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Ulcer: Pathogenesis, prevalence and management

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Abstract
Ulcers are a breach in the mucosa of the alimentary tract that extends through the muscularis mucosae into the submucosa or deeper. They can occur in any portion of the gastrointestinal tract exposed to the excessive amount of acid-peptic juices. Prevalence of peptic ulcer is approximately 11% to 14% for men and 8% to 11% for women during the age of 30 to 50 years. The occurrence of peptic ulcer is very rare above 60 years but produce death in 80% of cases. This review gives an overview of symptoms, diagnosis, treatment, prevalence and management of ulcers.

Keywords: ulcer, anti-ulcer, herbal medicine

Introduction
Ulcers are defined histologically as a breach in the mucosa of the alimentary tract that extends through the muscularis mucosae into the submucosa or deeper. They can occur in any portion of the gastrointestinal tract exposed to the excessive amount of acid-peptic juices [1]. The gastric ulcer are classified Aphthous Ulcers, Esophageal Ulcers and Peptic Ulcer on the basis of their occurrence in gastrointestinal tract in mouth, esophagus and stomach or the duodenum respectively [2].

Aphthous ulcers
Aphthous ulcers are typically recurrent round or oval sores or ulcers with yellow grayish pseudo membrane surrounded by raised margins and erythematus hole inside the mouth on areas where the skin is not tightly bound to the underlying bone, such as on the inside of the lips and cheeks or underneath the tongue. They are also known as aphthae, aphthosis, aphthous stomatitis and canker sores [3, 4]. Mouth ulcers are commonly having family history (up to 40%) and are usually due to trauma (Because of not proper fitting of dentures, fractured teeth, or fillings), Anemia, measles, viral infection, oral candidiasis, chronic infections, throat cancer, mouth cancer and vitamin B deficiency. It is estimated that 15-20% of the population worldwide and 50-66% in North America suffers from aphthous ulcers [2].
They are classified as minor ulcer (5-10 mm in size, 10-14 days duration and 75-80% prevalence), major ulcer (above 10 mm in size, more than 2 week duration and 10-15% prevalence) and herpetiform ulcer (below 5 mm in size, 10-14 days duration and 5-10% prevalence) [4].

Esophageal ulcers
Esophageal ulcers are lesions that occur at the end of esophagus due to gastroesophageal reflux disease (GERD) with 2-7% prevalence. They can be produce pain right below the breastbone. The etiology of esophageal ulcers is not well defined it is considered as it occurs due to peptic ulcer, carcinosa, corrosive substances, prolonged use of drugs like NSAIDs, and smoking. Esophageal ulcers also reported due to cytomegalovirus, herpes simplex virus, and human immune deficiency virus [2, 5].

Peptic ulcer
Peptic ulcers are chronic, most often solitary, lesions that occur in any portion of the gastrointestinal tract exposed to the aggressive action of acid-peptic juices. At least 98% of peptic ulcers are either in the first portion of the duodenum or in the stomach, in a ratio of about 4:1 [1]. The infection caused by the bacteria *H. pylori* and acid pepsin secretion are mostly responsible for generation of peptic ulcer while non-steroidal anti- inflammatory drugs (NSAIDs), shock, severe trauma, septicaemia, intracranial lesions, local irritant like alcohol, smoking and spiced food also responsible for production of peptic ulcers [7]. Symptoms of peptic ulcers include abdominal discomfort, pain, weight loss, poor appetite, bloating, nausea, and vomiting commonly and blood in stool and vomit rarely [2].

On the basis of site of occurrence peptic ulcers are categorized as gastric ulcer and duodenal ulcer, they occur in stomach and duodenum respectively. However they can also classified as acute and chronic ulcer on the basis of their severity. Acute peptic ulcers arise in the form of single or multiple lesions with depth up to the submucosa of all parts of stomach and in the first few centimeters of duodenum. Chronic peptic ulcers occur singly in the pyloric antrum of the stomach and in duodenum which may extend up to adjacent pancreas or liver by penetrating through the epithelial and muscle layers of stomach or duodenum wall [6]. They may produce complication like obstruction, hemorrhage, perforation and malignant transformation [7].

Pathogenesis

Peptic ulcers occur because of an imbalance between aggressive factors (gastric acid and pepsin secretion, *H. pylori* infection, NSAIDs, alcohol, etc.) and defensive factors (elaboration of prostaglandins, epithelial regenerative capacity, apical surface membrane transport, surface mucus secretion, and bicarbonate secretion). Among the "aggressive forces," *H. pylori* is very important, because involvement in 90% of duodenal ulcers and 70% of gastric ulcers. *H. pylori* stimulate an intense inflammatory and immune response with increased production of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor (TNF) which activate neutrophils and activation of T cells and B cells respectively. The organism also responsible for increased gastric acid secretion and impairs duodenal bicarbonate production result in alteration of gastric pH [1]. (Figure 1).

Diagnosis

Diagnosis of ulcer by symptoms is most common and depends on ulcer location and patient age. Gastric ulcer characterized by pain typically starts with empty stomach and generally relieved by antacids or food but provoked by alcohol and caffeine. However, Weight loss and gastrointestinal bleeding occur more frequently with gastric ulcers. Duodenal ulcers tend to produce more consistent pain generally in midmorning which relieved by food only and at night after few hours sleeping. Haemorrhage, repeated vomiting or evidence of abdominal pain is important in diagnosis of duodenal ulcers [8].

Peptic ulcer can be diagnosed specifically by direct visualization by endoscopy or radiology and by detection of *H. pylori* by various endoscopic and non-endoscopic tests. Endoscopic tests involve Histology, Culture of Biopsy, Rapid urease detection with ammonia, while non-endoscopic tests consist of detection of antibodies to *H. pylori* in serum, Urea breathe test (*H. pylori* urease breaks down ingested labelled C urea, patient exhales labelled CO_2) and Stool antigen test (presence of antigen against *H. pylori* in stool changes its color which can be detected visually or by spectrophotometer) [9].

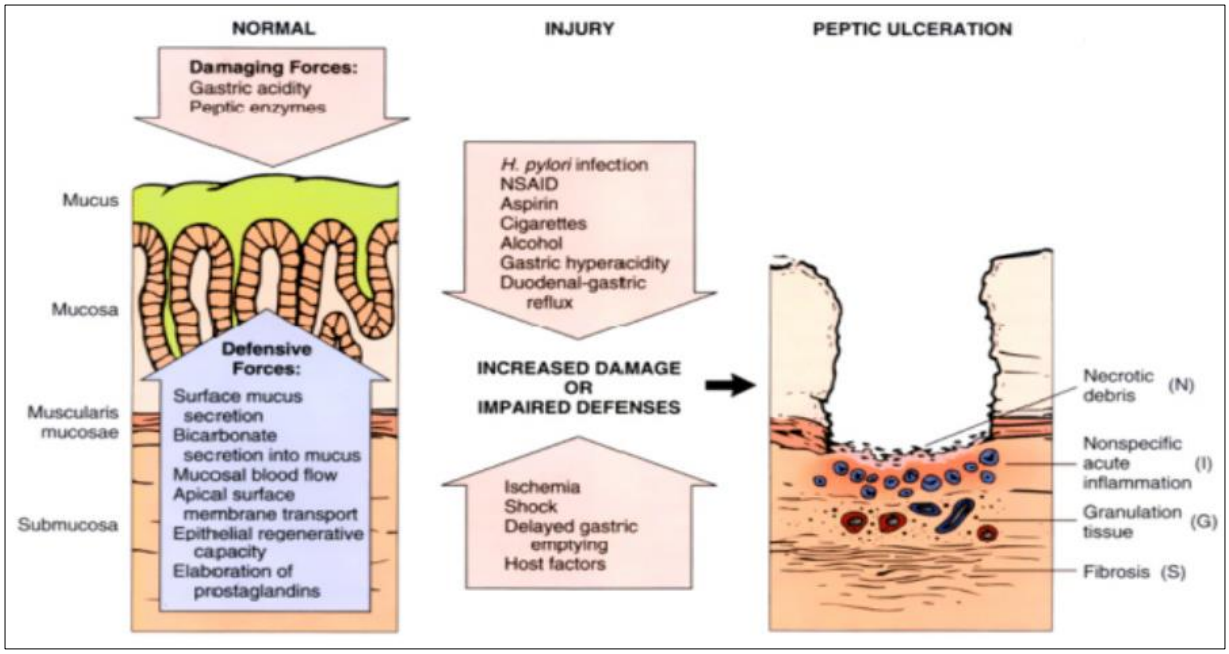

Fig 1: Pathogenesis of ulcer

Treatment

The management of peptic ulcers includes pain relief, ulcer heal, prevention of complication such as bleeding, perforation. The drugs used in treatment of ulcer classified as follows [10].

- Drugs reducing gastric acid secretion
  - Antihistamines like cimetidine, ranitidine, famotidine, roxatidinen
  - Proton pump inhibitors like omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, dexlansoprazole
  - Anticholinergic drugs like pirenzepine, propantheline, oxyphenonium
  - Prostaglandin analogue like misoprostol
- Antacid
  - Systemic antacids like sodium bicarbonate, sodium citrate.
  - Non-systemic antacids like magnesium hydroxide, magnesium trisilicates, aluminum hydroxide, calcium carbonate and magaldrate.
- Ulcer protective like sucralfate, colloidal bismuth subcitrate
- Antimicrobial agent against *H. pylori* infection like amoxicillin, clarithromycin, metronidazole tinidazole, tetracycline.

Prevalence

Prevalence of peptic ulcer is approximately 11% to 14% for men and 8% to 11% for women during the age of 30 to 50 years. The occurrence of peptic ulcer is very rare above 60 years but produce death in 80% of cases [8].

Methods for evaluation of anti-ulcer activity

Peptic ulcers generally induced in rodents by physiological, pharmacological or surgical treatments which have etiological importance for induction of peptic ulcers. Some models are mentioned in following which used experimentally for testing or evaluating anti peptic ulcer activity of drugs [11, 12].

- Stress ulcer through immobilization stress
- Ethanol induced mucosal damage in rats (cytoprotective activity)
- Sub-acute gastric ulcer in rats
- Gastric ischemia-reperfusion injury in rats
- Water-immersion stress or cold-water-restraint
- NSAIDs-(indomethacin, aspirin, and ibuprofen) induced gastric ulcers
- Acetic acid induced gastric ulcers
- Histamine induced gastric ulcers
- Reserpine induced gastric ulcers
- Serotonin induced gastric ulcers
- Pylorus-ligated-induced peptic ulcers
- Diethyl-dithio-carbamate (DDC)-induced peptic ulcers
- Methylene blue-induced ulcers
- Ischemia-reperfusion induced gastric ulcers
- Cysteamine induced duodenal ulcers
- Indomethacin-histamine-induced duodenal ulcers
- Ferrous iron-ascorbic acid-induced gastric ulcers
- Acetic acid-*H. pylori*-induced ulcers

Plants having anti-ulcer activity

Herbal medicines have been used to treat human gastric ulcers since ancient time. Several controlled clinical studies have showed that more than 90% of patient cures from peptic ulcer with herbal treatment [13]. Flavonoids, terpenoids and tannins are most important in anti-ulcer activity of plant because they consist of poly phenolic structure which can act as antioxidant. Some potent medicinal plants used in the treatment of ulcer are given in table 1 [14].

Table 1: List of plants having anti-ulcer activity

Sr. No.	Botanical name	Common name	Parts of plant	Active phytochemical
1	*Acacia nilotica* Fabaceae	Kikar	Aerial portion	Phenolic cumpounds, flavonoids, Tannins
2	*Ageratum conyzoides* Asteraceae	Goat weed	Leaf	flavonoids
3	*Albizia lebbeck* Fabaceae	Indian saris	Leaves, Bark, flower	Phenolic cumpounds, flavonoids, saponin
4	*Alove vera* Liliaceae	Grit kumari	Leaves	Barbaolion, Iso-barbaloin, saponins
5	*Azadirachta indica* Meliaceae	Neem	Leaves	Phenolic compound, saponin, flavonoids
6	*Basella rubra* Apocynaceae	Indian spinach	Leaf	flavonoids, saponin
7	*Curcuma longa* Zingiberaceae	Haldi	Rhizome	Phenolic compound, tannins, flavonoids
8	*Falcaria vulgaris* Umbelliferae	Ghazzyaghi	Seeds	Tannins and saponin
9	*Ficus arnottiana* Moraceae	Paras papal	Leaf	β – sitosterol, glunol acetate, sterol, alkaloids
10	*Glycyrrhiza glabra* Leguminosae	Liquorice	Root and Rhizomes	Glycyrrhizinic acid
11	*Jatropa curcas* Euphorbiaceae	Rattanjot	Leaves	Phenolic compound, flavonoids, saponin
12	*Manilkara hexandra* Saptoaceae	Milk tree	Bark	Phenolic compound, flavonoids, saponin, protein
13	*Nerium indicum* Apocynaceae	Kaner	Leaf, root	Phenolic cumpounds, flavonoids
14	*Nigella sativa* Ranunculaceae	Kalonji	Seed	Alkaloids, nigellicin, nigellidin, quinazoilin, tannins
15	*Panax ginseng* Araliaceae	Gurmar	Root, leaf, stem	Polysaccharides, flavonoids, amino acids triterpenoids
16	*Panax japonicas* Araliaceae	Japanese ginseng	Rhizomes	Phenolic cumpounds, flavonoids, saponin
17	*Terminalia billerica* Combertaceae	Baheda	Seed	Tannins, gallic acid, ellagic acid
18	*Terminalia chebula* Combertaceae	Harida	Seed	Tannins, gallic acid, chebulic acid, sorbitol
19	*Vetiveria ziziinoides* Graminae	Benachar	Root	Phenolic compound, flavonoids, saponin
20	*Zingiber officinale* Zingiberaceae	Ginger	Root	Phenolic cumpounds, flavonoids

Conclusion

The review might be useful to supplement information in regard of symptoms identification, diagnosis, treatment, prevalence, management and herbs used in treatment of ulcers. This article also motivates researchers and helps them during screening of medicinal plants.

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