



A REVIEW ON PEPTIC ULCER AND ITS MANAGEMENT OVERVIEW, PROGRESS AND TRAETMENT

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ABSTRACT

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Peptic ulcer diseases are commonly occurring disease in the World wide, around 0.10% - 0.19% peoples are suffering with PUD's annually and they identified 0.03% - 0.17% patients having PUD's during their treatment for other disorders. The main pathology involved in the formation of gastric ulcer is imbalance occur in the mucosal layer present in the stomach mainly due to over secretion of Hydrochloric acid and Pepsin which are regarded as aggressive factors and others are decreased-blood flow, formation of Prostaglandins and bicarbonates and mucus (defensive factors).The causative chemical factors of gastric ulcer and duodenal ulcers are regular intake of NSAID's, Acetylsalicylic acids and H. pylori bacteria. Certain peoples are also suffering from peptic ulcer due to heavy consumption of alcohol and smoking habits. Stress is also one of the cause for development of acid related disorder. H-K⁺ ATPase enzyme is the targeting enzyme other than by inhibiting the receptors to inhibit formation Hcl by concentrating on pumping of proton into lumen of the stomach, because it is the last step for formation of acid in stomach. Decreased production gastric acid which gives chance to attack opportunistic and Osteoporotic condition due Hypomagnesaemia, Vitamin B12 deficiency. Present world depends on herbal medicines for the treatment peptic ulcer because synthetic drugs will cause most severe side effects and will cause toxic to various organs. Peoples are using herbal medicines as a home remedy to manage acid production. This review highlights the cause, clinical symptoms and management of peptic ulcer.

INTRODUCTION:

Erosion of mucus layer of stomach or layer of skin which forms lesions called Ulcers. Process of ulcer healing is slow compared to other disorders. Ulcers which are present in the external surface of the body are called Leg and foot ulcers and which are invisible i.e., inside body are called as Peptic ulcers, which are present in internal lining of stomach or upper part of small intestine. Arterial ulcers, Venous ulcers, Mouth ulcers, Genital ulcers and Peptic ulcers are the different types of ulcer. Among these Peptic ulcers are commonly

occurring acid related disorder. [1] Finding of peptic ulcer disease in the region of stomach and duodenum was started since from last 20 years due to emergence of newer technology which is helpful to study gastric mucosa region. But in 19th century due to lack of technology there was no proper findings of pathological factors which are involving in acid related diseases at that time Chalk, Charcoal and Slope diets spend their time on to find out symptomatic relief from Gastric ulcer and duodenal ulcer mainly on dyspepsia.

In 17th century Chalk and Pearl juleps performed experiments on infants gastric disorder and they gave title in 17th century “De imbecillitate ventriculi” which states that Dyspepsia is the main causative factor for gastric ulcer. [3] Peptic ulcer can be grouped into Gastric ulcer and Duodenal ulcer based on their origin. Usually Peptic ulcer occur as diameter of about 0.5 cm which is penetrating around mucosal layer of the stomach or duodenal epithelial layer. Origin of Gastric ulcers takes place lesser curvature of the stomach and Duodenal ulcers found in bulb of duodenum where this area is exposed to more gastric content. 10% of present world's population is suffering with acid related diseases. The main pathology involved in the formation of gastric ulcer is imbalance occur in the mucosal layer present in the stomach mainly due to over secretion of Hydrochloric acid and Pepsin which are regarded as aggressive factors and others are decreased-blood flow, formation of Prostaglandins and bicarbonates and mucus (defensive factors). The causative chemical factors of gastric ulcer and duodenal ulcers are regular intake of NSAID's, Acetylsalicylic acids and H.pylori bacteria. Certain peoples are also suffering from peptic ulcer due to heavy consumption of alcohol and smoking habits. Stress is also one of the cause for development of acid related disorder. [8]

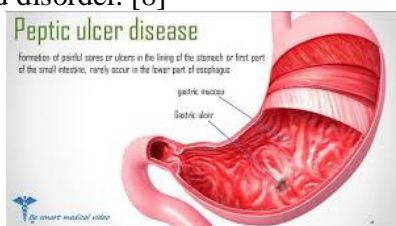


Fig 1: Peptic ulcer formation

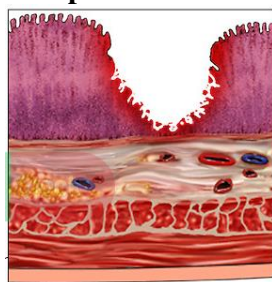


Fig 2: ulcerated area of stomach lining

EPIDOMOLOGICAL SURVEY

According to physician's diagnostic survey,

Peptic ulcer diseases are commonly occurring disease in the World wide, around 0.10% - 0.19% peoples are suffering with PUD's annually and they identified 0.03% - 0.17% patients having PUD's during their treatment for other disorders. Different country peoples are suffering with peptic ulcer disorder throughout the wold wide approximately about 90% which shown in the below chart [12]

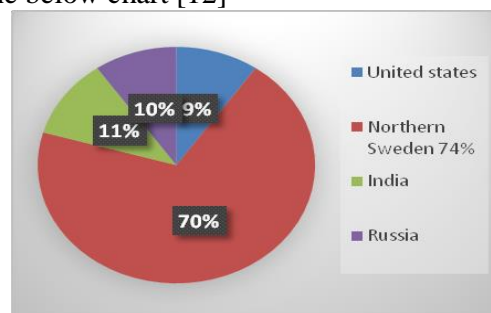


Fig 3: At present epidemiological status of peptic ulcer disease across the world

According to clinical trial data survey, Department of Surgery, R.G.Kar Medical College and Hospital they made epidemiological survey upto 1year on peptic ulcer survey during Jan 2016-June2017 and they reported occurrence of peptic ulcer diseases based on age groups. [12] As we know diseases which are occurred through microbes are very difficult to cure. One of the main cause for occurring Gastric ulcer is presence of Helicobacter pylori in the stomach. This is the only one organism which favours acid content and forms gastric ulcer and duodenal ulcer of about 80% and 90% respectively. Western countries peoples are more susceptible to duodenal ulcer compared to gastric ulcer of about forth folds. Before H.pylori infection was more in western side due to lack of hygiene but at present decreased incidence H.pylori infection can be seen because of high maintenance hygienic. But if we look in Asian countries especially in Korean peoples they are more susceptible to develop gastric ulcers because of H.pylori infection when compared duodenal infection due to lack of hygiene.

One of physician from Sweden revealed that at present occurrence of PUD's in Sweden population is like asymptomatic.

Clinical complications Internal

Haemorrhage: it is one of the acute complications occurs in 15%-20% ulcers. Internal haemorrhage is one of the factor which cause mortality and morbidity especially at the age of 65yrs. Chronic complication leads to ulcer perforation and formation of stricture.

1. Infection: peoples who are having Peptic ulcers especially due to H.pylori bacteria are more susceptible to get other infections in stomach because of deep perforation made by H.pylori bacteria.
2. Obstruction: Presence of peptic ulcer can cause vomiting because ulcer will act as a barrier for passage of food through digestive tract. Due to this weight loss can also be seen.

Symptoms

- Abdominal pain
- Vomiting
- Appearance of dark blood in stools
- Changes takes in Apatite
- Weight loss
- Feels like faint
- Breathing problems
- Nausea
- Heart burns
- Feeling of belching [4]

General mechanism of action Acid production in stomach : Daily stomach will produce around 2.5L of gastric juice that is why inside of the stomach is acidic in nature of about pH 1-2. There are two barriers present in the stomach i.e oesophageal sphincter which act as a barrier between acidic stomach and oesophagus and another is pylorus sphincter which act as a barrier between stomach and the duodenum. Hydrochloric acid is secreted in the stomach by parietal cell. Stomach cell consist of three layers mucosa, submucosa and muscralis. Stomach cells contains parietal cells which secrete HCL, enterochromaffin cells which secrete histamine and G-cells secrete Gastrin these three cells constitute to stimulate the release of HCL into the stomach. Stomach cell also contains D-cell which secrete Stomatostatin which inhibit the secretion of HCL by acting on G-cell, Enterochromaffin

cells and parietal cells. One more important cells present in the stomach is Mucus cell which secretes mucus to protect the stomach from acidic environment and CHIF cell which secretes pepsinogen to digest proteins.

Regulation of HCL in stomach

1. Parietal cells secrete HCL into the lumen of the stomach through H⁺/K⁺ ATPase pumps.
2. ECL liberates histamine which bind to histamine receptors present in the surface of Parietal cells which stimulate to release HCL into the lumen of the stomach.
3. G-cell releases gastrin into the blood stream which in turn bind to the gastrin receptors present on the ECL which stimulate parietal cells to release HCL.
4. The vagus nerve especially sympathetic nerve innervating in the stomach area will secrete acetylcholine which binds to musurinic receptors present on the surface the parietal cells and ECL promotes the secretion of HCL.
5. But stomatostatins and Prostaglandins E2 and PGI2 inhibits the secretion of HCL by acting on prostaglandin receptors present in the parietal cells. Another prostaglandin receptor present in the mucus cell to release bicarbonates and mucus, when PGE2 and PGI2 act on these receptors mucus cell releases mucus and bicarbonates to neutralize the acid content in the stomach.

Brief Description on individual etiological factors

A] Helicobacter pylori infection: This infection mainly causes acid related disorder especially gastric ulcer, duodenal ulcer and gastric cancer. WHO stated that H.pylori is a similar agent as carcinogen which will leads to develop gastric cancer as Adinocarcinoma and MALT (mucosa-associated lymphoid tissue) lymphoma

Because gastric cancer took 4th place around worldwide and 2nd most common death of population because of cancer. Increased acid production leads to formation of sever inflammation at the region of distal stomach and proximal duodenum calls juxtra-pyloric and duodenal ulcer diseases. [8].H.pylori is a gram negative bacteria which has spiral shape n adapted in acidic nature. It may acquire during childhood and become sever on age. As per epidemiological survey children's in US acquired infection during their childhood but appears with age around 60yrs. These was identified in 50% population of US peoples. Blacks, Asians are more susceptible to H.pylori infection. These bacteria can be cultured by using stools, saliva and even dental plaques. These disease is a type of contaminated disease which can be transmitted from oral to oral and faecal-oral transmission. If we treat H.pylori in earlier stages, it can prevents recurrence of bleeding around >90% of populations. If we treat in initial stages H. Pyloric infection then we can decrease the progression range of MALT lymphoma in the absence of translocation mechanism of genes. Eradication of H.pylori bacteria will prevent occurrence of gastric cancers and inhibits the formation of acute and chronic inflammation in the lining of

Methods for diagnosis of H.pylori infection

Two test methods are using at present to diagnosis the H.pylori infections in humans but actually fundamental therapy is antimicrobial therapy. Invasive method/ Tests

Example: Endoscopy and Histology, Non-invasive method

Example: Serology and Urea breath test [8]

B] ROLE OF NSAID'S IN PEPTIC ULCER

Regular intake of Non-steroidal anti-inflammatory drugs leads to develop gastro duodenal ulcer. NSAID's causes damage to mucosal epithelial layer by various mechanism which includes causing impairment to epithelial

the stomach. [13] Action of H.pylori for ulcer production mainly depends upon location on the stomach

- Antral-predominant infection mainly occur due to increased production of gastrin content which reflects by inhibiting the release of somatostatin leads to hypersecretion of gastric forms pre-pyloric and duodenal ulcers.
- Body-predominant infection occurs due to productions of various interleukins factors leads to gastric atropy and hyposecretion of gastric acid.
- H.pylori bacteria survives in acidic environment in stomach mainly due to presence of Ammonia and enzymes such are Cytotoxic and mucolytic enzymes are helps in erosion of mucosal layer in stomach.
- Development of cancer is possible if the patient having H.pylori infection in stomach.

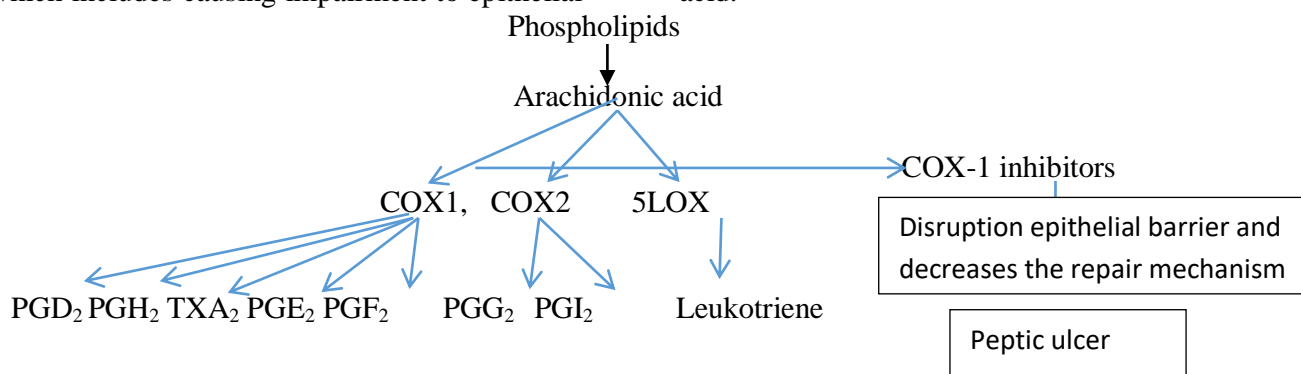
Mode of transmission of H.pylori infection

1. Faecal contamination
2. Gastro-oral
3. Oral-oral

barrier of mucosa, inhibition of Prostaglandins synthesis, decreasing blood flow and suppress the repairment of superficial epithelial layer of the stomach. NSAID's induced gastric ulcer can also be formed due to presence of gastric acid content in the lumen of the stomach and can also leads to internal bleeding. [7]

Examples: Indomethacin, Acetylsalicylic acid etc.

NSAID's Cytotoxic to epithelial cell of stomach (Disrupt the barriers present in the epithelial cells mainly phospholipids and glycoproteins), this enables more exposure to acid.



Treatment

Complete eradication of H. pylori bacteria from the stomach is the primary treatment for peptic ulcer and reducing the regular intake of Analgesics and NSAID's.

1. Eradication H. pylori infection by using antibiotics: if the H. pylori bacteria find in the digestive tract, a physician can prescribe combination of antibiotics such as Amoxicillin (Amoxil), Clarithromycin (Biaxin), Metronidazole (Flagyl), Tinidazole (Tindamax), Tetracycline (Tetracycline HCL) and Levofloxacin (Levaquin). [4]

Eradication of H. pylori bacteria involves different treatment regimens

A] First line treatment regimen for treating H.pylori infection with antibiotics

First line treatment includes three different antibiotic drugs i.e., BID PPI, either of Metronidazole or amoxicillin and clarithromycin. Hence it is called as Standard triple therapy. Usually this therapy should be given 7days but for effective therapy 14days is sufficient to eradicate 4-6% of H.pylori bacteria with less side effects.

Mechanism of action triple regimens of antibiotics

- Clarithromycin binds to 50s ribosomal sub unit of ribosomes which inhibit bacterial protein synthesis leads to bacterial death. This act as a Bacteriostatic agent.
- When Metronidazole enters into bacterial membrane it get solubilizes and forms toxic metabolites which is toxic to bacterial growth. Hence it is having bactericidal action.
- Amoxicillin act as a bactericidal agent which inhibit synthesis of bacterial cell wall.
- BID-PPI will increase the curing of ulcers upto the range of 6-10%.

This standard regimen therapy was following on during 1990's with good success ranging from >80 to >90% of population but it was declined after few years of treatment globally because H.pylori bacteria shows resistance towards clarithromycin treatment.

Resistance towards clarithromycin:

- H.pylori bacteria develops mutation on binding sites of 50s ribosomal which is binding site for clarithromycin for bacteriostatic action
- Efflux of drug from bacteria through

efflux channels and findings of different strains of H.pylori.

- If patient is continuously using macrolide antibiotics are more susceptible to clarithromycin resistance.
- Hence current guidelines established that this triple regimen should not be used in regional levels where clarithromycin resistance is at the range of >15-20%.

Resistance towards metronidazole:

- It is the most common resistance seen around worldwide, bacteria will forms mutations on certain enzymes which is responsible for solubilising metronidazole inside the bacterial membrane and forms inactive.

Resistance towards Amoxicillin's:

- Bacteria forms mutations in the binding site of amoxicillin i.e., penicillin binding site which is needed for bactericidal action for amoxicillin.

If this triple regimen is failed to eradicate H.pylori bacteria from the stomach then we can follow Quadrapole regimen for effective treatment for treating H.pylori infection.

Quadrapole regimen includes bismuth, BID PPI's and two kinds of antibiotics. These regimen should be followed upto 14 days of schedule. Compared to triple therapy quadrapole therapy is showing most compromising efficacy against metronidazole and clarithromycin resistance.

Different studies revealed that mixing of bismuth with clarithromycin or levofloxacin will increase the efficiency of treatment regimens. 14days regimen shows improved eradication of H.pylori bacteria in >90% of population and based on regional wise it showing around 30-40% up to 70-85% of eradication.

Mechanism of action of Bismuth: Bismuth will act as a bactericidal action against H.pylori

Resistance: It's resistance is still not had been reported in the management of peptic ulcer caused by H.pylori infection. But upon continuous usage it will cause severe side effects. [13]

Levofloxacin is used as alternative antibiotics in the eradication of H.pylori as Second line therapy drug for eradication of H.pylori bacteria. It act as bacteriostatic agent by inhibiting topoisomerase-II enzyme which is needed for bacterial sustain and their growth.

During 1st line therapy if a individual develops resistance towards clarithromycin then we can substitute clarithromycin with levofloxacin based on local pattern of resistance. Levofloxacin should not be given patient having a long history on continuous usage of antibiotics because there is a chance to develop early resistance towards levofloxacin regimen. At present world is using more levofloxacin against H.pylori hence Levofloxacin-resistance strains are growing worldwide. This resistance is mainly due to bacterial mutations in DNA gyrase. Alone levofloxacin may produce early resistance so for effective treatment combination with bismuth is essential. . [13]

Tetracycline: this is marketing under Pylera® which is formulated as combined pill includes tetracycline, bismuth and metronidazole. Tetracycline works as bactericidal action by inhibiting bacterial protein synthesis. Bacteria develops resistance by efflux mechanism but tetracycline resistance is low compared to clarithromycin and levofloxacin resistance. Application of this combined pill formulation around is good patient compliance. Tetracycline is considering as 2nd therapy regimen in the eradication of H.pylori infection. . [13]

Drawbacks of continuous usage of antibiotics: chronic usage of antibiotics can cause various adverse side effects which include nausea, vomiting, head ache, stomach ache, diarrhea, constipation and appearance of dark colour in stools.

2. Blocking of acid production: blocking of acid production receptors in the stomach cells can be achieved by using Proton pump inhibitors (PPI's). these PPI's can be given as OTC drugs they are Omeprazole (Prilosec), Lansoprazole (Prevacid), Rabeprazole (Aciphex), Esomeprazole (Nexium) and Pantoprazole (Protonix). [4]

Proton pump inhibitors:

H-K⁺ ATPase enzyme is the targeting enzyme other than by inhibiting the receptors to inhibit formation Hcl by concentrating on pumping of proton into lumen of the stomach, because it is the last step for formation of acid in stomach. Usually in normal state this H-K⁺ ATPase produces gastric acid to cytoplasmic tubular membranes but when it get stimulus from parietal cells due release of histamine and acetylcholine from enterochromaffin cells and muscarinic cells gastric acid will transfers to microvilli of the expanded secretory canaliculus

to release gastric acid. Hence, this forms intense morphological changes in the stomach leads to peptic ulcers. [8]

Proton pump inhibitors are created based on targeting this H-K⁺ ATPase enzyme. Mainly these are formulated in the form of prodrug, which will get activated in inside the stomach due to enzymatic reactions.

Application of Proton pump inhibitors

- PPI's are used in treatment of various acid related disorders especially as combination treatment regimen in the eradication of H.pylori infection inn both gastric ulcer, duodenal ulcer and gastric cancer.
- PPI's are used in the management of Zollinger-Ellison syndrome, Gastroesophageal reflux disease (GERD) and Barrett's oesophagus.

Examples of PPI's: **Timoprazole** was synthesized in 1975 which is a pyridylmethylsulfinyl benzimidazole moiety acting by inhibiting acid secretion. But its use was declined due to some draw backs i.e., for its activation it needs ATPase enzyme with acidic environment so it showed ineffective for treatment of peptic ulcers because it is a acid-activated prodrug. To overcome this in 1989 they invented **Omeprazole** for treatment of gastric ulcers and came to market for humans use. Then they synthesized S-enantiomer of omeprazole for effective treatment they are Lansoprazole, Rabiprazole or Pantaprazole.

Mechanism of action of Lansoprazole, Rabiprazole or Pantaprazole

Actually PPI's are weak basic in nature of pH around 3.8-4.9. Beacuse this weak basic nature they selectively accumulates in the acidic spaces in stomachs of pH 1.0 especially secretory canaliculus which are stimulated by parietal cells. Actually they are prodrug in nature hence in the second step they undergo cleavage to form activated thiophilic reagent which is highly reactive and forms crosslink disulphide bridges with each cysteine's of H,K-ATPase enzyme to inhibit acid secretion into the stomach.

Efficiency of each drug is based binding affinity of each PPI's on respective cysteine moiety and also based on pyridine and benzimidazole substituents.

Tenatoprazole > pantoprazole > omeprazole > lansoprazole > rabeprazole.

Duration of action of PPI's: conversion of

prodrug into active sulfenamide needs acidic environment then blocks the acid secretion. Omeprazole, rabeprazole, pantoprazole, and lansoprazole shows equal potency in blocking the acid secretion.

Draw backs: decreased production of Magnesium (Hypomagnesaemia), Vitamin B12 deficiency, excessive growth of intestinal bacteria due to decreased production gastric acid which gives chance to attack opportunistic and Osteoporotic condition can be appear. [15]

3. Drugs which reduces the acid-production: these drugs mainly used to reduce the acid release into the digestive tract mainly H₂ receptor blockers. Which also helps to reduce the stomach pain and promotes ulcer healing. Includes Ranitidine (Zantac), Famotidine (Pepcid), Cimetidine (Tagamet HB) and Nizatidine (Axid AR).

Ranitidine reversibly bind to histamine receptors especially H₂ receptors present in the parietal cells which prevent the binding of histamine to respective receptors which was secreted by enterochromaffin cells. By this mechanism it reduces the production of gastric acid and hydrogen concentration in stomach. Ranitidine was approved in 1984 October by FDA for management and recurrence of Peptic ulcer diseases. It is marketed under the brand name of Zantac or Zantac 75 and also is marketed in terms generic drugs. This is type of OTC drug but activation of this can be less in the presence of Azole derivatives of antibiotics especially drug which are having iron salts. It has been reported that less extent of teratogenic activity because it can secret through breast

Present world depends on herbal medicines for the treatment different ailments because synthetic drugs will cause most severe side effects and will cause toxic to various organs. Hence for the treatment of

milk to infants.

Famotidine (Pepcid), Cimetidine (Tagamet HB) and Nizatidine (Axid AR) these are other blockers of acid production used in the treatment n management of PUD's. [16]

Draw backs: constipation or diarrhea, dizziness, pain in muscle joints, weight gain, sleeping sickness are common side effects but rare side effects are allergic reactions like rashes, mental confusions, depression, changing of skin colour to yellow and visual disturbances.

4. Drugs which act as mucosal protective for stomach acids: these agents acts as a cytoprotective action form stomach linings and duodenal linings. They are Sucralfate (Carafate) and Misoprostol. [10]

Misoprostol is mainly a Prostaglandin E₁ analogue which stimulates the prostaglandin E₁ receptors present in the parietal cells which inhibit HCL secretion in stomach. One more mechanism is that it increases the concentration of mucus and bicarbonates in stomach which forms a dense protective layer around the stomach which prevents from ulcer occurrence. These are mainly used in the treatment of NSAID's induced peptic ulcer. It also used in the management of post-partum haemorrhage. [17]

Draw backs: back pain, nausea, vomiting, dizziness, constipation, skin irritation and insomnia. Some of the herbal medicines used to treat ulcers are described in below table 1 [18]

Herbal medicines used in the treatment of PUD's

PUD's peoples are using herbal medicines as a home remedy to manage acid production. For treating ulcer by plant extract it should contain active constituents such as Flavonoids, tannins and terpenoids.

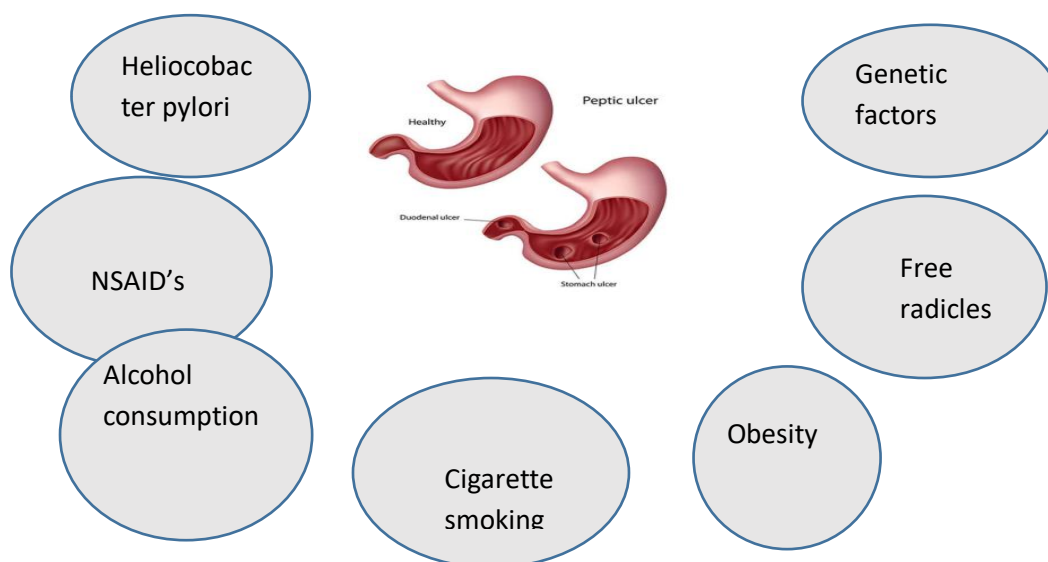


Fig 5: Diagrammatic representation of causative factors of PUD's

Table No 1: Herbal plants used to treat ulcers

Plant name	Family	Active constituents	Part used	Synonyms
Ficus arnottiana	Moraceae	β -sitosterol, Friedelin, alkaloids, Sterols, Tannins, Carbohydrates,, Phenols, Glucanolate and Glucose.	Fruits, leafs	paras papal
Alstonia scholaris R. Br.	Apocynaceae	Alkaloids, flavonoids, coumarins, phlobatannin, simple phenolic, reducing sugars, steroids, tannins and saponins	Plant	Saptaparna
Asparagus racemosus Willd	Asparagaceae	Shatavarin 1. Shatavarin 2-4, quercetin-3-glucuronide, shoots contain rutin, sitosterol	Tuberous roots and Shoots	Satawari
Azadirachta indica Juss.	Meliaceae	Azadirachtin, Nimbidin, Nimbin and Quercetin	Leaves, flower, seed and oil	Melia azadirachta L
Bauhinia variegata Linn	Fabaceae	Flavonoid, Quercetin, rutin, apigenin, saponins, sugars, tanins and apigenin 7-O-glucoside	Bark	Kachnar

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