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The role of herbal medicine in peptic ulcer disease management: A comprehensive review

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Abstract

Peptic ulcer disease (PUD) is a common gastrointestinal disorder characterized by mucosal lesions in the stomach and duodenum. The etiology of PUD is multifactorial, involving *Helicobacter pylori* infection, nonsteroidal anti-inflammatory drugs (NSAIDs), and stress-related mucosal damage. Conventional treatment options for PUD include proton pump inhibitors (PPIs), H2 receptor blockers, antacids, and cytoprotective agents. However, these treatments have several drawbacks, including osteoporosis, depression, and electrolyte imbalance. This review highlights the potential of herbal remedies in the treatment of PUD. Several plants, including *Allium sativum*, *Aloevera*, *Annona squamosa*, *Azadirachta indica*, *Camellia sinensis*, *Carica papaya*, *Curcuma longa*, *Fenugreek*, *Mangifera indica*, *Ocimum sanctum*, *Piper betle*, and *Zingiber officinalis*, have been traditionally used to treat ulcers. These plants possess anti-ulcerogenic, anti-inflammatory, and antioxidant properties, which may contribute to their therapeutic effects.

Keywords: Peptic ulcer disease, *Helicobacter pylori*, Herbs, Nonsteroidal anti-inflammatory drugs, *Carica papaya L*

Introduction

The word peptic comes from the Greek word peptikos, which meaning to digest. Peptic ulcers (PUs) are mucosal lesions that progress to the layer of muscularis mucosae, forming a hollow surrounded by acute or chronic inflammation^[1]. Peptic ulcer disease is characterized by erosion or lesion of the digestive tract's lining. It interferes with the integrity of the gastrointestinal mucosal layer of the esophagus, stomach, and the proximal region of the small intestine known as the duodenum. Peptic ulcer disease is becoming a common health concern around the world. Globally, peptic ulcer disease affects around 4 million people each year. Approximately 10 to 20% of people develop problems^[2]. With the highest incidence occurring between the ages of 55 and 65, ulcer disease primarily affects the elderly population. In men, duodenal ulcers are more common than gastric ulcers, while in women, the converse is true.^[3] Peptic ulcer disease (PUD) is often defined as a mucosal break greater than 3-5 mm in the stomach or duodenum with a visible depth. It is therefore an endoscopic diagnosis in contrast to dyspepsia, which is a clinical diagnosis based on symptoms alone. An imbalance between factors that harm the stomach and duodenal mucosa and those that protect it leads to peptic ulcer disease^[4]. Duodenal ulcers are those that develop in the first section of the duodenum, whereas gastric ulcers are those that originate in the gastric epithelium^[5]. The degree of mucosal layer damage depends on an individual's vulnerability to the toxicity of non-steroidal anti-inflammatory drugs (NSAIDs) and the virulence of *Helicobacter pylori*. The mucosa layer is uniquely able to withstand damage brought on by high peptic acid concentrations, bile inflow, and pepsin^[6]. The use of corticosteroids, the existence of a tumor, such as a gastric tumor or lymphoma, stress, or Zollinger-Ellison syndrome, which is brought on by an increase in acid production because of hypergastrinemia, are additional risk factors that have been documented^[7]. Important symptoms of Peptic Ulcer Disease include repeated episodes of heartburn, nausea, bloating, diarrhea, flatulence, and epigastric discomfort. Antacids can alleviate these symptoms, and a posterior ulcer may cause back pain^[8]. Bleeding is the most frequent consequence of peptic ulcers in emergency rooms, occurring in about 100 to 170 cases per 100,000 people worldwide. A dangerous medical disease called peptic ulcer bleeding can result in hematemesis, melena (tarry stool), or hematochezia.

If treatment is delayed, patients may develop anemia, hypovolemic shock, multiorgan failure, or possibly pass away. About 5% to 12% of people die from bleeding from peptic ulcers [9]. Because of the negative side effects, allopathic ulcer treatment has a negative impact on health. It prevents the organ that has that membrane from carrying out its regular tasks. It comes in a variety of forms and can be found both inside and outside the human body. Numerous ulcer varieties, including peptic, corneal, stomach, foot, and leg ulcers, are currently recognized in medicine [10]. Although there are many conventional and non-traditional therapy techniques available for managing ulcers, each has drawbacks such as toxicity, poor efficacy, and high expense. It is important to emphasize that a variety of active ingredients that have both beneficial and harmful effects can be found in botanical products. Therefore, it is crucial to employ herbal therapy and establish laws to guarantee the quality of herbal products, particularly in the context of conducting additional randomized trials to determine the safety and efficacy of various products in treating ulcer problems [11]. These days, identifying novel and creative agents is highly valued. Because they are affordable, efficient, and easily accessible, herbal remedies are therefore frequently used in situations where medications are taken for extended periods of time [12]. This article looks at the properties of some plants that have been suggested to have ulcer-healing and antiulcer properties.

Anatomy of the normal stomach

The stomach is a muscular organ located on the upper left side of the abdomen. Food passes into the stomach via the oesophagus. Food can pass from the oesophagus into the stomach through a muscular valve called the lower esophageal sphincter. To aid in the digestion of meals, the stomach secretes digestive enzymes and acid. Ruae are the ridges of muscle tissue that round the stomach. By churning the food, regular contractions of the stomach muscles aid in digestion. To allow food to go from the stomach into the small intestine, a muscle valve known as the pyloric sphincter opens [13].

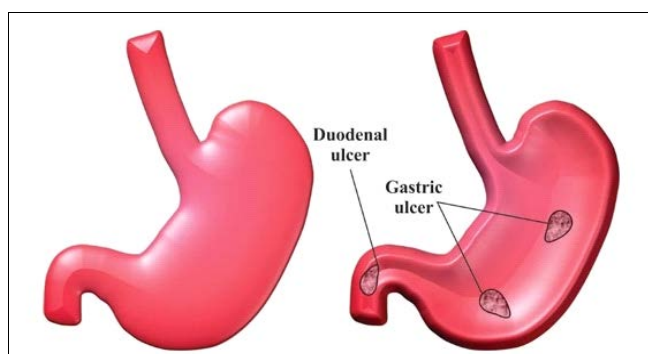


Fig 1: The left side is a healthy stomach, and the right side is a stomach that got a gastric ulcer and a duodenal ulcer [14].

Types of peptic ulcers

Gastric Ulcers: The stomach lining is the site of these ulcers,

which are frequently linked to excessive acid production and ongoing inflammation.

Duodenal Ulcers: An imbalance between defensive and aggressive components in the digestive system is often the origin of duodenal ulcers, which are found in the duodenum, the top portion of the small intestine [15].

Etiology of Peptic Ulcer

Peptic ulcers, despite being a frequent gastrointestinal ailment, have a complex and multiple cause. Understanding the numerous causes that lead to ulcer development is critical for optimal therapy and prevention. Peptic ulcers are mostly caused by *Helicobacter pylori* (*H. pylori*) infection, the use of nonsteroidal anti-inflammatory medicines (NSAIDs), and, less commonly, stress-related mucosal injury.

Helicobacter pylori

One of the major causes of peptic ulcers, *Helicobacter pylori*, results in inflammation of neutrophils, lymphocytes, and macrophages as well as the degeneration and damage of epithelial cells. The symptoms of an *H. pylori* infection include decreased somatostatin levels and increased gastric juice output, which are caused by cytokines that inhibit parietal cell secretion. This causes the parietal cells to produce more histamine, which in turn causes them to secrete more stomach acid [16].

Non-steroidal Anti-Inflammatory Medicines (NSAIDs)

Although NSAIDs harm the gastroduodenal mucosa in both systemic and local ways, the primary mechanism is thought to be the systemic suppression of prostaglandins generated from constitutively expressed cyclooxygenase 1 (COX-1). The maintenance of mucosal integrity depends on reduced mucosal prostaglandin levels, which are linked to low mucus and bicarbonate secretion, suppression of cell proliferation, and decreased mucosal blood flow [17].

Stress-Related Mucosal Damage

People are more susceptible to stress-related mucosal damage and ulceration if they have experienced severe physiological stress, such as trauma, major surgery, burns, or a life-threatening illness. Stress triggers the release of stress hormones, such as catecholamines and cortisol, which impair mucosal blood flow, reduce mucosal protective factors, and raise gastric acid secretion, all of which contribute to the development of ulcers [18].

Emotional factors and ulcer exacerbation

Psychological variables not only contribute to the development of peptic ulcers, but they can also affect the disease's progression. Emotional stressors and negative affective states have been linked to more ulcer symptoms, slower healing, and higher chances of ulcer recurrence. Understanding these processes is critical to creating comprehensive treatment options [19].

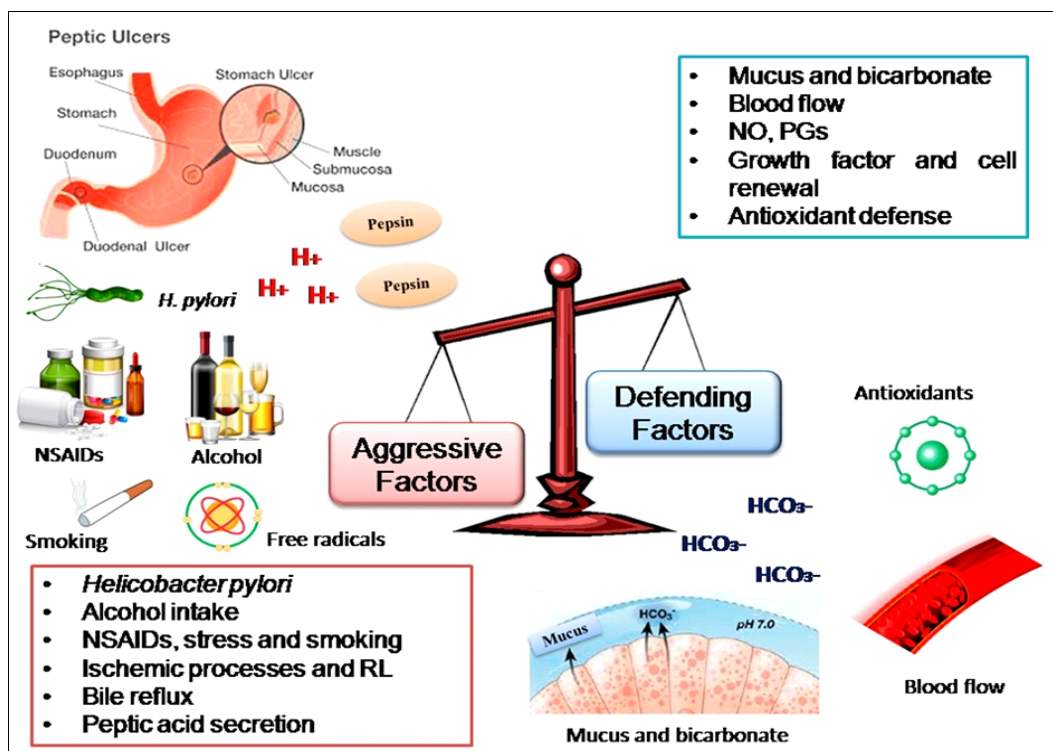


Fig 2: Schematic representation of peptic ulcer etiopathogenesis [20].

Diagnosis of ulcer

Ulcer diagnosis is based on prior symptoms detected and the patient's history, such as drunkenness, smoking, NSAID therapy, or any stress. Endoscopy (Gastroscopy) is the most reliable procedure for diagnosing ulcers since it allows for the observation of the ulcer's area and size. *H. pylori* is another cause of ulcers that can be detected using a variety of methods, including a urea breath test and the stool antigen test. Other supportive tests include a complete blood count to determine whether there is blood loss in situations of bleeding ulcers, a tissue culture test to detect any bacterial or fungal infections, and a stomach biopsy. Following a proper diagnosis, patients are given appropriate pharmacological therapy (antacids, antiseptics, or antibiotics) [21].

Treatments of peptic ulcer

The purpose of peptic ulcer disease treatment is to alleviate symptoms, heal craters, prevent recurrences, and avoid complications. Medical therapy should comprise medication treatment and seek to achieve the following goals:

1. Reduce gastric acidity by inhibiting or neutralizing acid release.
2. Coat ulcer craters to prevent acid and pepsin from seeping into the ulcer base.
3. Provide a prostaglandin analog.
4. Eliminate environmental hazards including NSAIDs and smoking, and
5. Minimize emotional stress (for some patients) [22].

Epidemiology: PUD continues to cause significant morbidity and mortality worldwide, with more than half of the world population infected. It is thought to be responsible for high health care Costs of greater than \$3 billion annually. The

lifetime prevalence of PUD is estimated as high as 10% and is less prevalent in developed countries [23]. In the general population, the lifetime prevalence of Peptic Ulcer disease is estimated to be approximately 51%, with an annual incidence of 1%-3%. Epidemiological Studies have revealed a sharp decrease in the disease's incidence, rates of hospitalisation, and mortality over the last 20-30 years, the prevalence and incidence of Peptic Ulcer Disease are now likely to be lower than these estimates worldwide, particularly in high-income countries [24].

Herbs commonly used for Peptic Ulcer Treatment:

This overview includes a summary of some of the main plants that have been mentioned in classical writings and recent studies that have demonstrated antiulcer capabilities.

Allium sativum

Allium sativum is a member of the Liliaceae family. "Garlic" is the common name for it. In India, it is grown in gardens everywhere. This bulb's chemical components include sugar, albumin, mucilage, starch, and acrid volatile oil. The oil in seeds is fragrant. Juice that is high in vitamins, iodine, salicylic acid, sulfur, and a few other minerals. Garlic can be fried in mustard or coconut oil to treat ulcer-infesting maggots. Garlic and three to four parts distilled water can be used to cleanse wounds and sores [25]. Garlic is a useful therapy in ancient Indian medicine that can be used as a tonic, roborans, to treat rheumatism, cough, skin conditions, hemorrhoids, and general weakness. The purpose of garlic is to lower body temperature. To combat constipation, they made a beverage with solid resin and garlic. Additionally, garlic emulsion can be applied to reduce inflammation in the muscles [26].



Fig 3: *Allium sativum* [27]

Aloevera

Aloevera is a member of the liliaceae family. The gel of aloe vera has gastroprotective qualities. Aloe gel, the mucilage found in this plant, has a number of therapeutic uses. A substance called glucomannan is responsible for its therapeutic properties [28]. Some persons with ulcerative colitis, an inflammatory bowel disease, may benefit from its juice. When used internally, aloe has been promoted as a treatment for a variety of ailments, including coughs, wounds, ulcers, gastritis, diabetes, cancer, headaches, arthritis, and immune system deficits. Nonetheless, it is typically used internally as a laxative [29]. In America, leaves are being utilized to treat chronic ulcers locally with success. After a few weeks, the ulcers heal, and the pain initially goes away [30].



Fig 4: *Aloevera* [31]

Annona squamosa

Annona squamosa (annonaceae) is frequently referred to as "custard apple". It is grown in gardens throughout India and is known locally as "sitapalam". This plant's chemical constituents include alkaloids, flavonoids, saponins, and tannins. Anti-ulcer activity. To treat unhealthy ulcers, apply a paste formed from leaves without adding water. The aqueous

leaf extract prevented pylorus ligation and ethanol-induced stomach ulcers in rats. Tannic acid is considered an active component [32].



Fig 5: *Annona squamosa* [33]

***Azadirachta indica* (Neem)**

One of the most effective commercially viable common medicinal herbs in India is neem. While tannins offer a barrier against the elevated acidity, flavonoids and nimbin have been linked to their anti-ulcer effects by inhibiting the proton pump or killing bacteria [34]. The antiulcer and cytoprotective properties of *Azadirachta indica* (Neem) stem bark extract can be tested in albino rats. *Azadirachta indica* dramatically reduced stomach ulcers caused by indomethacin. This activity led to a dose-dependent decrease in overall stomach acidity. It is claimed that *Azadirachta indica* probably acts via the histamine H₂ receptor. It primarily works by preventing acid production and preventing the stomach mucosa from becoming oxidatively damaged. H⁺ K⁺ ATPase activity inhibition verified the inhibition of acid secretion. However, the scavenging of endogenous hydroxyl radicals (OH) and the inhibition of lipid peroxidation demonstrated the blockade of oxidative damage to the stomach mucosa [35]. *Azadirachta indica*, it has anti-inflammatory, anti-ulcer, anti-fungal, anti-bacterial, anti-malarial, anti-hypertensive, anti-ulcerogenic, anti-hyperglycemic, hepatoprotective, anti-infertility, anti-pyretic, analgesic, anti-cancer, anti-oxidant, and

immunostimulant properties. It can also treat dental disorders, skin diseases, and microbial infections [36].



Fig 6: *Azadirachta indica* (Neem) [37].

Camellia sinensis

The plant *C. sinensis*, which belongs to the Theaceae family, is known locally as "cha" in Bangladesh and as "blacktea" elsewhere. Many active ingredients, including flavonoids (such as thearubigins, theaflavins, and catechins), vitamins, amino acids, carotene, chlorogenic acids, volatile compounds, carbohydrates, phenolic acids (such as gallic acid, caffeic acid, and cauramic acid), proteins, lipids, and fluoride, are found in the leaves, stems, and twigs [38]. *Camellia sinensis* extract is shown in numerous similar investigations to increase cell vacuolation by vacuolating cytotoxin A (vacA) and urea conduction in *H. pylori* infection, thereby demonstrating its inhibitory impact. Consequently, it might exhibit *in vivo* anti-*H. pylori* action [39].



Fig 7: *Camellia sinensis* [40].

Carica papaya L

Carica papaya L. is from the Caricaceae family. The *Carica papaya* has pharmacological properties such as antithrombocytopenic, analgesic, and antibacterial [41]. Pyloric ligation, ethanol, acetic acid, and indomethacin-induced ulcer models are among the ulcer models used to assess the anti-ulcerogenic properties of *C. papaya* methanolic extract. Treatment with aqueous and methanolic

extracts demonstrated gastroprotective benefits by significantly reducing stomach acidity and increasing mucus production and GSH levels [42].



Fig 8: *Carica papaya L.* [43]

Curcuma longa

Turmeric, derived from the rhizome of *C. longa*, a member of the Zingiberaceae family, has long been used in Ayurvedic and Chinese medicine to cure gastric ulcers. Curcumin, an active component found in turmeric, has received attention for its extraordinary gastroprotective qualities. In rat models, studies have shown that it is efficacious against a variety of ulcer-inducing substances including indomethacin, ethanol, stress, and pylorus ligation [44]. It is used to treat oxidative and inflammatory disorders, metabolic syndrome, arthritis, anxiety, and hyperlipidemia [45].



Fig 9: *Curcuma longa* [46]

Fenugreek

Fenugreek is well-known for its potent therapeutic effects and other health advantages.

It can also be used to treat stomach ulcers. *Fenugreek*, which is high in a mucilaginous component, coats the stomach lining like mucus to protect it and aids in the healing process. Use: Bring two cups of water to a boil with one teaspoon of fenugreek seeds. Add a small amount of honey, strain, and drink [47].



Fig 10: Fenugreek [48]

Mangifera indica

Mangifera indica (Anacardiaceae), also known as the "mango tree," is a tropical fruit tree that is grown all over the world. For the Maasai, it is their own word. It is grown all throughout the Indian subcontinent. Alkaloids, sterols, flavonoids, saponins, and tannins are all present in this plant [49]. Likewise having several essential oils, such as nerol, linalool, ocimene, elemene, humulene, and many more. Additionally, the plant has water-soluble nutrients such as thiamine, riboflavin, niacin, and ascorbic acid. For minerals like Na, Ca, Mg, K, Zn, P, Cu, and Cd, it is a good source. To treat ulcers, leaf extracts were dissolved in rice oil and administered orally. The plant is generally thought to have antiulcer properties [50].



Fig 11: *Mangifera indica* [51]

Ocimum sanctum

Ocimum sanctum belongs to the Lamiaceae family. Commonly called basil, holy basil, or sacred basil, it is also known locally as govindapushpam, krishnathulasi, tulsi, thrithavu, and karuthathrithavu. This plant is a subshrub in Kerala [52]. Tulsi can also be referred to as the "life elixir." The plant's leaves, both fresh and dried, are its most advantageous portions. The volatile oil (0.7%) in the leaves is mostly composed of eugenol (71%) and methyl eugenol

(20%). From the leaf extract, molludistin, C-glycosyl compound, ursolic acid, apigenin, luteolin, apigenin-7-O glucuronide, and luteolin-7-O glucuronide can be extracted [53]. Tulsi leaf extract is used to treat ulcers, Tulsi is a tea made from tulsi leaves that is frequently used to treat digestive issues [54].



Fig 12: *Ocimum sanctum* [55]

Piper betle

Piper betle Linn, known as "paan" in the local tongue, belongs to the Piperaceae family. The annual creeper known as *piper betle* (or betel leaf in English) can grow to a height of several meters. According to a study using indomethacin-induced stomach ulcer models, ethanolic *Piper betle* leaf extract significantly aided in ulcer healing. When taken orally for seven days, the extracted component allyl pyrocatechol (APC) stabilized basal acid output with comparable adequacy to misoprostol [56]. Additional research examined the function of allylpyrocatechol, the main antioxidant component found in *Piper betle*, which has gastroprotective properties [57].



Fig 13: *Piper betle* [58].

Zingiber officinalis

Zingiber officinalis is a member of the Zingiberaceae family.

It is frequently referred to as "ginger." This rhizome contains terpenes, phenolic chemicals, lipids, and carbohydrates as chemical components. Gingerol, paradols, and shogaol are phenolic chemicals, while zingiberene and β -bisabolene zingerone are terpene components^[59]. Originally from India, ginger currently thrives in Ghana and other African nations. Traditional medicine uses *Zingiber officinale* to treat a variety of ailments, including diabetes, rheumatism, bloated stomach, asthma, hemorrhoids, bronchitis, nausea, influenza, vomiting, rheumatism, and persistent osteoarthritis. Antimicrobial, antibacterial, antidiabetic, antiemetic, antifungal, anthelmintic, anti-inflammatory, antithrombotic, antiviral, antitumor, antitussive, antiulcer, and antioxidant qualities have all been discovered in *Zingiber officinale*^[60].



Fig 14: *Zingiber officinalis*^[61]

Drawbacks of conventional treatment for peptic ulcer

Proton Pump Inhibitors (PPIs)- Osteoporosis, flatulence, constipation, and a lack of vitamin B12

H₂ Receptor Blockers- Depression, anxiety, lightheadedness, heart attacks, and thrombocytopenia

Antacids- Chalky taste, constipation, diarrhea, discomfort in the abdomen, electrolyte imbalance, and hypophosphatemia

Potassium-Competitive Acid Blocker- Back ache, eczema, upper respiratory tract irritation, and nasopharyngitis

Cytoprotective Agents- Headache, constipation, and abdominal pain^[62].

Conclusion

Peptic ulcer disease is a widespread and complex condition that affects millions of people worldwide. The conventional treatment options, such as proton pump inhibitors and H₂ receptor antagonists, have several drawbacks, including side effects and the development of antibiotic-resistant bacteria. Therefore, there is a growing interest in alternative treatments, including herbal remedies. This review has highlighted the potential benefits of several herbs, including *Allium sativum*, *Aloevera*, *Annona squamosa*, *Azadirachta indica*, *Camellia sinensis*, *Carica papaya*, *Curcuma longa*, *Fenugreek*, *Mangifera indica*, *Ocimum sanctum*, *Piper betle*, and *Zingiber officinalis*, in the treatment and prevention of peptic ulcer disease. These herbs have been shown to possess anti-ulcer, anti-inflammatory, and antioxidant properties, which may contribute to their therapeutic effects. Further research is needed to fully elucidate the mechanisms of action and potential benefits of these herbs in the treatment of peptic ulcer disease.

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