Study of Some Causal Factors that Help in Understanding of Pathogenesis of Ulcers

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Abstract:*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. In this paper, we discuss some causal factors that help in understanding of pathogenesis of ulcers*

Keywords:**Ulcer, Gastric, Mucosal, duodenum, Esophagus, Disease.**

1. Introduction

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) ingestion is associated with erosions, type C gastritis, ulceration, interference with ulcer healing, complications and injury to the small and large intestine. 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 degrees of protection afforded by (1) the gastro-duodenal mucosal barrier and (2) the neutralization of the gastric acid by duodenal juices. The defect in defensive protectors like bicarbonate, mucus is first step towards the ulcer formation than other causative factors like acid, pepsin.

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 diseases due to recurrence after cessation of the treatment. In conventional therapy many antiulcer drugs are the there, such as H 2 receptor antagonists, proton pump inhibitors and cytoprotecatants but all these drugs have side effects and limitations.

For H.Pylori infection, now a days, the most effective proven treatment comprises of a 2-weeks course called "triple therapy" involves taking who antibiotics to kill the bacteria and either an acid suppressant or gastric epithelial lining shield. Ulcer associated with the NSAIDs remains a major problem which has not been resolved through introduction of selective inhibitors of COX2. 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.

2. Distribution of dupA cluster and allelic form of dupA in Indian population

The novel virulence factor, dupA gene is homologous to virB4 which is a component of type IV secretion system (T4SS). This T4SS is located in the plasticity region and it has been proposed that this dupA gene is associated with DU (Lu et al., 2005). However, the role of dupA as a virulence marker is still controversial (Arachchi et al., 2007, Schmidt et al., 2009, Queiroz et al., 2011, Hussein et al., 2010, Douraghi et al., 2008, Argent et al., 2007, Alam et al., 2012). Although recent meta-analysis showed that dupA was associated with DU (Shiota et al., 2010). Recently it has been reported that there were frameshift mutation which created premature stop codon and may have a considerable effect on protein expression or function (Gomes et al., 2008, Hussein et al., 2010, Queiroz et al., 2011, Moura et al., 2012, Takashi et al., 2012).

It was confirmed that strains having mutated dupA gene were not able to produce intact DupA protein. In our study, we have found that the intact dupA gene without any mutation was 13/35 (37.1%) in Indian population, which was consistent with the finding of Hussein et al., (2012), where they have showed that the intact dupA gene was 11/33 (33%) and called the intact dupA gene as dupA1. However, our result showed that intact dupA without frameshift mutation was more prevalent in DU than NUD, consistent with the finding of other studies (Gomes et al., 2008, Moura et al., 2012,, Queiroz et al., 2011, Hussein et al., 2012) which reflects that the detection of dupA by PCR is not enough to characterize an intact dupA because frameshift mutation is common along the length of gene, so PCR as well as sequencing is must for the detection of intact dupA gene. Here, we propose the use of the primer walking methodology to sequence the complete dupA gene to search for frameshift mutations that create stop codon and to exclude possible false-positive dupA strains from the analyses. All the strains we studied here for the analysis of frameshift mutation by sequencing had the jhp0917 and jhp0918 genes as well as the C insertion after the position 1385 of the jhp0917. We found that all strains had the „A" insertion at the 3' end of dupA (after position 1733) which was consistent with the finding of Hussein et al. (2010) that extend the product to 1884 bp that, characterizes the dupA1 strains. We found that there was frameshift mutation due to deletion of nucleotides at different position of dupA gene in different strains that leads to a truncated dupA gene. The full sequenced data of H. pylori revealed that the length of the dupA depends on the strains; dupA of strain Shi470 is approximately 600 bp longer than that of strain J99 owing to the extension of the 5′ region of dupA (Kersulyte et al., 2009, 2010). Strains Gambia94/24 and J99 are chimera in comparison with other strains. The recombination point is located at the position 67 bp from the start codon of jhp0917 of J99. It is not clear whether the evolution of dupA is related with this 96 chimera or not. In all previous studies, the 5′ region has not been taken into account in investigating the importance of dupA. In 2012, Takashi et al first reported about the existence of additional 600bp in the 5' region of dupA gene in some Okinawa strains that extend the length of dupA gene to 2.5kb and classified the dupA gene into two alleles: long type and short type dupA gene and proposed that long type dupA was significantly associated with gastroduodenal diseases rather than short type dupA. We conducted the studies on the presence of this addition length that distinguish dupA into long type and short type dupA with primer designed from the full genome sequenced Indian strain SNT49 and found that both form of dupA alleles was present in almost equal proportion and there was no significant association of either long type or short type with diseases outcome but the prevalence of long type as well as short type are more in DU than NUD among isolates of Indian population (table 5.8) which was inconsistent with the finding of Takashi et al., 2012. In addition, we found that frameshift mutation in long type and short type dupA was 9/18 (50%) and 13/17 (76.4%) respectively which was inconsistent with previous studies (Takashi et al., 2012). The intact long type dupA was more prevalent in DU patients then in NUD. Interestingly, all four intact short type dupA was DU samples. The intact long type dupA and short type dupA gene without frameshift mutation might produce functional dupA protein. In contrast, non-intact long-type dupA may not produce functional DupA protein. This might be the reason why the importance of dupA on clinical outcomes was conflicting in different studies. It is necessary to examine whether intact long-type dupA strains can induce the inflammation or not in the future study. The six vir genes homologues (virB8, virB9, virB10, virB11, virD2 and virD4) around the dupA gene called dupA cluster formed a novel putative T4SS (tfs3a) which plays a pathogenic role like other T4SS (Kersulyte et al., 2009). Our observations suggest that only intact dupA positive strains that form a novel T4SS might be involved in gastroduodenal diseases. In Indian population, the prevalence of complete intact long type dupA cluster without frameshift mutation was more prevalent in DU then NUD which was consistent with the finding of Jung et al. (2012), where complete dupA cluster (possessing dupA and all adjacent vir genes) was significantly associated with DU in the United States (Jung et al., 2012). Interestingly, complete intact short type dupA without frameshift mutation was only 97 strain and that was DU sample. A complete intact dupA cluster might be important in promoting DU formation, just as an intact cagPAI is thought to be important in H. pylori related diseases (Ali et al.., 2005, Ikenoue et al., 2001). dupA gene and all 6 adjacent vir homologues encodes the protein that act similarly to the cagPAI and T4SS of Agrobacterium tumefaciens (Backert et al., 1998, Vergunst et al., 2000). Like cagPAI, dupA cluster might responsible for the translocation of some toxin to the host epithelial cell. Additionally, intact

dupA without frameshift mutation should be detected by measuring intact dupA protein using Immunoblotting techniques. The intact long type as well as intact short type dupA gene might produce a functional dupA protein. Further study from other geographic area will help to elucidate the importance of intact long-type and short type dupA and complete dupA cluster. Of vir proteins encoded by vir gene homologues in the dupA cluster, VirB8, VirB9, and VirB10 are thought to form a membrane traversing transporter channel, and VirB4, VirB11, and VirD4 may be localized to the inner bacterial membrane and encode proteins with ATPase activity, similarly to cag PAI and T4SS of Agrobacterium tumefaciens (Backert et al., 1998, Vergunt et al., 2000). In A. tumefaciens, the VirD4 protein links the T-DNA complex directly to the exporting membrane channel in Ti-plasmid and conjugative plasmid DNA transfer systems, and VirD2 plays an important role in carrying nuclear targeting signals and mediating the transport of the transferred DNA (T-DNA) complex into the nucleus, where the T-DNA integrates into the plant cell genome (Backert et al., 1998, Vergunt et al., 2000). Interestingly, dupA cluster has virD2 gene that is not in the cag PAI and ComB T4SSs. A complete dupA cluster might be associated with normal bacterial conjugation processes and/or the transfer of DNA to infected gastric epithelial cells through T-DNA transport. In addition, like CagA that is injected into the host epithelial cells by cag PAI, the dupA cluster might be responsible for transport of some new effectors to the host cells. Based on the Phylogenetic tree of dupA gene, there was formation of two different clusters. The first group designated as “groupI”, composed of two clusters, East Asian cluster comprised of 10 strains, 5 strains from Japan and 5 strains from China and Indian cluster composed of 6 strains from different parts of India. The second group was designated as “GroupII”, called European cluster comprised of 7 strains, 5 strains from Brazil and one strain from Colombia and one from United Kingdom. Four strains 9368, AB21, AB31 and AB43 from United Kingdom have a similarity with Indian strains so these four strains clustered together with Indian cluster. This data showed that distribution of dupA gene from Indian population is somehow different from distribution of other virulence factors like cagA and vacA. These two most important virulence factors form two different clusters, first one is 98 East Asian and the second one is Indian and ethnic European cluster (Mukhopadhyay et al., 2000) but in this study, the dupA gene from Indian population is showing similarity with the dupA gene from East Asian strains and distinct from Western strains. The exact reason for this different cluster of dupA is not known yet fully but the possibility is that as this gene is found in hypervariable region so anyhow by recombination the plasticity region of H. pylori get exchanged or intermingled with East Asian strains. However, there is a need of independent confirmation from other parts of India to establish a word wide accepted relationship of virulence factor dupA with East Asian and western countries.

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

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), which secrete large quantities of pepsinogen; and (3) pariental (or oxyntic) cells, which secrete hydrochloric acid and intrinsic factor.

Gastric parietal (oxyntic) cells secrete isotonic hydrochloric acid. The parietal cells secretion is an isotonic solution of essentially pure HCl. The PH 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 (HCO3-) is exchanged wit 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 membrance 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.

Hydrochloric acid is secreted by the parietal cell, which contain receptors for histamine, gastrin, and acetylcoline. 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 sever peptic ulcer disease.

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

The main goal for protection of the gastric mucosa from gastric acid is pharmacologica control of gastric acid secretion. 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 modulated cell-cell and cell extracellular matrix interaction. Their expression is regulated by several cytokines and local hormones.

4. 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.Chronic use of NSAID's suppresses mucosal prostaglandin synthesis. Prostagalandin 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. At high does asprin 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. NSAID's induced ulcers achlorhydric individuals has contributed the belief that acid is not involved in the pathogenesis of these lesions.However, by inhibition of prostaglandin synthesis, it increases the gastric acid secretion. Acids may contribute to NSAIDS induced ulcer formation by several ways like. Acid can inactivated growth factors that are important for the maintenance of mucosal integrity. Since these growth factors are acid labile. Acid and convert superficial injury to deeper mucosal necrosis.
A high dose of famotidin (40 mg twice daily) and omeprazol could significantly reduce the incidence of NSAIDs induced ulcer.

5. Incidence of Apoptosis

Apoptosis is cell dying process. In this, process goes through defined morphological change that involvechromath 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. 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. Disturbance of this balance could result in either cell loss, leading to mucosal damage and ulcer formation, or cell accumulation, leading to cancer development.

6.Prevention of Gastric Ulcer

New strategies for prevention of gastric ulcer disease

6.1 Conventional Drug Therapy

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

6.2 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 submuscosa and stimulates the production of protective mucus. Pregencey (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 tripotassiumdicitratobismuthate precipitates at acid pH to form a layer over the mucosal surface and ulcer base, where it combines with the proteins of the ulcer exudates. This coat is protective against acid and pepsin digestion. It also stimulates mucus production and may chelate with pepsin, thus speeding ulcer healing.

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

6.3 Antidepressant Drugs used in the Ulcer

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

HakanDursun et al reported that fluvoxamine has antiulcer effects. Indomethacin causes gastric damages by not only inhibiting cyto-protective, such as GSH, NO, MPO, and MDA. Fluvoxamine appears to exerts its antiulcer effects by activation of antioxidant mechanisms and inhibition of toxic oxidant mechanisms in stomach tissues.

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 studied in pyloric ligated rate revealed that drug at a does of 100 mg/kg significantly reduced that acidity, gastric output and protein content.

HalisSuleyman 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 rate 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).

Bickel M. et al. tested the effectiveness of the antidepressant agentsnomifensine and amitriptyline on various ulcer models. Oral application of 3 mg/kg nomifensine resulted in a 50% decreased of stress ulcers produced by water immersion. Using an immobilization 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 hypothanalmus could possible play an important role.

6.4. Grape Seed Extract and Procyanidins

Makoto Saito, Hiroshi Kosoyama 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) andProcyanidins 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 scavengine activity on the stomach surface against radical injury induced by HCI/EtOH solution and the defense action of procyanidins covering the stomach surface by their strong ability to bind protein.

6.5 Immunosuppressive Agent LikeTacrolimusProduced Positive Effect on Peptic Ulceration

Shailijasood 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 tacrolimusFKBPcomplex interacts with calcineurin which inhibits the catalytic activity of calcineurin, this activity of tacrolimus explored for its antiulcer potential.This study showed that the immunosuppressing 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.

6.6 GastroprotectiveEffects 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 enterochromaffinlike cells.

Use of nitro-vasodilators in animal studies may reduce the NSAID-associated gastri 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. Dykhizen et al. reported that chemical sources of NO and peroxynitrite have a direct toxic effect of H. pylori.

6.7 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 cell 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 increased during healing in experimental models of actue gastric damage, while the pre-treatment of rats with a single does of oral VEGF exerted a protective effect against acute ethanol damage in the gastric mucosa. 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. 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 and ulceration index decreased significantly after VEGF application. The results demonstrate the gastroprotective effect of VEGF on stress-induced ulceration. 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 and secretion. Vongthavaravatet. al. have concluded that: 1) TGF-α caused dose-dependent gastroprotection against ulceration, 2) TGF- 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.

6.8 Copper Complexes as Anti-Ulcer Agents

Sorenson pioneered the research on the activity of copper complexes including the copper nicotinate in ulcer. 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 acitivity of their antiulcer effect achieved by their intermediary role as a transport form of copper-dependent enzymes. 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.

6.9 Probiotics

Probiotics are live micro-organisms, which could interact with the GIT, Probiotics are consisting of Saccharomyces boulardii yeast or actic acid bacteria e.g. lactobacillus and bifidobacterium species. The probiotics have ability to eradicate the h.pylori infection. The yeast and actobacilli found in yogurt secrete soluble factors like some organic by product of fermentation capable of killing H.pylori infection. Probiotics also stimulate the gastro-intestinal immune system.

6.10 Herbal Drugs

Tuorkey et al reported antiulcer activity of curcuma longa curcumin, a yellow colour compound has antiulcer activity arise from its antioxidant activity.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. P.Thirunavukkarasu, L.Ramkumar and T.Ramanathan reported Anti-ulcer Activity of Excoecariaagallocha 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. Raju. D et. al. evaluated the Anti-ulcer activity

of methanolic extract of Terminaliachebula 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. S.Pandit et al evaluated anti-ulcer effect of Shankhabhasma in rats. Shankhabhasma caused significant reduction in ulcer index ($P < 0.001$) in both the indomethacin and cold restraint models Shankhabhasma induced dose dependent protection against experimental gastric ulcers. E.M.Galati et al studied Antiulcer activity of Opuntiaficusindica (L.) Mill. (Cactaceae). In Sicily folk medicine, O. Ficus India (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.ficusindica lyophilized cladodes generally maintains the cytoarchitecture of the gastric mucosa in the normal arrangement of its components. S.S. Deshpande and G.B. Shah evaluated antiulcer activity of tephrosiapurpurea in rats. Results suggest that aetp (aqueous extract of tephrosiapurpurea) 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. C.V. Ukwe1 et al. Studied antiulcer activity of root of zapotecaportoricensis (fam. fabiaceae). The roots of Zapotecaportricensis is a common remedy in the treatment gastrointestinal disorders used by tradomedical practitioners in Eastern Nigeria. This study had shown that roots of Zapotecaportoricensis possess antiulcer activity against alcohol and indomethacin ulcers in rats. 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 gstric secretion and peptic activity and prevent the formation of gastric ulcer. Raghuveer Gupta et al. reported anti-ulcer effect of root of Curcuma Zedozaria in rats. Curcuma Zedoaria is the chief 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. M.A.Abdulla, F.H.Al- Bayaty, L.T. Younis and M.I. Abu Hussan reported Anti ulcer activity of Centella Asiatic leaf extract against ethanol-induced gastric mucosal injury in rats.

7. Conclusions

Finally we say that 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 may herbal drugs produced positive results in ulcer treatment in rats or mice. The present aper 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. The growth of dupA mutant H. pylori was less as compared to their respective wild type strains. The exact reason of this reduced growth

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