the largest known ion gradient in vertebrates, with an intracellular pH of about 7.3 and an intracanalicular pH of about 0.8. [(7)]

Hydrochloric acid is secreted by the parietal cells, which contain receptors for histamine, gastrin, and acetylcholine. Gastrin is secreted by endocrine cells in the gastric antrum and duodenum. Zollinger–Ellison syndrome is an uncommon disorder caused by a gastrinsecreting adenoma associated with very severe peptic ulcer disease. [(5)]

Pepsinogen, the inactive precursor of pepsin, is secreted by the chief cells located in the gastric fundus. Pepsin is activated by acid $p^H$ (optimal pH of 1.8 to 3.5), inactivated reversibly at pH 4, and irreversibly destroyed at $p^H$ 7.

The main goal for protection of the gastric mucosa from gastric acid is pharmacologic control of gastric acid secretion. [(8)]

Mucins are heavily glycosylated glycoproteins that are the major components of the mucus viscous gel covering epithelial tissues. They form lubricants protective selective barrier on epithelial surfaces, and modulates cell-cell and cell extracellular matrix interaction. Their expression is regulated by several cytokines and local hormones. [(9)]

**B) NON-STEROIDAL ANTI-INFLAMMATORY DRUGS**

Nonselective NSAIDs including aspirin cause gastric mucosal damage by two important mechanisms: (a) direct or topical irritation of the gastric epithelium and (b) systemic inhibition of endogenous mucosal prostaglandin synthesis. [(2)]

Chronic use of NSAID'S suppresses mucosal prostaglandin synthesis.Prostaglandin E2 (the principal prostaglandin synthesized in the stomach) is an important gastro protective mediator. It inhibits secretion of acid, promotes secretion of protective mucus and causes vasodilatation of sub mucosal blood vessels. [(5)]

At high doses aspirin in the acidic environment of gastric juice becomes un-ionized and freely penetrate the mucosal barrier reaching to gastric wall. Due to weak basic nature of cytoplasm of gastric mucosal cells, aspirin could accumulate at higher concentrations into mucosal cells, and yields negatively charged anion that is unable to exit the cell. Thus, superficial or deeper erosions are produced and bleeding takes places within minute. [(10)]

NSAIDs-induced ulcers develops in achlorhydric individuals, has contributed the belief that acid is not involved in the pathogenesis of these lesions. [(11)]

However, by inhibition of prostaglandin synthesis, it increases the gastric acid secretion. Acids may contribute to NSAIDS induced ulcer formation by several ways like

a) Acid can inactivate growth factors that are important for the maintenance of mucosal integrity. Since these growth factors are acid labile.

b) Acid can convert superficial injury to deeper mucosal necrosis. [(12)]

A high dose of famotidin (40 mg twice daily) and omeprazol could significantly reduce the incidence of NSAIDs induced ulcer. [(13)]

**C) HELICOBACTER PYLORI**

H. pylori have been found to be associated with gastric and duodenal ulcer and gastric cancer. [(14)]

The presence of the bacterium Helicobacter pylori has now been established as a major causative factor in the etiology of peptic ulcer disease. Although commonly found in the gastric antrum, it may also colonize other areas of the stomach, as well as patches of gastric Helicobacter pylori is a spiral-shaped, pH-sensitive, gram-negative, micro aerophilic bacterium that resides between the mucus layer and surface epithelial cells in the stomach, or any location where gastric type epithelium is found.

The exact method by which HP initially induces hypochlorhydria is unclear. One theory is that HP produces large amounts of urease, which hydrolyzes urea in the gastric juice and converts it to ammonia and carbon dioxide. The local buffering effect of ammonia creates a neutral microenvironment within and surrounding the bacterium, which protects it from the lethal effect of acid. HP also produces acid-inhibitory proteins, which allows it to adapt to the low-pH environment of the stomach. HP attaches to gastric-type epithelium by adherence pedestals, which prevent the organism from being shed metaplasia in the duodenum during cell turnover and mucus secretion.

Colonization of the body of the stomach is associated with gastric ulcer. After exclusion of gastric ulcers caused by non-steroidal anti-inflammatory drug therapy and Zollinger–Ellison syndrome, the incidence of H. pylori infection in patients with gastric ulcer approaches 100%. The strongest evidence of a causal relationship between H. pylori and peptic ulcer disease is the marked reduction in ulcer recurrence and complications following successful eradication of the organism. It has been shown that the speed of ulcer healing obtained with acid-suppressing agents is accelerated if H. pylori eradication is achieved concomitantly. [(5)]

H. pylori infected gastric mucosa showed infiltration of polymorphonuclear leucocytes, lymphocytes, and monocytes. [(15)]

H. pylori-induced inflammation is implicated in the development of mucosal damage and these changes lead to apoptosis and proliferation of mucosal layer. [(16)]

Certain cytokines released in H. pylori gastritis like TNF-α and specific products of H. pylori like ammonia release gastrin from G cells. The infection diminishes mucosal expression of somatostatin. These changes in gastrin and somatostatin increase acid secretion and lead to duodenal ulcer.H. pylori infection causes chronic inflammation that results in the release of pro-inflammatory cytokines that may reduce acid secretion. [(17)]

**D) Histamine**

Histamine is a chemical messenger that mediates cellular responses, including allergic and inflammatory reactions, gastric acid secretion and possibly neurotransmission in parts of the brain.

Additionally, it is secreted by mast cells as a result of allergic reactions or trauma. Pharmacologically, histamine produces vasodilatation and increase in permeability of blood vessel walls that may contribute to gastric hemorrhage [(10)].

In the experimental animal, increased mucosal histamine has been reported to elicit gastric secretion and mucosal lesion. Since, histamine may cause increase in gastric mucosal permeability to electrolytes and renders the stomach more susceptible to acid-induced damage. The role of histamine in the secretion of acid from acid-producing parietal cells is widely reported. Where, histamine

activates histamine-2 receptors on the acid-producing parietal cells to stimulate acid production, the over production of acid inhibits through low antral pH gastrin release from G-cells, thus preventing the stimulatory effect of gastrin on enterochromaffin-like (ECL) cells and further histamine release. This inhibitory control is mediated via the release of somatostatin from D-cells situated in close proximity to the G-cells. [(5)]

**E) Oxidative stress**:-

Oxidative stress is believed to initiate and aggravate many diseases including peptic ulcers and gastric carcinoma. One of the common denominators for the genesis of these diseases is the involvement of free radicals. Reactive oxygen species (ROS) are generated through numerous normal metabolic processes and are needed for normal functioning of the organism.

Various antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT) and gluthathione peroxidase (GPX) control their accumulation. Any imbalance in the activity of these enzymes normally leads to faulty disposal of free radicals and its accumulation. These ROS are responsible for oxidation of tissues leading to lipid peroxidation and tissue damage. They are also responsible for oxidation of bases in cellular DNA making them mutagenic, cytotoxic and crosslinking agents, which in turn causes uncontrolled expression of certain genes causing increased multiplication of cells leading to cancer.

Antioxidants seemed to have protective role in gastric ulcers. Stress causes both sympathetic (causes direct arteriolar vasoconstriction) and parasympathetic (induces an increased motility and muscular contraction) stimulation of stomach leading to local hypoxia and near or actual "ischemia". The ischemic condition caused an increase in the level of H2O2 (by the action of SOD), which, in conjugation with O2 generates OH via the methyl catalyzed Haber-Weiss reaction Hydroxyl radicals thus generated, oxidizes important cellular constituents such as structural and functional proteins membrane lipids and depletes glutathione. Lipid peroxidation causes loss of membrane fluidity, impaired ion transport and membrane integrity and finally loss of cellular functions. [(18)]

**F) Incidence of apoptosis**

Apoptosis is cells dying process. In this, process goes through defined morphological changes that involve chromatin condensation, cytoplasmic and nuclear blebbing, and eventual cellular demise without loss of membrane integrity.

Under normal physiological conditions, the balance between gastric epithelial cell proliferation and death is of great importance in maintaining gastric mucosal integrity.

Since, the balance between cell apoptosis and cell proliferation has important role to keep the gastric mucosa healthy [(19)].

Since, the gastric epithelial cells proliferate in the lower part of the glandular neck and migrate up the crypt towards the surface and then are shed into the lumen by apoptosis [(16).]

Disturbance of this balance could result in either cell loss, leading to mucosal damage and ulcer formation, or cell accumulation, leading to cancer development. [(20).]

**G) Bile acid**

Bile acids are synthesis in the liver. There are four different bile acids like taurocholic acids, taurodeoxycholic acids, tauro—chenodeoxy-cholic acids and tauroursodeoxycholic acid. The most resulting compounds cholic acid and chenodeoxy-cholic acid conjugated to a taurin or glycin molecules. This new compounds called as bile salts. Bile salts are known to destroy the permeability barrier of gastric mucosa and increase mucosal permeability to acids. It may produces direct injury to the surface cells of the stomach and renders gastric mucosa more susceptible to acid injury. [(21)]

**H) Other factors:-**

- Life style factors like - Smoking may increase the risk of relapse of PUD. Smoking is harmful to the gastroduodenal mucosa, and *H pylori* infiltration is denser in the gastric antrum of smokers.
- Hypersecretion of gastric acid (eg., zollinger- Ellison syndrome)
- Viral infection (eg., cytomegalovirus)\
- Radiation
- Chemotherapy (eg, hepatic artery infusion)
- The risk of upper GI tract bleeding may be increased in users of the diuretic spironolactone or serotonin reuptake inhibitors with moderate to high affinity for serotonin transporter. [(5)]

**New strategies for prevention of gastric ulcer disease:-**

**I) CONVENTIONAL DRUG THERAPY:-**

*Reduction of acidity:*

**Antacids** like sodium bicarbonate, calcium carbonate, magnesium salts, aluminium hydroxide. Sodium bicarbonate

may produce carbon dioxide, causing belching and distension; excess can cause metabolic alkalosis; best avoided in renal and cardiovascular disease. Calcium carbonate may cause acid rebound; excess may cause hypercalcaemia and constipation.

• $H_2$-receptor antagonists are effective in healing both gastric and duodenal ulcers. A four-week course is usually adequate. $H_2$-receptor antagonists like cimetidin, ranitidine widely used.

• Proton-pump inhibitors like omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole. The proton-pump inhibitors inhibit gastric acid by blocking the $H^+/K^+$-adenosine triphosphatase enzyme system.

• muscarinic blockers (pirenzapine).

*Mucosal protection:*

• Misoprostol (also reduces gastric acid secretion) Misoprostol is a synthetic analogue of prostaglandin E1 which inhibits gastric acid secretion, causes vasodilatation in the submucosa and stimulates the production of protective mucus. Pregnancy (or desired pregnancy) is an absolute contraindication to the use of misoprostol, as the latter cause's abortion.

• Bismuth chelate (also toxic to H. pylori) Colloidal tripotassium dicitratobismuthate precipitates at acid pH to form a layer over the mucosal surface and ulcer base, where it combines with the proteins of the ulcer exudate. This coat is protective against acid and pepsin digestion. It also stimulates mucus production and may chelate with pepsin, thus speeding ulcer healing.

• sucralfate

• carbenoxolone (rarely prescribed).

Sucralfate has been recommended for use in pregnancy in the USA, and this is rational as it is not systemically absorbed. [(5)]

**II) Antidepressant drugs used in the ulcer**

Tricyclic antidepressants (TCA) are particularly useful in the treatment of endogenous depression.Many TCA have been evaluated for their antiulcer effects. Imipramine and amitryptiline, two TCAs have been reported to prevent gastric ulcer.

**Hakan Dursun** et al reported that fluvoxamine has antiulcer effects. Indomethacin causes gastric damage by not only inhibiting cyto-protective PG synthesis, but also by affecting oxidant and antioxidant mechanisms, such as GSH, NO, MPO, and MDA. Fluvoxamine appears to exert its antiulcer effects by activation of antioxidant mechanisms and inhibition of toxic oxidant mechanisms in stomach tissues. [(22)]

**T. Sen et al** investigated effect of dothiepin on gastric ulceration. Dothiepin, a tricyclic antidepressant, significantly inhibited the development of gastric ulcers induced by alcohol, aspirin, indomethacin and Shay's pyloric ligation. Antisecretory studies in pyloric ligated rats revealed that the drug at a dose of 100 mg/kg significantly reduced total acidity, gastric output and protein content. [(23)]

**Halis Suleyman et al.** investigated the antiulcer activities of tianeptine, trazodone, and venlafaxine on indomethacin-induced ulcers in rats; and evaluated tianeptine's effects on oxidant and antioxidant parameters in rat stomach tissue. The results show that trazodone and venlafaxine did not prevent indomethacin-induced ulcers. Tianeptine, however, decreased indomethacin-induced ulcers significantly at all doses used (6, 12, and 25 mg/kg). [(24)]

**Bickel M. et al.** tested the effectiveness of the antidepressant agents nomifensine and amitriptyline on various ulcer models. Oral application of 3 mg/kg nomifensine resulted in a 50% decrease of stress ulcers produced by water immersion. Using an immobilisation ulcer model the ID50 of nomifensine was calculated to be 1.89 mg/kg p.o. Amitriptyline proved to be less active in both models. Thus peripheral gastric effects of nomifensine could be ruled out; its antiulcer properties may be of central nervous origin. Affecting noradrenergic mechanisms in the hypothalamus could possibly play an important role. [(25)]

**III) Grape Seed Extract and Procyanidins**

Makoto Saito,Hiroshi Hosoyama et al evaluated effect of grape seed extract on ulcer . It is known that procyanidins, which are contained in grape seeds, are antioxidative and have certain biological effects. Antiulcer activities of grape seed extracts (GSE-I and GSE-II) and procyanidins were investigated using rats. GSE-I (with low flavanol content), GSE-II (with high flavanol content), and procyanidins at a dose of 200 mg/kg strongly inhibited the stomach mucosal injury induced by 60% ethanol containing 150 mM hydrochloride. The mechanism of antiulcer activity may be the protection by radical scavenging activity on the stomach surface against radical injury induced by HCl/EtOH solution and the defense action of procyanidins covering the stomach surface by their strong ability to bind protein. [(26)]

**IV) Immunosuppressive agent like Tacrolimus produced positive effect on peptic ulceration**

**Shailja sood et al** reported activity of tacrolimus in pyloric

ligation induced peptic ulcer in rats.

Tacrolimus is a potent immunosuppressive drug that has been widely used for organ transplantation and atopic dermatitis. The ulcer protective activity of tacrolimus may be through its antisecretory, antioxidant and anti-inflammatory action and its inactivation of immune cells.

Tacrolimus binds to the FK506 binding protein and this tacrolimus-FKBPcomplex interacts with calcineurin which inhibits the catalytic activity of calcineurin, this activity of tacrolimus explored for its antiulcer potential.

This study showed that the immunosuppresing agent tacrolimus prevented PL induced gastric ulceration in rats and demonstrated that this agent also potentially alters the levels of gastric volume, total and free acidity, ulcerative index and biochemical parameters. [27]

**V) Gastroprotective effects of Nitric Oxide**

Gastroprotective effects of nitric oxide may be due to it is rapid reactivity with various oxygen species in the biologic system. That also causes additional decrease in acid secretion. Nitric oxide inhibits gastric secretion by suppression of histamine release from enterochromaffin-like cells. [28]

Use of nitro-vasodilators in animal studies may reduce the NSAID-associated gastric damage, but nitric oxide may also inhibit platelet aggregation. The results from a large case-control study, Lanas et al. suggested that nitro-vasodilators are associated with a decreased risk of ulcer. Dykhuizen et al. reported that chemical sources of NO and peroxynitrite have a direct toxic effect on H. pylori. [29, 30]

**VI) Role of growth factor in gastric ulcer healing (VEGF)**

Growth factors are local polypeptide hormones that modulate the rate of cellular proliferation of their target cells. Vascular endothelial growth VEGF is released by endothelial cells themselves, and by platelets. Indeed, release of VEGF is likely to be a primary mechanism through which platelets contribute to ulcer healing.

Jones et al Showed that the expression of VEGF increases during healing in experimental models of acute gastric damage, while the pre-treatment of rats with a single dose of oral VEGF exerted a protective effect against acute ethanol damage in the gastric mucosa. [31]

Szabo et al. found that the daily administration of VEGF promote the healing of cysteamine duodenal ulcer in rats by stimulation of angiogenesis and formation of granulation tissue. [12]

Wozniak et al. have been determined the role of vascular endothelial growth factor (VEGF) administered intraperitoneally in the gastroprotective response to stress-number of blood vessels was observed when VEGF was injected 24 h before stress exposure. Gastric secretion, depth of ulceration and ulceration index decreased significantly after VEGF application. The results demonstrate the gastroprotective effect of VEGF on stress-induced ulceration. [32]

TGF-α is released locally in the gastric mucosa, particularly when the mucosa is exposed to topical irritants. TGF-α includes the stimulation of the restitution and proliferation of mucosal cells, gastroprotection, vasodilatation, gastric adaptation to noxious substances, healing of acute and chronic lesions and inhibition of gastric acid secretion.

Vongthavaravat et al. have concluded that: 1) TGF- α caused dose-dependent gastroprotection against ulceration, 2) TGF-α mediates gastric mucosal protection is prevented by capsaicin-induced sensory denervation and, 3) stress-induced injury was associated with significant reduction in gastric content of TGF-α. [33]

**VII) COPPER COMPLEXES AS ANTIULCER AGENTS:-**

Sorenson pioneered the research on the activity of copper complexes including the copper nicotinate in ulcer. [34]

Copper is mobilized from the liver in a complex form with ceruloplasmin, albumin and amino acids. These complexes facilitate copper absorption, tissue distribution and utilization. The anti-inflammatory action of copper complexes is an important activity of their antiulcer effect achieved by their intermediary role as a transport form of copper-dependent enzymes. [35]

Copper effect enzyme activity both as a cofactor and a prosthetic component of several cuproenzymes controlling oxidation-reduction reactions including cytochrome c- oxidase, superoxide dismutase. [36]

**VIII) PROBIOTICS**

Probiotics are live micro-organisms, which could interact with the GIT. Probiotics are consisting of Saccharomyces boulardii yeast or lactic acid bacteria. E.g. lactobacillus and bifidobacterium species. The probiotics have ability to eradicate the h. pylori infection. [10]

The yeast and lactobacilli found in yogurt secrete soluble factors like some organic by-product of fermentation capable of killing H. pylori infection. [37]

Probiotics also stimulate the gastro-intestinal immune system. [38]

**IX) HERBAL DRUGS**

Tuorkey et al reported antiulcer activity of curcuma longa. Curcumin, a yellow colour compound has antiulcer activity arise from its antioxidant activity. [5]

Curcumin also showed immense therapeutic potentials against H. pylori infection as it was highly effective in eradication of H. pylori from infected mice as well as in restoration of H. pylori induced gastric damage. (39)

P. Thirunavukkarasu, L. Ramkumar and T. Ramanathan reported Anti-ulcer Activity of Excoecaria agallocha bark on NSAID-induced Gastric Ulcer in Albino Rats.The present study showed that pretreatment with the leaf extract (both hot water and cold water) of E. agallocha caused a beneficial effect on NSAID induced gastric ulcer in rats as evidenced by the reduction in the ulcer score. (40)

Raju.D et al evaluated the Anti-ulcer activity of methanolic extract of Terminalia chebula fruits in experimental rats. The extract shows protection against characteristic lesions produced by ethanol administration this antiulcer effect of METC may be due to both reductions in gastric acid secretion and gastric cytoprotection. **(41)**

S. PANDIT et al evaluated anti-ulcer effect of shankha bhasma in rats. Shankha bhasma caused significant reduction in ulcer index ($P<0.001$) in both the indomethacin and cold restraint models Shankha bhasma induced dose dependent protection against experimental gastric ulcers. (42)

E.M. Galati et al studied Antiulcer activity of Opuntia ficus indica (L.) Mill. (Cactaceae). In Sicily folk medicine, O.ficus indica (L.) Mill. Cladodes (modified stems in cacti) are used for the treatment of gastric ulcer. From the results of this work, it is evident that acute administration of O. ficus indica lyophilized cladodes generally maintains the cytoarchitecture of the gastric mucosa in the normal arrangement of its components. (43).

S.S. Deshpande and G.B. Shah evaluated antiulcer activity of tephrosia purpurea in rats. Results suggest that aetp (aqueous extract of tephrosia purpurea) possesses significant antiulcer property which could be either due to cytoprotective action of the drug or by strengthening of gastric and duodenal mucosa and thus enhancing mucosal defense. (44)

C. V. Ukwe1 et al. Studied antiulcer activity of roots of zapoteca portoricensis (fam. fabiaceae) The roots of Zapoteca portricensis is a common remedy in the treatment gastrointestinal disorders used by tradomedical practitioners in Eastern Nigeria. This study had shown that roots of Zapoteca portoricensis possess antiulcer activity against alcohol and indomethacin ulcers in rats. (45)

V.I.Borikar et al reported the Study of Antiulcer Activity of Bauhinia racemosa (stem bark) Lam in rats it was confirmed that the plant Bauhinia racemosa has significantly decreased the no of ulcers in Paracetamol induced gastric ulcers in rats. This may due to the presence of flavonoids which may reduce the gastric secretion and peptic activity and prevent the formation of gastric ulcer. (46)

Raghuveer Gupta et al reported anti-ulcer effect of root of Curcuma zedoaria in rats. Curcuma zedoaria is thechief ingredient in several Unani preparations used to treat peptic ulcer. Therefore antiulcer activity of root of C.zedoaria was studied in pyloric-ligated albino rats. This study justifies the use of C. zedoaria in various formulations of Unani system of medicine for the treatment of peptic ulcer. (47)

M. A. Abdulla, F. H. AL-Bayaty, L. T. Younis and M. I. Abu Hassan reported Anti-ulcer activity of Centella asiatica leaf extract against ethanol-induced gastric mucosal injury in rats. (48)

**CONCLUSION:-**

Ulcer disease is one of the main prevalent still unresolved medical problems that face many patients. After discovery of H.pylori infection as a causal factor, various researches are done in that field. There are many causal factors in which very few reports are available like bile acid, oxidative stress, and apoptosis. Bile acids have strong preventive effect against overgrowth of intraluminal bacteria but very few data are available on these.

Due to relapses after cessation of treatment, further search for curative and safe agents are going on. Probiotics, copper complexes, nitric oxide are new approaches for the treatment of ulcer disease. Data revealed that they have antiulcer activity. Reports suggested that many herbal drugs produced positive results in ulcer treatment in rats or mice. The present review summarizes some causal factors that help in understanding of pathogenesis of ulcers and various treatments that can be further investigated to achieve safe and curative agents for ulcer treatment.

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