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A comprehensive review of the mechanism of action in peptic ulcer pathogenesis

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Abstract

Up to 10% of people worldwide suffer from peptic ulcer disease, making it a common yet serious chronic condition. Peptic ulcers develop when stomach juice pH is high and mucosal defenses are weakened. The infection with Helicobacter pylori (H.) and nonsteroidal anti-inflammatory medicines (NSAIDs) have been linked to decreased mucosal resilience to damage. Internal gastrointestinal (GI) disruption due to the production of gastric acid or pepsin is what defines peptic ulcer disease (PUD). The stomach and the first part of the duodenum are common sites for the phenomenon. The jejunum, distal duodenum, and lower esophagus might be affected. Patients with gastric ulcers often have epigastric discomfort 15-30 minutes after eating, whereas those with duodenal ulcers suffer pain 2-3 hours after eating. Side effects, relapses, and medication interactions have been reported with peptic ulcer therapies such as proton pump inhibition chemicals and histamine (H2) receptor inhibitor molecules. However, the chemical compounds found in medicinal plants may be used to cure and prevent various illnesses. Therefore, this analysis will look at some of the most often-used medicinal plants for peptic ulcers and how they may be used in these capacities.

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INTRODUCTION

Infected mucosa lining with the defect spreading across the layer beneath the mucosa or propria characterizes the occurrence of peptic ulcer infection that develops in the lining of the stomach or proximal duodenum due to the presence of stomach acid. [1]. Although recent investigations involving the occurrence of peptic ulcers have demonstrated a decline in the incidence, hospital admission rates, and death rates related to peptic ulcers [2], the condition is still thought to impact 5-10% of the general population. This is probably because of the drop in the number of H. pylori infections that have come from the availability of new medicines and better cleanliness. Historically, it has been thought that an acidic environment with more secretion, in combination with dietary

variables or stress, is to blame for mucosal disturbance in individuals with acid-peptic illness. Infection with the bacterium Helicobacter pylori, use of alcohol and cigarettes, NSAIDs, and Zollinger-Ellison syndrome are all associated with an increased risk of peptic ulcer [3]. Both infection with Helicobacter pylori and nonsteroidal medicines with anti-inflammatory effects and usage are major negative factors for causing stomach and duodenal ulcers. Susceptibility to infection is critical in the early stages of mucosal injury since only a tiny population is shown in the percentage form as patients infected with H. pylori or taking nonsteroidal medicines with anti-inflammatory effects acquire peptic ulcer disease. Peptic ulcers are linked to functional polymorphisms in many cytokine genes. Mucosal interleukin production is altered by IL1B polymorphisms, which in turn contribute to H. pylori-associated gastroduodenal disorders [4]. However, peptic ulcer complications are elevated by a factor of four in nonsteroidal infection with anti-inflammation in the users and by a factor of two in aspirin consumers [5].

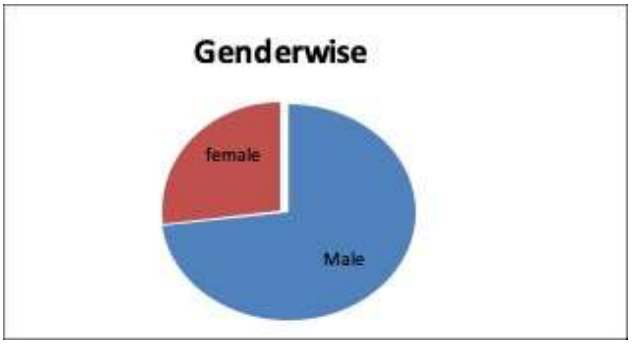

Figure 1 Gender-wise incidence of peptic ulcers

Upper gastrointestinal bleeding is more likely to occur when anticoagulants, corticosteroids, or selective serotonin reuptake inhibitors are used with nonsteroidal anti-inflammatory medicines or aspirin. Peptic ulcer disease is common in those who use anti-inflammation nonsteroidal drugs (NSAIDs). However, the role of NSAIDs and H. pylori in developing this condition is still up for debate. Peptic ulcer disease risk is increased by nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin usage, and infection with Helicobacter pylori separately, according to a meta-analysis of qualitative research [6]. About 20% of patients with peptic ulcer disease have what is known as an idiopathic ulceration since they test negative for H. pylori, NSAIDs, and aspirin [7]. However, the pathogenic processes underlying the onset of idiopathic peptic ulcers remain unclear. This condition is brought on by a dichotomy between elements that support mucosal integrity and inflammatory insults. According to research out of Denmark [8], peptic ulcer rates might rise due to emotional distress. Ischemia (steroidal medicines, agents used in chemotherapy), radiation, viruses, histamine, which infiltration of eosinophils or the microbes that cause infection during bypass surgery, metabolic abnormalities, and other conditions may also cause this [9]. As shown in Figure 1, males are higher than females.

SIGNS AND SYMPTOMS

Depending on the location of the disease and age, the signs and symptoms of peptic ulcer disease can change. Differentiating between gastric and duodenal ulcers depends on when they manifest themselves in meals. Duodenal ulcers commonly cause nighttime pain. People who have a gastric outlet obstruction frequently describe having a bloated or full abdomen in the past.

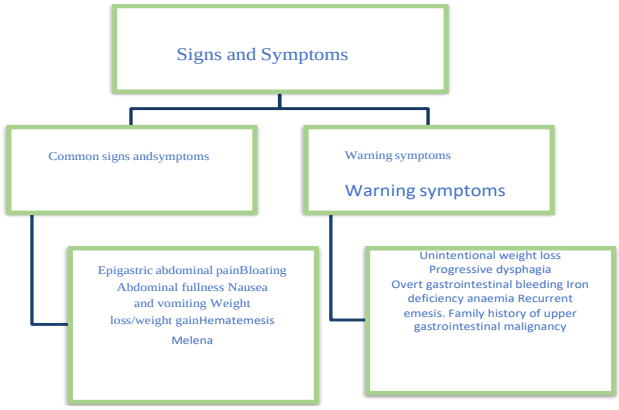

Figure 2 Signs and Symptoms of Peptic Ulcer

H. pylori is still a leading cause of peptic ulcer disease, affecting about half of the world's population [10]. African, Central American, Central Asian, and Eastern European nations had a higher H. pylori prevalence. The majority of cases occur in children living in low-income countries with poor sanitation and overcrowding. Through an inflammatory response including lymphocytes, plasma cells, neutrophils, and macrophages, H. pylori induces cells of epithelium degradation and damage, which is often more severe in the antrum. It is unclear how H. pylori triggers the formation of various lesions in the

gastric and duodenal mucosa. Peptic ulcer type determines whether H. pylori infection causes hypochlorhydria or hyperchlorhydria. However, H. pylori may also directly influence the –subunit of hydrogen and potassium ATPase infection, stimulate calcitonin gene-related neurons with sensory nerve endings connected to somatostatin, or limit gastrin synthesis [11]. The significant transmitters of the disease caused by H. pylori are cytokines that restrict cell secretion in the parietal region of the stomach in about a range of 10%-15% of the individuals infected with H. pylori infection exhibit increased secretion in the digestive system, and a content of somatostatin hormone present in the lower antrum region [12], even though gastric ulcer development is related with hyposecretion. Due to histamine release, the result is increased acid and pepsin production from the parietal or gastric cell. When H. pylori is eliminated, gastrin mRNA expression drops, but somatostatin mRNA expression rises [13]. Gastric ulcers are linked to mucosal shrinkage in the vast majority of the remaining individuals suffering from peptic ulcer infection. Damage to the gastroduodenal mucosa is caused by nonsteroidal anti-inflammatory drugs (NSAIDs) because of their systematic inhibition of continually expressed (COX-1) called cyclooxygenase, the enzyme responsible for the synthesis of prostaglandin hormone. This results in a reduced mucosal blood movement with a decrease in mucus production, a decrease in the secretion of bicarbonate ions, and an inhibition of response, which causes the movement of the ions inside the cell.

Nonsteroidal anti-inflammatory medicines inhibit this enzyme, although the effect is reversible and dose-dependent. Using cyclooxygenase-2 (COX-2) selective nonsteroidal medicines with anti-inflammation mechanisms and exogenous prostaglandins decreases mucosal damage and ulcer risk [14]. However, NSAIDs' toxicity varies due to changes in their physicochemical characteristics. NSAIDs initiate damage to the mucosa because they alter mucus phospholipids and cause separation of mitochondrial oxidative phosphorylation. Gastric juice has a pH of 2; thus, when NSAIDs are exposed to this acidic environment, they get protonated, pass lipid membranes, and enter epithelial cells with a pH of 7.4. In this configuration, NSAIDs cannot penetrate the lipid membrane and accumulate within epithelial cells, where they cause mitochondrial dysfunction, cellular permeability, and a loss of cellular integrity. Large-risk groups for NSAID-induced ulcers include patients with previous instances of the occurrence of ulcers in the gastric region or bleeding, patients who are above 65 years, patients using steroids or anticoagulant medications, and those taking large dosages or a combination of NSAIDs [15].

The diagram showing the mechanism of action of different medicines for treating peptic ulcer is given below as follows:

Inhibitors of Helicobacter pylori:

1. Bismuth
2. Metronidazole
3. Tetracycline
4. Clarithromycin
5. Amoxicillin

Mechanism of action of vonoprazan for treating peptic ulcer

Pharmacological mode of action with the mechanism of action of Vonoprazan medicine:

The maximum concentration in the blood (Cmax) of vonoprazan rises from 10 to 60 ng/mL in just 1.5-2 hr, making it acid-stable and possible to function as a fast-release treatment. In addition, intestinal meal absorption significantly impacts its duration of action, with an area calculated in the graph region ranging from 0 to beyond scope levels with a dose range of 1.14 to 1.32 ng. Hr/mL [16]. Vonoprazan has a larger beneficial Cmax, AUC, and half-life than PPI. Still, the two have no significant variations regarding retention ratios at pH > 4 and time to achieve Cmax. Since it is found in more significant concentrations in the secretion canaliculi that are present in stomach cells in the parietal region in comparison to the levels present in the plasma fluid and has more significant positively charged ions [17], the negative logarithmic of acid solubility constant (pKa) is more than 9.0. Alpha-1 acid glycoprotein and albumin are required for its dispersal. Vonoprazan, in contrast to PPI, does not need to be activated by acid. To a lesser extent, cytochrome P450 2B6, CYP2C19, CYP2D6, and SULT2A1 are involved in its hepatic metabolism [18].

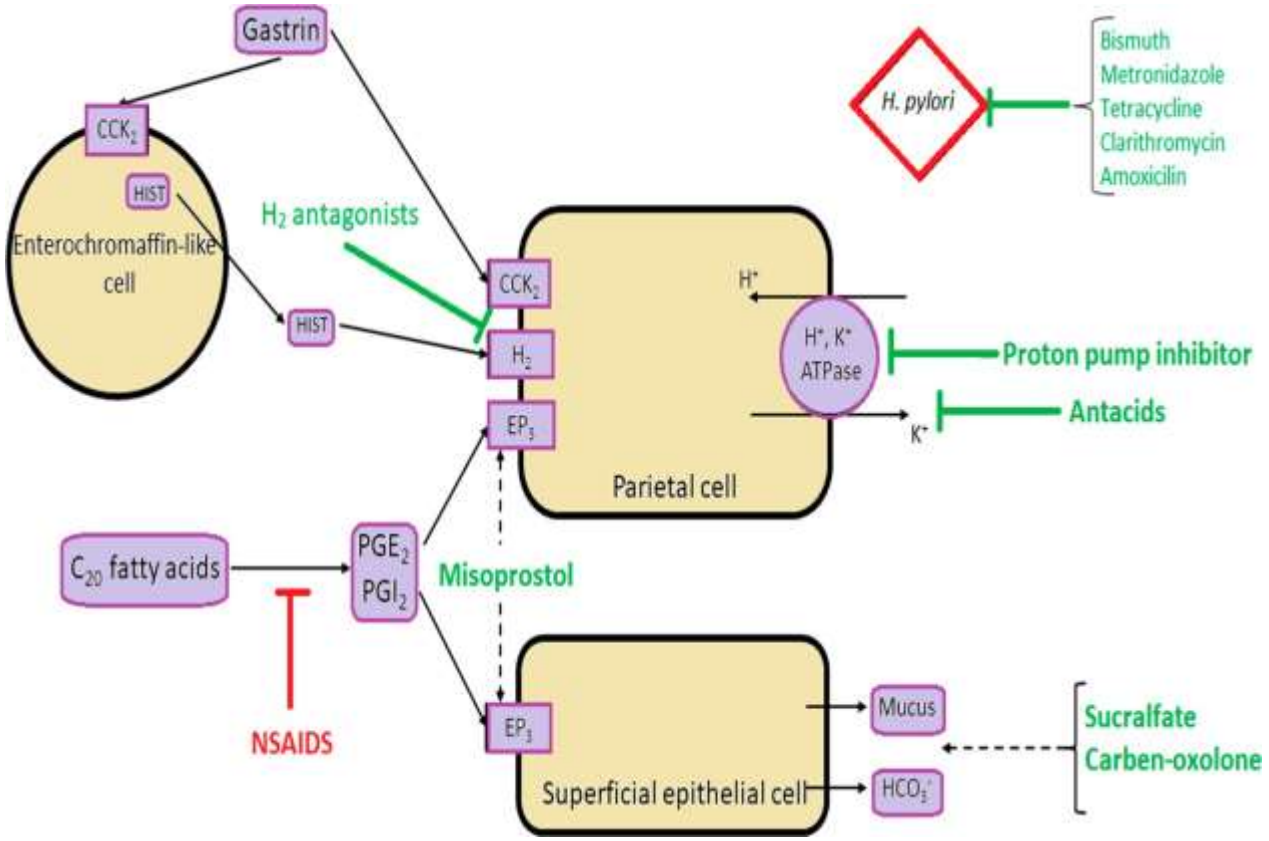

Figure 3 Schematic presentation of main pathophysiological mechanisms involved in developing peptic ulcer disease and the sites of action of the most commonly used pharmacological options in treating peptic ulcer disease. CCK_2 = Cholecystokinin Receptor; PGE_2 = Prostaglandin E_2; PGI_2 = Prostaglandin I_2; EP_3 = Prostaglandin E receptor 3; HIST = Histamine

Table 1 Shows the name of the peptic ulcer treatment medicine, the mechanism of action, and the side effects of these medicines on the body

Type of peptic ulcer medicine	Name of medicine	Mechanism of action of peptic ulcer medicine	Side effects of medicines
1. Proton-pump inhibitor medicine	Omeprazole, Lansoprazole, Pantoprazole	The mechanism involves inhibiting the H^+-K^+ATPase channel, which consists of the movement of the ions.	Headache, pain in the abdomen, vomiting, vitamin deficiency, and flatulence.
2. Histamine receptor-inhibiting medicines	Cimetidine, Famotidine, Ranitidine	Inhibits the secretion of histamine in the parietal cells lining the digestive system.	The side or adverse effects are anxiety, depression, and dizziness.
3. Antacid treatment medicines	Use of aluminum hydroxide and magnesium hydroxide powder.	Aluminum hydroxide blocks the action of the pepsin enzyme. Magnesium hydroxide causes the retention of osmotic fluid in the body.	The side effects are vomiting, bad mouth taste, cramping in the abdomen, and imbalance of electrolytes.
4. Protective medicines	Misoprostol and Sucralfate	Enhances the secretion of the mucous fluid and augments the development of the lining of the gastrointestinal tract.	The side effects are pain in the head, pain in the body, and pain in the abdomen.

Since clarithromycin is a potent CYP3A4 inhibitor, it synergizes vonoprazan's pharmacokinetics by decreasing the drug's metabolism. However, CYP2C19 is predominantly responsible for the metabolism of PPI, and there is a wide range of polymorphisms and metabolism changes that influence proton pump inhibition efficiencies and the activation of drug metabolism [19]. After learning that H+/K+-ATPase was essential for the last step in gastric acid release, research on the suppression of acid drugs took off. Acid activates PPI, a prodrug that forms disulfide bonds to the cysteine in H+/K+-ATPase. After three to five days of therapy, PPI achieves peak acid stability. Researchers have been looking at other acid-suppressing medicines since PPI cannot provide a base environment in the stomach. Alternate mechanisms for limiting H+/K+-ATPase activity include decreased concentrations of potassium ions [20]. By interacting with the sodium-potassium ATPase pump, P-CAB medicines like vonoprazan function as inhibitors that act reversibly in the competition of potassium ions. The non-covalent binding of vonoprazan to H+/K+-ATPase allows it to survive in the acidic stomach secretory canaliculi environment. By slowly dissociating and inhibiting H+/K+-ATPase production over time, vonoprazan raises stomach pH to around 7 in about 4 hours.

RESULTS AND ANALYSIS

Effect of Korean Red Ginseng on peptic ulcer:

By limiting the transcription of inflammatory response chemicals like IL-8 and 5-LOX mRNA, as well as by decreasing the production of 5(S)-hydroxyeicosatetraenoic acid, an extract of Korean ginseng which is red, plays a crucial role in reducing 5-LOX activity produced by H. pylori. As a result, these processes lessen stomach carcinogenesis. The production of 5-hydroxy-eicosatetraenoic acid is diminished, and Korean ginseng with red color has been demonstrated to be helpful in this regard by inhibiting (5-LOX) mRNA of 5-lipo-oxygenase enzyme and the activity of the other enzymes. Similar to how the antioxidant properties of green tea extract may inhibit the activation of TLR-4 in response to lipopolysaccharide from Helicobacter pylori, it may also inhibit the activation of cyclooxygenase-2 (COX-2) and stimulated nitric oxide synthase (iNOS) transcription variables and their target genes. As a result, these blockades amplify the inflammatory factors that cause stomach mucosal lesions. Korean red ginseng has been shown to protect against in vitro cytotoxicity resulting from H. pylori. On the other hand, Korean red ginseng was shown to improve eradication levels of H. pylori, decrease stomach inflammation, and protect against reactive damage to DNA and apoptosis in a prior clinical trial.

Effects of Allium sativum on controlling peptic ulcer:

The primary usage of Allium sativum throughout history has been for its therapeutic characteristics, and the advantages of garlic for health have been widely established. The organosulfur compounds in Allium sativum are responsible for their biological effects; these include cysteine with allyl functional group (SAC) sulfoxides and a peptide consisting of glutamate with allyl and cysteine functional group. Bioactivity may be easily removed from raw Allium sativum. As a result, several extract types have been prepared, each with a unique profile of active components, and their effectiveness has been the subject of extensive study. Antioxidant effects, including the removal of free radicals, the blocking of lipoprotein oxidation, and the reduction of the serum glucose stimulation of antioxidant enzymes, have been identified as the primary function of Allium sativum extract. In addition, it had an inhibitory tumorigenic action by increasing apoptosis and the activation of arrest and inhibition of the cell cycle mechanism. It also inhibited H. pylori-induced inflammation of the stomach regions in vivo. Growth of H. pylori was inhibited in in vitro studies when the extracts of acetone. Allium sativum was used. This was due to the chemical named allicin and a chemical containing allyl and methyl functional groups with thio and sulfur groups.

Effect of Cistus Laurifolius on peptic ulcer treatment:

Flavonoids play a crucial function in organisms and are responsible for various biological activities, including antioxidant protection. Because of their scarcity and high price, scientists have discovered a fast method to synthesize polyoxygenated flavones from readily available and cheap flavanones. To create a limited flavone with antibacterial action against H. pylori, the

methoxylation and bromination technique 30-demethoxysudachitin was used.

Cistus laurifolius extract was used in a wide variety of flavonoid studies. Microbial activity with inhibition testing against H. pylori has shown that 3'-sudachitin metabolite containing a hydroxymethyl functional group and sudachitin are the most effective metabolites that prevent the growth and proliferation of microbes and thus prove to be very effective medicinally. Similar research also found that a Cistus laurifolius extract dissolved in organic solvent chloroform and had potent anti-microbial action against Helicobacter pylori. These studies suggest that isolated flavonoids may be utilized as a supplement to the current therapy for infection with Helicobacter pylori. Several isoflavones were studied with varying degrees of activity against H. pylori. In this study, the antibacterial activity of many series of metronidazole-flavonoid preparations against H. pylori was assessed. One component is responsible for the dramatic increase in the secretion levels of Interleukin-8 levels in gastric cells caused by an H. pylori water extraction. However, novel flavonoids 6, 7, and (2S)-40,7-dihydroxy-with methyl-flavan functional group have been demonstrated to be highly potent molecules against H. pylori in studies conducted. Similar results against H. pylori were found in an extract of chloroform of Cistus laurels. Therefore, isolated flavonoids may be utilized as a substance apart from or in addition to the standard therapy for infection with Helicobacter pylori.

Effect of Zingiber Officinalis and Zingiber Zerumbet on controlling peptic ulcer infection:

Ginger, or Zingiber officinalis, is a popular spice used in cooking. The plant extract inhibited the development of colon cancer cells, increased DNA synthesis, and induced apoptosis, demonstrating its anticancer properties. Further, 6-gingerol is the primary aromatic phenolic component of Zingiber officinalis, and it has several pharmacological actions. Prostaglandin E2 (PGE2) suppression is more accessible by gingerol-rich Zingiber officinalis preparations. However, phenolic substances like gingerol and zingerone significantly inhibit the parietal cell H+ K+ -ATPase. Because of inhibitory action, gingerol and zingerone's action is crucial for inhibiting the proton pump and decreasing stomach acid output. In addition, it has been shown to prevent H. pylori-related ulcers. Zingiber officinalis has been shown to have a curative effect as an antioxidant that works for stomach ulcers. Zingiber officinalis extract shows fast digestion, so a local therapeutic effect can't be elicited; many medications indicate a limited transit duration of between 2-4 hours in the layers of the stomach; whatever component is soluble will be immediately absorbed, and they reported some limitations of free Zingiber officinalis extracts.

Zingiber zerumbet's zerumbone has been shown to have an essential role in the protection of the secretion of gastric juice and action against an induced ulcer in the organ stomach caused by the addition of ethanol model in rats, according to research. They found that giving rats zerumbone or omeprazole before they developed ulcers considerably reduced the ulcers' surface areas relative to the ulcers' control group counterparts. Pre-treatment with 20 mg/kg of omeprazole prevented 76.77 percent of ulcers from forming (p 0.05). In contrast, pre-treatment with 5 and 10 mg/kg of zerumbone prevented 75.59 and 88.75 percent of ulcers from forming, respectively. However, additional ulcer models were not used to evaluate zerumbone's gastroprotective processes; hence, additional processes may be involved, and their effect has to be researched and understood.

DISCUSSION

The global trend in using herbal supplements has coincided with an increase in reports of adverse occurrences and medication interactions. Pharmacokinetic or pharmacodynamic interactions between an herbal supplement and a pharmaceutical may exist. A pharmacokinetic interaction occurs when an herbal supplement and a pharmaceutical medication have the same ingestion, distribution, metabolism, or excretion route. This results in a shift in the concentration of the pharmaceutical drug in the blood and a modification of the drug's pharmacologic effect. Antagonizing or amplifying the clinical impact of a co-administered medicine is an example of a pharmacodynamic interaction. This kind of interaction does not need a change in the concentration of the co-administered drug. P-gp transporters like digoxin, doxorubicin, rosuvastatin, and verapamil are inhibited by

Allium sativum extract. Despite extensive research, controlled clinical studies have not validated the suspected interaction between Allium sativum and warfarin.

Also, since it prevents platelets from sticking together, it must be administered with care in patients with clotting abnormalities or who are receiving anticoagulant medication. Although preliminary evidence suggests that Zingiber officinalis increases blood flow time by inhibiting the thromboxane synthesis enzyme called synthetase, this has not yet been verified in a trial study to be performed experimentally. Due to its potential to impede platelet aggregation, Ginkgo biloba may increase the risk of blood flow or bleeding, mainly when used with anticoagulant medications. Ginkgo biloba flavonoids exhibit antiplatelet action; however, they do not affect human blood clotting or platelet function. When used with an NSAID, it might increase the risk of bleeding.

Calcium channel ion movement block medicines, several medicines lowering the incidence of hypertension and statin drugs, and some depression-lowering medicines may all have their efficacy reduced by the induction of cytochrome P450 3A4 (CYP3A4) by Panax ginseng.

Patients with diabetes may benefit from Panax ginseng's hypoglycaemic properties, but those using phenelzine may have side effects, including headache, shaking, and mania, if they take the herb simultaneously. Anion movement-causing enzyme 1a1 and anion-carrying protein 1a12 are essential for transporting quinolone ring structure molecules, beta-blocking agents, and imatinib medicine, respectively; green tea ingredients and components have been proven experimentally to boost the chemical simvastatin chemical in the body or to inhibit this transport of the drugs inside the cells of the body.

Cimetidine's multiple medication interactions stand out among the standard antiulcer treatments. Many medications, including warfarin, phenytoin, diazepam, chlormethiazole, beta-blocker, and lidocaine, have been shown to interact in clinically significant ways, according to studies. Caffeine's oxidative metabolism in the liver is reduced by cimetidine; therefore, drinking green tea with it may have a more significant impact. This is because cimetidine inhibits CYP1A2, the enzyme responsible for this process.

CONCLUSION

Peptic ulcer disease is still a common clinical issue that affects individuals of all ages. This widespread condition is projected to continue to have a substantial worldwide influence on healthcare delivery, medical economics, and patient quality of life as the incidence of peptic ulcer disorder rises with age. Peptic ulcer disease is still a common clinical issue that affects individuals of all ages. It is predicted that peptic ulcer disease, which becomes more frequent as people age, will continue to significantly influence healthcare delivery, health economics, and patient quality of life worldwide.

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