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Peptic Ulcer Disease: A Brief Overview of Traditional Therapeutic Approaches and Herbal Remedies

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Abstract:

Peptic ulceration is a persistent medical condition that impacts around 10% of the global populace. The development of peptic ulcers is contingent upon the acidity level of gastric juice and the subsequent reduction in protective mechanisms of the mucosal lining. The disruption of mucosal resistance to damage is mostly attributed to two key factors: non-steroidal anti-inflammatory medications (NSAIDs) and Helicobacter pylori (H. pylori) infection. The side effects, relapses, and medication interactions associated with conventional therapies of peptic ulcers, which include proton pump inhibitors (PPIs) and histamine-2 (H2) receptor antagonists, have been well-documented. In contrast, medicinal plants and their associated chemical components provide considerable use in the prevention and treatment of a wide range of ailments. Therefore, the purpose of this study is to provide an overview of often used medicinal herbs that have the potential to be employed in the management or prophylaxis of peptic ulcers. The topic of interest is to peptic ulcer disease (PUD) and its association with Helicobacter pylori (H. pylori) infection, as well as the potential use of herbal treatments in managing this condition.

Keywords: Peptic Ulcer Disease; H-Pylori Infection; Herbal Treatment; Proton Pump Inhibitor

Introduction:

Peptic ulcer is an acid-induced digestive tract lesion that causes denuded mucosa and extends into the submucosa or muscularis propria in the stomach or proximal duodenum. [1]. Peptic ulcer disease is estimated to affect 5–10% of the general population [2], however recent epidemiological studies have demonstrated a reduction in incidence, hospital admissions, and death [3,4]. This is likely due to new medicines and increased cleanliness, which reduced H. pylori infections.

Mucosal disruption in acid peptic illness patients is usually caused by a hypersecretory acidic environment, food, or stress. H. pylori infection, alcohol and cigarette usage, NSAID use, and Zollinger–Ellison syndrome increase peptic ulcer risk [5]. H. pylori and NSAIDs are major risk factors for gastric and duodenal ulcers [6]. Only a tiny percentage of H. pylori or NSAID users develop peptic ulcer disease, therefore individual susceptibility is essential early in mucosal injury. Functional polymorphisms in cytokine genes are linked to peptic ulcers. IL1B polymorphisms impact mucosal I 1β production, leading to H. pylori-related gastroduodenal disorders [7].

However, NSAID users had four times the risk of peptic ulcer complications and aspirin users two times [8]. Combining NSAIDs or aspirin with anticoagulants, corticosteroids, and selective serotonin reuptake inhibitors increases upper gastrointestinal bleeding risk [9]. Many persons who use NSAIDs or aspirin also have H. pylori infection, although their role in peptic ulcer disease is unclear. A meta-analysis of observational studies found that NSAIDs, aspirin, and H. pylori infection independently increase peptic ulcer disease risk [10].

Idiopathic H. pylori-negative, NSAID-negative, and aspirin-negative peptic ulcer disease may be detected in 20% of patients [11]. Idiopathic peptic ulcer is induced by an imbalance between mucosal integrity factors and aggressive insults, although the pathogenic processes are unclear [5]. A Danish research found that psychological stress increased peptic ulcers [12]. Ischemia, hormones, chemotherapeutic medications, radiation, viruses, histamine, eosinophilic infiltration, gastric bypass surgery, and metabolic abnormalities are further causes [13].

Peptic Ulcer Pathogenesis

H. pylori, a leading cause of peptic ulcer disease, colonises about half the globe [14]. H. pylori is more common in underdeveloped nations such Africa, Central America, Central Asia, and Eastern Europe [15]. The organism is generally acquired in infancy in dirty and overcrowded nations with poor socioeconomic position. H. pylori's inflammatory response involving neutrophils, lymphocytes, plasma cells, and macrophages degenerates and damages epithelial cells, especially in the antrum.

The way in which by which H. pylori causes various diseases in the gastroduodenal mucosa remains unclear. H. pylori infection causes hypo or hyperchlorhydria, defining peptic ulcer type. Infection by H. pylori is mediated by cytokines that block parietal cell secretion, H+/K+ ATPase α-subunit, CGRP-linked sensory neurons, or gastrin synthesis [16]. Despite hyposecretion, 10–15% of H. pylori patients had increased gastric secretion due to hypergastrinemia and lower antral somatostatin [17]. This results in enhanced histamine production and subsequent acid or pepsin release from parietal and gastric cells. H. pylori eradication also decreases gastrin mRNA and increases somatostatin [18]. Most individuals with stomach ulcers have hypochlorhydria and mucosal atrophy.

NSAIDs damage the gastroduodenal mucosa by systemically inhibiting constitutively expressed cyclooxygenase-1 (COX-1), which synthesises prostaglandins and decreases mucosal blood flow, mucus and bicarbonate secretion, and cell proliferation. Reversible, concentration-dependent enzyme inhibition by NSAIDs. The use of exogenous prostaglandins and COX-2-selective NSAIDs lowers mucosal damage and ulcer risk [19]. NSAID toxicity varies according to its physicochemical features [20]. NSAIDs tear down mucus phospholipids and uncouple mitochondrial oxidative phosphorylation, damaging mucosa. NSAIDs protonate in acidic gastric juice (pH 2) and pass lipid membranes to ionise and release H+ in epithelial cells (pH 7.4). NSAIDs bound in epithelial cells cannot penetrate the lipid barrier, causing oxidative phosphorylation uncoupling, decreased mitochondrial energy output, increased cellular permeability, and impaired cellular integrity. Patients with a history of peptic ulcers or haemorrhage, over 65, using steroids or anticoagulants, and taking large dosages or combinations of NSAIDs are most at risk for NSAID-induced ulcers. [1] Figure 1 depicts main pathophysiological pathways and antiulcer therapy locations.

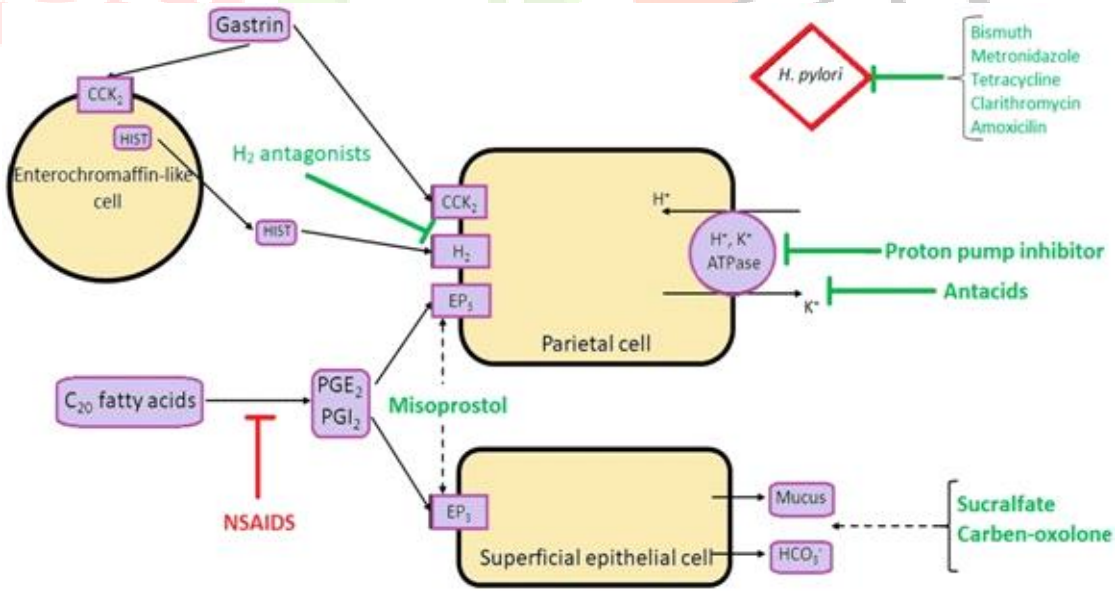

Figure 1: A presentation in the form of a schematic of the primary pathophysiological processes that play a role in the growth of peptic ulcer illness, as well as the sites where action occurs of the pharmacological choices that are most typically utilised during the management of this condition.

Cholecystokinin Receptor 2 (CCK2), Prostaglandin E2 (PGE2), Prostaglandin I2 (PGI2), Prostaglandin E Receptor 3 (EP3), and Histamine (HIST) are the abbreviations used here.

Treatment:

Tables 1 and 2 provide a concise summary of the many traditional antiulcer therapy methods available.

Table 1: Mechanisms of action and bad effects of the antiulcer treatments that are most often used by patients

Medicine		Mechanism of Action	Adverse Effects	References
Proton Pump Inhibitors (PPIs)	Omeprazole Lansoprazole Rabeprazole Esomeprazole Pantoprazole	Inhibition of the gastric H^+/K^+-ATPase (proton pump) enzyme system	Headache Abdominal pain Diarrhea Nausea Vomiting Constipation Flatulence Vitamin B12 deficiency Osteoporosis	[21,22]
H2 Receptor Blockers	Cimetidine Famotidine Nizatidine Ranitidine	Blocking the action of histamine at the histamine H2 receptors of parietal cells	Headache Anxiety Depression Dizziness Cardiovascular events Thrombocytopenia	[23]
Antacids	Aluminum hydroxide	Increases gastric pH to greater than four, and inhibits the proteolytic activity of pepsin	Frequency not defined: Nausea Vomiting Hypophosphatemia Chalky taste Constipation Abdominal cramping Diarrhea Electrolyte imbalance	[24]
	Magnesium hydroxide	Causes osmotic retention of fluid		

Potassium-Competitive Acid Blocker	Vonoprazan	Inhibits H^+, K^+-ATPase in gastric parietal cells at the final stage of the acid secretory pathway	Nasopharyngitis Fall Contusion Diarrhea Upper respiratory tract inflammation Eczema Constipation Back pain	[25,26,27,28,29]
Cytoprotective Agents	Misoprostol	Stimulate mucus production and enhance blood flow throughout the lining of the gastrointestinal tract	Diarrhea Abdominal pain Headache Constipation	[30,31]

Table 2: Various treatment approaches available to eradicate Helicobacter pylori (H. pylori), along with their rates of success.

Type	Duration	Efficiency	References
First line			
Standard triple therapy:			
PPI + two antibiotics (clarithromycin + metronidazile or amoxicilin)	7–14 days	70–85%	[32]
Second line			
Bismuth-containing quadruple therapy:			
PPI + bismuth salt + tetracycline + metronidazole	14 days	77–93%	[33,34]
Non-bismuth based concomitant therapy:			
PPI + clarithromycin + amoxicillin + metronidazole	14 days	75–90%	
Levofloxacin triple therapy:			
PPI + amoxicillin + levofloxacin	14 days	74–81%	
Salvage regimens			
Rifabutin-based triple therapy:			
PPI + rifabutin + amoxicillin	10 days	66–70%	[35]

Helicobacter pylori elimination:

PPIs block proton pumps:

Despite the importance of H. pylori eradication for mending peptic ulcers and avoiding relapses, antibiotic resistance makes it a worldwide issue. Bismuth, doxycycline, and metronidazole were administered for two weeks as the first successful treatment in the 1980s [14]. A proton pump inhibitor (PPI) and two antibiotics, such as clarithromycin plus amoxicillin or metronidazole, are administered for seven to 14 days as first-line treatment [32]. Over the past 10–15 years, triple treatment has been less effective due to antibiotic resistance, notably for clarithromycin. Base H. pylori eradication on antimicrobial susceptibility testing. Since susceptibility testing is rarely available in clinical practise, first-line therapies should be based on local antibiotic resistance, and clarithromycin-based regimens should be abandoned in areas with more than 15% resistance [36]. High-dose PPI and 14-day treatment may boost eradication [37].

The standard first-line treatment is a bismuth-containing quadruple therapy for 14 days (PPI, a bismuth salt, tetracycline, and metronidazole) or a 14-day concomitant therapy for bismuth-intolerant patients (PPI, clarithromycin, amoxicillin, and metronidazole) with eradication rates above 90% [38].

If the first line fails, the second line should not contain metronidazole or clarithromycin [39]. Levofloxacin triple treatment (PPI, amoxicillin, and levofloxacin) for 14 days yields 74–81% eradication [33]. H. pylori seldom develops amoxicillin resistance, thus bismuth quadruple therapy with eradication rates of 77–93% or a high-dose dual-therapy regimen with amoxicillin and a PPI is favoured after clarithromycin-based first-line treatment [34]. Even with well-recommended treatment regimens, 5–10% of individuals have chronic infection. Suboptimal compliance or H. pylori antibiotic resistance are the main causes of two-treatment failure, hence susceptibility testing is advised.

After at least three options fail, rifabutin-based triple therapy (PPI, rifabutin, and amoxicillin) for 10 days has eradication rates of 66–70% [35], but myelotoxicity and red secretions should be considered [40].

NSAID-Related Ulcers and PPIs:

Many methods may avoid NSAID and aspirin-associated gastroduodenal ulcers and their consequences, including co-therapy with a PPI, H2 receptor antagonist, or misoprostol, COX-2-selective NSAIDs, or gastroprotective agents. PPIs are the most effective and popular preventans [41]. Permanent attachment to the hydrogen/potassium ATPase enzyme on the cells of the gastric parietal cells reduces stomach acid generation. COX-2-selective NSAIDs and PPIs protect against gastrointestinal complications best [42]. Standard dosages of agonists of the H2 receptor cannot prevent stomach ulcers [43]. Despite preventing peptic ulcer complications, misoprostol's abortifacient and gastrointestinal effects restrict its gastric

protective application. Taking off the problematic substance for six to eight weeks heals ulcers in around 85% of patients. All gastric ulcers need repeat endoscopy to assess healing. Check medicine compliance if ulcers don't heal. Refractory ulcers are commonly treated by increasing PPI dosage for six to eight weeks, despite inadequate evidence. After ruling out false-negative H. pylori, malignancies, infections, Crohn's disease, vasculitis, upper abdominal radiation, cocaine usage, and Zollinger–Ellison syndrome should be considered for peptic ulcers.

One of the most overprescribed drugs worldwide is PPI [44]. PPI side effects include headaches, diarrhoea, constipation, and stomach pain are mild and manageable. However, new research have linked PPI usage to various dangerous side effects, which has alarmed patients and doctors. Ingested microbial pathogens that would have been eliminated by stomach acid may colonise the upper gastrointestinal tract and induce infections due to PPI suppression. PPIs may increase the incidence of Salmonella and Campylobacter enteric infections, community-acquired pneumonia, Clostridium difficile infections, and spontaneous bacterial peritonitis [45–47].

No stimulation of endocrine D cells to make somatostatin and no inhibition of G cells for gastrin release results in hypergastrinemia with gastric acid suppression. Gastrin promotes Barrett metaplasia and colon development [48]. Human PPI-induced hypergastrinemia is usually modest and seldom generates carcinoid tumours unless there is a hereditary mutation [49]. Since PPIs repair reflux esophagitis' persistent esophageal inflammation, they may prevent Barrett's oesophagus against cancer.

PPIs suppress gastric acid, which affects vitamin, mineral, and drug absorption. PPI users might develop vitamin B12 insufficiency and iron deficiency anaemia [50]. PPIs may also increase the risk of osteoporosis and bone fractures by interfering with calcium salt ionisation and solubilization [51]. The cause of hypomagnesemia is unknown. PPI-induced stomach acid reduction reduces ketoconazole absorption and increases digoxin absorption [52]. PPIs may also delay the clearance of warfarin, diazepam, and phenytoin, which are metabolised by the CYP P450 system. Since both are metabolised by CYP2C19, PPIs may impair clopidogrel's antiplatelet effect [53]. Although the clinical significance of the interaction is debated, the FDA advises against taking omeprazole or esomeprazole with clopidogrel.

Over the last several years, PPI-related myocardial infarction, stroke, acute and chronic renal disease, and eosinophilic esophagitis have increased dramatically. Patients on clopidogrel who also take PPIs may have more cardiovascular events due to the drugs competing for metabolism by CYP2C19, but PPIs may also have cardiovascular effects by decreasing nitric oxide production and altering vascular homeostasis [54]. PPIs may cause eosinophilic esophagitis by affecting peptic digestion [55]. Acid suppression. Gastric pH rises and pepsin is inactivated, preventing peptide intake and breakdown and triggering small intestinal allergies.

Potassium-Competitive Acid Blockers:

Lansoprazole still causes ulcer recurrence in up to 13% of patients, so alternate treatments are being sought. Vonoprazan, a potassium-competitive acid blocker, inhibits H+, K+-ATPase in gastric parietal cells near the end of acid secretion [25]. Vonoprazan inhibits the enzyme in a K+-competitive and reversible way without an acidic environment, unlike PPIs. Vonoprazan controls intragastric acidity quickly and long-term [26]. Vonoprazan at 10 mg and 20 mg was non-inferior to lansoprazole for preventing peptic ulcer recurrence in Japanese patients on NSAID therapy [25] or who needed aspirin for cardiovascular or cerebrovascular protection [27], with good tolerance, similar safety, and no new safety issues. Vonoprazan decreased post-endoscopic submucosal dissection bleeding in five weeks compared to eight weeks with PPIs [28]. It scarred fake ulcers better than esomeprazole [29] and rabeprazole [26], making endoscopic submucosal dissection safer.

Alternative Peptic Ulcer Treatment:

The use of medicinal plants to treat many ailments is called phytotherapy and is as ancient as humans. Alternative treatments and herbal goods, especially medicinal plant items, have grown in popularity in recent years [59,60]. Due to the negative effects of traditional medications for many ailments, medicinal plants are the main source of novel drugs. Plant extracts and crude are the main sources of novel medications and have showed promise in treating stomach ulcers [61]. Proton pump inhibitors, anticholinergics, antacids, antimicrobials, H2-receptor antagonists, sucralfate, and bismuth are ineffective and cause impotence, arrhythmia, hematopoietic alterations, hypersensitivity, and gynecomastia [62,63]. Due to it, screening plant extracts for novel pharmacologically active compounds revealed useful and safe gastroprotective medicines. Herbal ulcer disease treatments focus on antioxidant-rich herbs [63].

Phytochemical components, or secondary metabolites, provide medicinal plants their therapeutic powers. Thus, many plants employ phytochemicals to fight diseases [64]. However, the rise of resistance infections has forced pharmaceutical corporations to rethink their antibiotic research approach and produce plant-based antimicrobials [65]. However, synthetic antibiotics remain the primary antibacterial medications.

In the past 30 years, infectious illness occurrences have increased, including infections with various features and novel infections, and 60% of them are zoonotic. H. pylori, a significant member of that group, may cause chronic gastritis, peptic ulcer disease, and stomach cancer [66]. This study sought to identify medicinal herbs with strong antibacterial and antioxidant action against H. pylori and peptic ulcer disease. Some plants lose effectiveness against H. pylori due to resistance strains. Thus, ingredient separation from the most active plant extracts is promoted [67].

Herbal products may include bioactive elements with harmful and good effects. Therefore, doctors and patients need more herbal therapy education and legislation to control herbal product quality, especially for further randomised trials to determine the efficacy and safety of many products in digestive and other disorders [68]. Finally, Ayurvedic and contemporary medicine might create safer antiulcer medications from medicinal plants [69]. Table 3 lists medicinal herbs with strong antibacterial activity against H. pylori and advantages for gastric ulcer illness.

Table 3: Overview of traditional antiulcer treatments and how well they get rid of H. pylori.

Medicinal Plant	Possible Mechanisms	Effect	Adverse Effects	References
Korean red ginseng	Inhibition of *H. pylori*-induced 5-lipoxygenase (5-LOX) activity; preventing pro-inflammatory interleukin (IL)-8 or 5-LOX mRNA	Anti-inflammatory effect; increase eradication rates of *H. pylori*; reduction of gastric inflammation and oxidative DNA damage	Interaction with conventional drugs	[69,70]
Allium sativum	Inhibition of lipoprotein oxidation and lower serum glucose induction of antioxidant enzymes; mechanisms need to be more investigated	Antioxidant; suppressive effect of *H. pylori*-induced gastric inflammation in vivo and in vitro	Interaction with conventional drugs	[71]
Curcuma loga	Inhibition of *H. pylori*-induced 5-LOX activity	Anti-inflammatory; antioxidant	Not determined	[72]
Zingiber officinalis	Inhibition of PGE2 and parietal cell H^+, K^+-ATPase	Anti-inflammatory effect; antioxidant	Nausea and vomiting in pregnant women; restless, heartburn; interaction with conventional drugs (anticoagulants,	[73,74,75]

			analgesics)	
Zingiber zerumbet	Gastroprotective mechanism of zerumbone (significant increased in the endogenous antioxidant GSH, reduction of lipid peroxidation level); other mechanism need to be investigated	Antioxidant, antiproliferative, anti-inflammatory, antisecretory effect; reduction of ulcer area formation	Nausea and vomiting in pregnant women; restless, heartburn; interaction with conventional drugs (anticoagulants, analgesics)	[75,76]
Camellia sinensis (Green tea polyphenols)	Suppression of tumor necrosis factor-alpha (TNF-α) gene expression; inhibition of urease	Antioxidant; improvement in the function of intestinal bacterial flora	Interaction with conventional drugs; dizziness, diarrhea, headaches, insomnia, heartbeat, may cause deficiency of iron	[77,78]

Impact on H. pylori Elimination:

Conventional therapeutic failure has several causes. These include poor antibiotic bioavailability because the gastric mucus layer blocks antibiotic delivery to the underlying gastric epithelium [70]; the stomach's pH ranges from acidic to neutral, and only a few antibiotics as a are active in a variety of pH levels [79]; bacterial antagonism to antibiotics, where mutual infection with multiple strains is important [80]; and patient permissiveness.

Various medicinal plants have been studied for their anti-H. pylori properties. Recent research has shown that suppressing enzymatic (dihydrofolate reductase, DNA gyrase, myeloperoxidase N-acetyltransferase, and urease) and adhesive activities, high redox potential, and hydrophilic/hydrophobic constituents are key anti-H. pylori mechanisms. H. pylori-induced stomach inflammation may cause superficial, atrophic, and cancerous gastritis. Anti-inflammatory properties of natural products are attributed to inhibiting nuclear factor-κB and mitogen-activated protein kinase pathway activation and suppressing oxidative stress. Eradication alone cannot prevent H. pylori-related stomach malignancies because it ascends carcinogenesis rather than directly causes it [81].

Allium sativum, Zingiber officinalis, Korean red ginseng, and Cistus laurifolius suppress H. pylori colonisation, reduce the inflammation of the stomach by chemokine release, inhibit cytokine, and suppress precancerous changes by suppressing nuclear factor-kappa B DNA binding, which suppresses mutagenesis and produces abundant apoptosis. Before phytoceuticals become conventional treatment for H. pylori infection, other difficulties must be overcome [82].

Interactions between herbs and drugs:

As herbal supplement usage rises globally, so are adverse occurrences and medication interactions. Herbal supplements and drugs may interact pharmacokinetically or pharmacodynamically. Pharmacokinetic interaction occurs when a herbal supplement and a co-administered medication use the same mechanism of absorption, distribution, metabolism, or excretion, changing the drug's blood concentration and pharmacologic activity. Pharmacodynamic interactions affect a co-administered drug's mechanism of action without affecting its concentration, simply by antagonising or worsening its clinical effects [77-90].

P-gp-transported medicines such digoxin, doxorubicin, rosuvastatin, and verapamil are reduced by Allium sativum extract [91-102]. Warfarin is the most researched Allium sativum interaction, however controlled clinical studies have not verified this. Due to its platelet aggregation inhibitor, it should be taken cautiously in individuals with clotting problems or anticoagulants [103]. Zingiber officinalis inhibits thromboxane synthetase, which prolongs bleeding duration, however a clinical investigation has not shown this [104]. Due to platelet aggregation suppression, Ginkgo biloba may increase bleeding risk, particularly when used with anticoagulants. In humans, Ginkgo biloba flavonoids exhibit antiplatelet action but do not impact blood coagulation or platelet function [103]. In conjunction with NSAIDs, it might induce serious bleeding [105].

Panax ginseng induced CYP3A4, which reduces the efficacy of calcium channel blockers, statins, antihypertensives, and antidepressants [106]. In diabetic patients, panax ginseng has hypoglycemic action, and phenelzine may produce headache, shaking, and manic behaviour [107].

Green tea extract can increase simvastatin concentrations [108] or inhibit the drug transporters OATP1A1 and OATP1A2, which transport fluoroquinolones, beta blockers, and imatinib [77].

Among standard antiulcer treatments, cimetidine has significant medication interactions [109]. Studies have shown clinically significant interactions with warfarin, phenytoin, diazepam, chlormethiazole, propranolol, lidocaine, and others [110]. Cimetidine increases green tea's impact by inhibiting CYP1A2, which reduces caffeine's hepatic oxidative metabolism [111].

Conclusions:

Herbal items and traditional anti-gastric ulcer medications may work synergistically to fight H. pylori and enhance gastric ulcer outcomes. With limited human research, further clinical trials with bigger sample

numbers are needed to determine the effectiveness and safety of antiulcer medicinal plants. Design research to examine and clarify the mechanisms of action of medicinal plants used to cure or prevent peptic ulcer. To improve safety and quality and guarantee that randomised controlled trials confirm effectiveness, medicinal herbal products must be licensed. Despite rising herb–drug interactions, this sector has inadequate research and no solutions. Thus, chemists and physicians should be aware of the hazards of using herbal products alone or in conjunction with other herbal or conventional therapies.

Conflicts of Interest: The authors declare no conflict of interest.

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