Review Article

Integrative Strategies for Peptic Ulcer Disease: Therapeutic Synergy Between Conventional Treatments and Herbal Remedies in *Helicobacter pylori* Management

Bishal Sarkar[1*], Sanju Sarkar[2]

1. Department of Pharmaceutics, Mata Gujri College of Pharmacy, Kishanganj, Bihar, 855107, India.
2. Department of Pharmaceutics, BCDA College of Pharmacy & Technology, Hridaypur, Barasat, Kolkata, 700127, India.

***Corresponding author's E-mail:** grpbishal@gmail.com

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ABSTRACT

Peptic ulcer disease (PUD), a multifactorial and prevalent gastrointestinal disease, is predominantly associated with *Helicobacter pylori* (H. *pylori*) infection and chronic non-steroidal anti-inflammatory drug (NSAID) consumption. Although proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs), and antibiotic-based eradication therapy have transformed outcomes, rising antibiotic resistance and drug side effects necessitate the development of alternative therapy. Herbal compounds have gained major attention due to their gastroprotective, anti-inflammatory, antimicrobial, and antioxidant activities. In this review, the pathogenesis of PUD with special reference to H. *pylori* infection is critically discussed, the traditional pharmacological treatment strategies are evaluated, and the potential of herbal plants as adjunct therapy is explored. Representative phytotherapeutics like *Panax ginseng, Allium sativum, Curcuma longa, Zingiber officinalis, Zingiber zerumbet, and Camellia sinensis* have exhibited mechanisms like inhibition of H. *pylori* virulence factors, suppression of pro-inflammatory cytokines, mucosal defense strengthening, and modulation of oxidative stress. Interestingly, some herbal compounds modulate cytochrome P450 enzymes and drug transporters, thus raising safety concerns in polypharmacy status. Although promising in vitro, in vivo data, well-designed large-scale clinical trials establishing the efficacy, safety, and herb–drug interaction profile of these agents in human beings are few. Standardization of herbal extracts, quality control, and regulatory standards are also absent, therefore making them a challenge to be included in evidence-based clinical practice. This review highlights the importance of interdisciplinary coordination in assessing the therapeutic potential of herbal medicine in PUD management and in promoting safer and more effective integrative approaches in the battle against H. *pylori*-mediated gastric disorders.

Keywords: Peptic ulcer disease, *Helicobacter pylori*, herbal medicine, proton pump inhibitors, phytotherapy, herb–drug interactions, integrative therapy.

INTRODUCTION

Peptic ulcer disease (PUD) is a chronic, multifactorial gastrointestinal illness characterized by mucosal lesions invading the muscularis mucosae and most commonly occurring in the stomach (gastric ulcers) or proximal duodenum (duodenal ulcers)[1,2]. Acid-peptic lesions arise when the balance between offending agents—gastric acid, pepsin, and *Helicobacter pylori* (H. *pylori*)—and defense systems in the mucosa is disrupted. Global prevalence of PUD has been estimated to be present in 5–10% of the population at some point in their lifetime[3], although more recent epidemiological data have suggested a trend of declining incidence, hospitalization, and mortality rates[4,5]. These declines have primarily been because of better sanitation, awareness, and the overall usage of proton pump inhibitors (PPIs) and H. *pylori* eradication therapy.

Classically, PUD was ascribed primarily to stress, spicy food, and acid hypersecretion. Current understanding places strong emphasis on the significant role of H. *pylori* infection and consumption of non-steroidal anti-inflammatory drugs (NSAIDs) as the most significant etiologic factors[6,7]. Alcohol consumption, smoking, advanced age, genetic predisposition, and systemic diseases such as Zollinger-Ellison syndrome, resulting in hypergastrinemia and acid hypersecretion, are other risk factors contributing to it[6]. Despite the prevalence of H. *pylori* infection and widespread use of NSAIDs, very few people get ulcers, which suggests a host susceptibility, including genetic and immunologic factors.

Functional polymorphisms in cytokine genes— for example, *interleukin-1 beta* (IL1B)—that are involved in modulation of mucosal inflammatory responses and the outcome of H. *pylori* infection were described recently[8]. The genetic variation can affect acid output and gastric mucosal inflammation as well as add to ulcer risk. Moreover, patients taking NSAIDs and aspirin have between two- to four-fold greater risk for developing complications of ulcers, e.g., bleeding and perforation[9]. The risk is even more dramatically enhanced when NSAIDs or aspirin are co-administered with anticoagulants, corticosteroids, or selective serotonin reuptake inhibitors (SSRIs) due to the interaction synergistic effect on mucosal injury and disturbed clotting mechanisms[10].

The interaction among NSAIDs, aspirin, and H. *pylori* infection in the pathogenesis of PUD remains multifaceted. Although all of them commonly exist together, they have each been shown to independently increase the risk of the development of ulcers, as seen from a systematic review of observational studies[11]. Interestingly, there is also a group

of patients between 15–20% with idiopathic peptic ulcers, wherein there is no clear-cut etiological factor such as H. *pylori*, NSAID, or aspirin can be discernible[12]. The ulcers are both diagnostic and therapeutic challenges, and their pathogenic processes are poorly explained. Postulated hypotheses include mucosal defense alterations, ischemia, systemic inflammatory disorders, or insidious genetic predisposition.

Psychological stress has also been recognized as a potential aggravating factor in PUD. A extremely large Danish cohort study showed a significant link between stress and development of peptic ulcer, conceivably by neuroendocrine and immunological pathways that impair mucosal defenses[13]. Other rarer but important etiologic factors are ischemic injury, viral infection (i.e., cytomegalovirus), drugs such as corticosteroids and chemotherapeutic agents, radiotherapy, histamine-secreting neoplasms, eosinophilic infiltration, metabolic disturbances, and surgical alterations such as gastric bypass surgery[14].

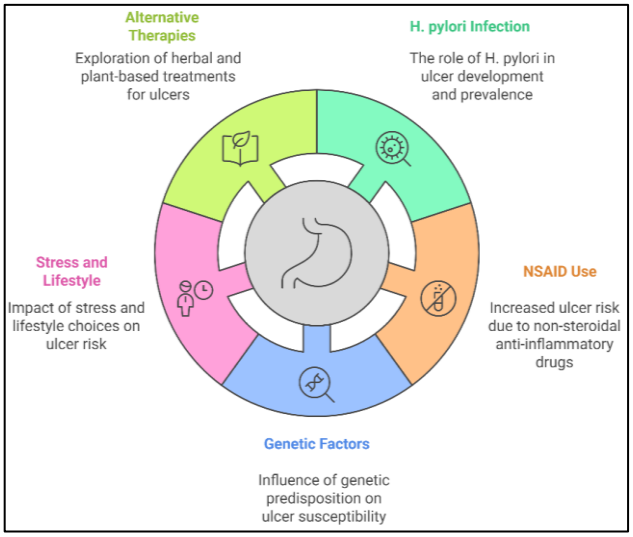

Figure 1: Overview of PUD

As the multifactorial etiology of PUD and the limitations of current pharmacotherapy—recurrence, side effects, and the developing antimicrobial resistance—persist, interest in the consideration of other therapeutic modalities is increasing. Herbal and plant medicines, in general, have come into focus due to their centuries-old history, broad pharmacological profiles, and relatively broad margins of safety. The aim of this review is to provide a general overview of conventional treatment of PUD and critically evaluate the role of herbal treatment modalities.

PATHOGENESIS OF PEPTIC ULCER

Peptic ulcer disease (PUD) is a multifactorial illness due to an imbalance between aggressive luminal factors—e.g., gastric acid, pepsin, and microbial agents—and defensive mechanisms of the gastroduodenal mucosa. One of the most significant etiologic agents is *Helicobacter pylori* (H. *pylori*), a gram-negative, spiral bacterium that resides in the gastric mucosa. Globally, it is estimated that about 50% of the population carries H. *pylori*, which is one of the most prevalent chronic bacterial diseases[15]. Prevalence is particularly rampant in low- and middle-income nations in Africa, Central America, Central Asia, and Eastern Europe, where overcrowding, inadequate sanitation, and low socioeconomic status allow for early-life acquisition[16].

H. *pylori* infection results in chronic gastritis, predominantly of gastric antrum, and leads to mucosal injury by an aggressive inflammatory process involving neutrophils, lymphocytes, plasma cells, and macrophages. The organism produces virulence factors like CagA, VacA, urease, and lipopolysaccharides that induce epithelial damage, apoptosis, and immune deregulation. Although the exact mechanisms through which H. *pylori* induces typical mucosal lesions remain to be studied, but it is believed that the acid-secreting pattern (hypochlorhydria vs. hyperchlorhydria) being controlled by infection dictates the ulcer location and type.

In peptic ulcers, H. *pylori* produce hypochlorhydria through damage to acid-secreting parietal cells and through cytokines such as *interleukin-1β* (IL-1β), which inhibit gastric acid secretion[17]. In contrast, around 10–15% of infected individuals develop increased acid secretion due to hypergastrinemia, low levels of somatostatin, and excessive stimulation of enterochromaffin-like cells, producing duodenal ulcers[18]. H. *pylori* can also influence H+/K+ ATPase activity, disrupt calcitonin gene-related peptide (CGRP) pathways, and alter gastrin and somatostatin mRNA expression levels. Remarkably, effective eradication of the infection corrects these changes, lowering gastrin expression and elevating somatostatin levels, thus normalizing acid regulation[19].

Other than H. *pylori*, ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) is another top etiology for peptic ulcer pathogenesis. Systemic inhibition of *cyclooxygenase-1* (COX-1) by NSAIDs is the major mechanism of their damage[20]. COX-1 is an enzyme that participates in the synthesis of cytoprotective prostaglandins which maintain mucosal blood flow, mucus and bicarbonate secretion, and regeneration of epithelium. Inhibition of prostaglandin synthesis by NSAIDs interferes with healing, reduces mucosal resistance, and enhances vulnerability to acid-peptic damage.

In addition, NSAIDs cause direct topical injury to gastric epithelial cells. At acidic gastric pH (~2), NSAIDs are in non-ionized form and can penetrate lipid membranes. Inside epithelial cells (~7.4 pH), they ionize, get trapped, and disrupt mitochondrial oxidative phosphorylation, causing ATP depletion, increased cell permeability, and epithelial necrosis[21]. NSAIDs may also bind to surface phospholipids, compromising the mucus barrier.

Severity of NSAID-induced mucosal damage is variable on the basis of a number of factors including drug potency, dose, duration, and physicochemical properties. The risk is markedly enhanced in elderly patients (≥65 years), those with prior history of PUD or gastrointestinal bleeding, and

in concomitantly treated patients on corticosteroids, anticoagulants, or dual NSAID therapy[1,2]. While COX-2 selective inhibitors and exogenous prostaglandin analogs (e.g., misoprostol) offer protective advantages, the toxic profile of NSAIDs is still a major clinical concern. Finally, the pathogenesis of PUD is an intricate interplay between microbial, pharmacologic, host genetic, and environmental factors. Awareness of these processes not only guides rational choice of drugs but also highlights the importance of preventive strategies—especially in risk groups.

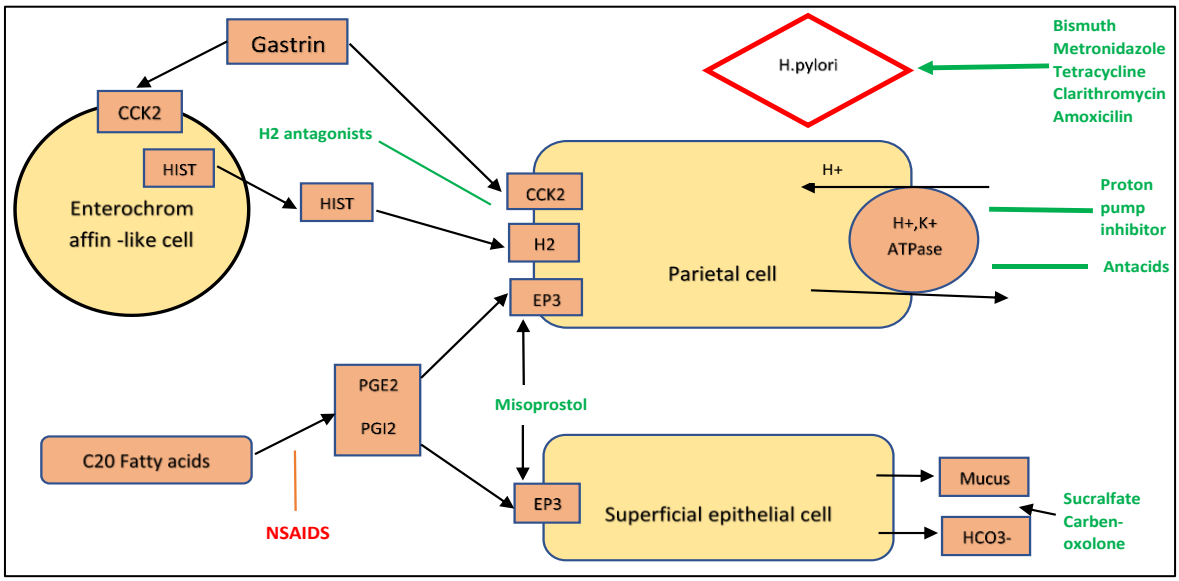

Figure 2: A schematic representation illustrating the principal pathophysiological mechanisms involved in the development of peptic ulcer disease, highlighting key molecular targets such as CCK2 (Cholecystokinin-2 receptor), PGE_2 (Prostaglandin E_2), PGI_2 (Prostaglandin I_2), EP_3 (Prostaglandin E receptor subtype 3), and HIST (Histamine), along with the primary pharmacological intervention sites of commonly used anti-ulcer agents.

Table 1: Pharmacological Agents for Peptic Ulcer Disease: Classification, Mechanisms, and Adverse Effects

Drug Class	Examples	Pharmacological Mechanism	Adverse Effects	References
Proton Pump Inhibitors (PPIs)	Esomeprazole Omeprazole Pantoprazole Rabeprazole Lansoprazole	Irreversible inhibition of the H+/K+ ATPase (proton pump) enzyme in gastric parietal cells, leading to profound suppression of gastric acid secretion.	Headache, gastrointestinal disturbances (nausea, vomiting, diarrhea, constipation), Vitamin B12 deficiency, osteoporosis, hypomagnesemia	22,23
H2 Receptor Blockers	Famotidine Cimetidine Nizatidine Ranitidine	Competitive inhibition of histamine H2 receptors on gastric parietal cells, reducing basal and stimulated gastric acid secretion.	Central nervous system effects (dizziness, confusion), thrombocytopenia, rare cardiac events, depression, gynecomastia (notably with cimetidine)	24
Antacids	Magnesium hydroxide Aluminum hydroxide	Direct chemical neutralization of gastric hydrochloric acid; magnesium salts may also exert osmotic laxative effects.	Diarrhea (magnesium-based), constipation (aluminum-based), electrolyte disturbances, hypophosphatemia, unpalatable taste	25
Potassium-Competitive Acid Blockers (P-CABs)	Vonoprazan Misoprostol	Vonoprazan acts as a reversible competitive inhibitor of H+/K+ ATPase (proton pump) enzyme; misoprostol, a prostaglandin E1 analogue, protects gastric mucosa by increasing mucus and bicarbonate secretion.	Diarrhea, abdominal discomfort, nasopharyngitis, skin reactions, uterine contractions (misoprostol), musculoskeletal pain	26–30
Cytoprotective Agents	Sucralfate	Forms a protective complex with ulcerated mucosa; stimulates local prostaglandin and bicarbonate secretion and improves mucosal blood flow.	Constipation, dry mouth, nausea, potential aluminium accumulation in renal impairment	31,32

HELICOBACTER PYLORI ERADICATION

H. *pylori* eradication is a cornerstone in the management of peptic ulcer disease, essential not only for healing ulcers but also for prevention of recurrence, complications, and gastric malignancies. Over the past two decades, however, the process of total eradication has become increasingly challenging with the global rise in antibiotic resistance, particularly to clarithromycin, metronidazole, and levofloxacin.

The initial effective H. *pylori* eradication therapy was introduced in the 1980s and was a 14-day treatment of bismuth, tetracycline, and metronidazole[15]. The "classic triple therapy" was eventually replaced by the current first-line treatment: a proton pump inhibitor (PPI) combined with two antibiotics—most often clarithromycin combined with amoxicillin or metronidazole—treated for 7 to 14 days[33].

Though this triple therapy worked well in the beginning, its efficacy in the past 10–15 years has significantly declined due to the rise in clarithromycin resistance. The local resistance pattern should be employed to individualize the treatment, and regimens centered on clarithromycin should be avoided where resistance is more than 15%[37]. Even antimicrobial susceptibility testing is not practiced in most general clinical settings, so evidence-based regimen selection is not feasible.

To increase the eradication rate, increasing treatment duration to 14 days and doubling the PPI dose has been shown to improve outcomes[38]. There are now two large first-line treatments that are recommended universally:

1. Bismuth quadruple therapy:

- PPI + bismuth salt + tetracycline + metronidazole
- Typically administered for 10–14 days
- Eradiates >90% [39]

2. Concomitant therapy (for patient's intolerant to bismuth):

- PPI + clarithromycin + amoxicillin + metronidazole
- Administered for 10–14 days
- Eradicates also >90% [39]

Second-line regimens are indicated in case of failure of first-line treatment. These should not include reuse of failed earlier antibiotics, particularly clarithromycin or metronidazole. An effective second-line regimen is levofloxacin-containing triple therapy—PPI, amoxicillin, and levofloxacin for 14 days—with eradication rates of 74–81% [34]. As an alternative, patients previously treated with clarithromycin-containing regimens can be switched to bismuth quadruple therapy or high-dose dual therapy (PPI + amoxicillin), with eradication rates of 77–93% [35].

In particular, resistance to amoxicillin remains rare and is a sturdy pillar in first-line and second-line regimens. Despite rigorous guidelines, 5–10% of the patients will have a residual infection after two courses of treatment. Failure in such cases is most likely to be due to lack of patient compliance or antibiotic resistance and should be confirmed with eradication confirmation and where feasible, susceptibility testing.

In the event of failure with multiple lines of therapy, salvage regimens are considered. One of them is rifabutin-based triple therapy with PPI, rifabutin, and amoxicillin for 10 days. The eradication rates of 66–70% [36] are obtained by this regimen. However, the clinicians must be careful about the side effects of rifabutin such as myelotoxicity and orange-red discoloration of body fluids [41].

Lastly, while eradication of H. *pylori* remains a significant goal in the treatment of peptic ulcer, the choice of therapy will have to rely on resistance patterns, pretreatment, and patient tolerance. The future of eradication therapy may increasingly rely on individualized therapy based on molecular diagnostics and genotypic resistance testing.

Table 2: *Helicobacter pylori* Eradication: Treatment Modalities, Duration, and Efficacy

Regimen Type	Therapeutic Approach	Duration	Reported Eradication Rate	References
First-Line Therapy	**Standard Triple Therapy** – Proton Pump Inhibitor (PPI) + Clarithromycin + Amoxicillin or Metronidazole	7–14 days	70–85%	33
Second-Line Therapies	**Bismuth-Containing Quadruple Therapy** – PPI + Bismuth salt + Tetracycline + Metronidazole	14 days	77–90%	34,35
	Non-Bismuth Concomitant Therapy – PPI + Clarithromycin + Amoxicillin + Metronidazole	14 days	75–90%	
	Levofloxacin-Based Triple Therapy – PPI + Amoxicillin + Levofloxacin	14 days	74–81%	
Salvage Regimen	**Rifabutin-Based Triple Therapy** – PPI + Rifabutin + Amoxicillin	10 days	66–70%	36

NSAID-ASSOCIATED ULCER DISEASE AND THE USE OF PROTON PUMP INHIBITORS (PPIS)

Aspirin and NSAIDs are already established as etiologic agents of gastroduodenal ulcers and complications thereof like perforation and bleeding. Numerous measures to prevent such toxic effects have been implemented such as co-therapy with gastroytoprotectors such as proton pump inhibitors (PPIs), H_2 receptor antagonists (H_2RAs), or misoprostol and use of preferentially COX-2-selective NSAIDs [42].

Among these, PPIs remain the most effective and widely used agents for prophylaxis of ulcers in patients at risk of NSAID-induced gastrointestinal toxicity. PPIs block the hydrogen/potassium ATPase enzyme (proton pump) on gastric parietal cells irreversibly, leading to effective and prolonged inhibition of gastric acid secretion [42]. Evidence suggests that the combination of a COX-2-selective NSAID and a PPI is most effective in preventing ulcer complications, particularly in high-risk patients [43].

Standard-dose H_2RAs are less effective in preventing the development of NSAID-induced gastric ulcers and are therefore not optimal for prophylaxis[44]. By contrast, misoprostol, a prostaglandin E1 analogue, substantially reduces the risk of NSAID-induced ulcer complications. Its clinical use is, however, limited by frequent gastrointestinal side effects like abdominal cramping and diarrhea and by its abortifacient effect, which restricts its use in women of childbearing potential.

When NSAID therapy is discontinued, more than 85% of gastric ulcers will resolve within 6 to 8 weeks of PPI therapy. Endoscopy follow-up is often needed to confirm healing, especially in symptomatic patients. If refractory ulcers do develop, noncompliance with medication should first be ruled out. With adequate compliance, doubling of the PPI dose for an additional 6 to 8 weeks is typically recommended, although little evidence exists to recommend this. Additionally, investigation for atypical causes of refractory ulcers like malignancy, infections, Crohn's disease, vasculitis, radiation injury, cocaine use, and Zollinger–Ellison syndrome should be undertaken after ruling out false-negative H. *pylori* test results.

Though effective, PPIs are some of the most overprescribed drugs worldwide, often used without clear indications [45]. Though generally safe, PPIs are associated with several possible side effects, some of which have raised significant concern in recent years.

Side effects are usually common and include headache, diarrhea, constipation, and abdominal pain. Acid suppression, however, may compromise the stomach's own defense mechanisms, allowing ingested pathogens to survive and colonize the upper gastrointestinal tract. Observational studies have linked long-term PPI use with an increased risk of enteric infections such as Salmonella and Campylobacter, and Clostridioides difficile infection, community-acquired pneumonia, and spontaneous bacterial peritonitis[46–48].

Long-term PPI treatment has also been hypothesized to cause hypergastrinemia by inhibiting the release of somatostatin from gastric D cells with subsequent stimulation of gastrin release from G cells. Gastrin is a trophic hormone that enhances the growth of enterochromaffin-like cells, and this has generated theoretic concern for the induction of gastric carcinoid tumors. Yet, in the majority of individuals, hypergastrinemia induced by PPIs is transient and only presents a serious neoplastic risk in those with permissive diseases such as MEN1[49,50]. Conversely, by healing reflux esophagitis and preventing inflammation, PPIs may reduce cancer risk in patients with Barrett's esophagus.

In addition, acid suppression may affect the absorption of essential micronutrients and certain medications. Growing evidence indicates that long-term PPI therapy is associated with iron deficiency anemia and vitamin B12 deficiency due to impaired release of nutrients from food matrices[51]. Even calcium absorption is reduced, particularly in the elderly, potentially contributing to a heightened risk for osteoporosis and fractures[52]. The pathophysiology of PPI-associated hypomagnesemia is not yet well understood, but it remains a focus of clinical concern.

Gastric acid suppression also alters the pharmacokinetics of medications. For instance, PPIs increase bioavailability of digoxin and reduce absorption of drugs like ketoconazole that are solubilized by an acidic medium[53]. PPIs can also block drugs metabolized by the cytochrome P450 enzyme system, namely CYP2C19. Such an interaction has been held responsible for reduced efficacy of clopidogrel, a prodrug that is converted to its active form by CYP2C19. While the clinical significance of this interaction is questioned, alerts against concomitant use of clopidogrel with omeprazole or esomeprazole have been released by the U.S. FDA[54].

More recently, studies have proposed potential associations of long-term PPI therapy with unforeseen complications like myocardial infarction, stroke, acute and chronic kidney disease, and eosinophilic esophagitis. Even though some of these are confounded by comorbid conditions, potential pathophysiology includes reduced nitric oxide bioavailability, vascular function modification, and disruption of immune or gastrointestinal pathways[55]. In eosinophilic esophagitis, pepsin inactivity due to increased gastric pH may impair peptide digestion and lead to increased exposure to allergen and triggering of immune response within the small intestine[56].

POTASSIUM-COMPETITIVE ACID BLOCKERS (P-CABS)

Despite prevalent proton pump inhibitor (PPI) exposure, recurrent ulceration still torments approximately 13% of patients treated with lansoprazole and underscores the continued necessity for stronger or alternative acid-suppressive treatment[26]. Potassium-competitive acid blockers (P-CABs) represent one newer class of drug. These medications inhibit the final step of gastric acid secretion by reversibly blocking the H^+,K^+-ATPase enzyme on gastric parietal cells, in a potassium-competitive manner—

mechanistically different from irreversible proton pump blockade with PPIs[26].

Vonoprazan, a first-in-class P-CAB, has been reported to possess some pharmacokinetic and pharmacodynamic advantages over standard PPIs. Vonoprazan, unlike PPIs, is not required to be activated within an acidic condition, allowing rapid onset of action and prolonged intragastric pH increase[27]. These properties are particularly beneficial in clinical situations where rapid acid suppression is required.

In Japanese patients on NSAID treatment, vonoprazan 10 mg once daily and 20 mg once daily was found to be noninferior to lansoprazole in the prevention of recurrence of NSAID-induced peptic ulcers[26,28]. Also, in patients on long-term aspirin treatment for cardiovascular or cerebrovascular protection, vonoprazan was found to be as safe and well tolerated as PPIs, with no additional safety concerns.

Vonoprazan has also proved to be effective in post-endoscopic submucosal dissection (ESD) therapy. Compared with PPI therapy, vonoprazan was shown to significantly decrease the rate of delayed bleeding within five weeks of treatment but took eight weeks for traditional PPIs to offer equal protection[29]. Vonoprazan also proved to be more effective than rabeprazole and esomeprazole in promoting scarring and healing of artificial ulcers created during endoscopy[26,30]. These findings offer the possible advantage of vonoprazan to enhance the efficacy and safety of endoscopic therapy.

With its new mechanism of action, rapid acid suppression, and favorable safety profile, vonoprazan is a promising new therapeutic agent for acid-related disorders, such as NSAID ulcers, especially in patients with partial PPI response or requiring rapid acid inhibition.

FUTURE RESEARCH DIRECTIONS

While the worldwide burden of *Helicobacter pylori* infection and secondary peptic ulcer disease is slowly diminishing, emerging challenges have refocused the research agenda. Notably, augmented antibiotic resistance continues to undermine the efficacy of standard H. *pylori* eradication treatment, as improper use and prolonged dependence on proton pump inhibitors (PPIs) have generated rare side effects[57].

In addition, a growing prevalence of idiopathic peptic ulcers occurs that are unconnected to either H. *pylori* infection or NSAID treatment and which have increased fatality rates. Even so, it is as yet unclear what optimal management regime there should be for idiopathic ulcers and which requires increased focussed studies in their cause and treatment[58].

The second unresolved issue is the interaction between H. *pylori* infection and NSAID or aspirin exposure. While both are major risk factors for peptic ulceration, the nature of the interaction between them remains to be clearly defined, especially in patients with both. Evidence-based research should be conducted on how to manage such patients.

Pathogenically, while it is certain that H. *pylori* induces mucosal injury by a synergy of bacterial virulence factors and host immunity, the pathogenic mechanisms in this process are not fully clarified. Specifically, additional investigation is required to explain how host polymorphisms at certain genes interact with H. *pylori* virulence factors and why some persons are more susceptible to H. *pylori*-induced ulceration. Furthermore, genetic basis for gastrointestinal toxicity of NSAIDs and aspirin remains a current field of investigation.

Despite the widespread historical acceptance of H. *pylori* urease as a potential target for treatment, drug development has been sluggish. Although a variety of good in vitro urease inhibitors have been described, selectivity issues, dosing, treatment costs, and associated bleeding complications have to a considerable extent prevented their use in clinics. Recent findings in molecular biology of H. *pylori* pathogenesis have referred to bacterial mechanisms of adhesion as being relevant targets for therapy. Nevertheless, genetic diversity and high-affinity binding at receptor-binding sites represent a significant obstacle to the production of broad-spectrum antivirulence drugs[59].

Attempts have also been made toward targeting more conserved components of H. *pylori*'s assembly and secretion machinery, particularly in the context of the proteomic diversity observed in virulence factors. These conserved pathways could be very valuable sources of guidance for future antivirulence therapy, though much work will be required to determine their translational relevance.

To this effect, comorbidities are now also the predominant cause of mortality among patients with peptic ulcer disease, yet concurrently, despite this, gastrointestinal bleeding is still a critical and life-threatening complication. Large prospective studies and randomized controlled trials are urgently required to determine the best prevention and management policies in high-risk populations.

Until new treatments are realized, strict adherence to existing clinical guidelines, correct diagnosis, and prevention of suboptimal treatment regimens of H. *pylori* will remain vital to continued success in managing peptic ulcer disease.

ALTERNATIVE THERAPY FOR PEPTIC ULCER

As a whole phytotherapy originated from the experience of people concerning the utilization of medicinal plants aimed at treating wide ranges of human diseases in human history[60, 61]." With past years of keen interest among more and more human beings on Alternative and complementary medicinal practices specially drug products developed based on plants medicine[60,61] this gained as a matter because of recent observation of variety as well adverse outcomes of convention treatment drugs. Medicinal plants have also come to be seen more and more as a great reservoir of potentially new, safer medicines, particularly in the management of peptic ulcer disease[62].

Traditional ulcer treatments—proton pump inhibitors (PPIs), H_2-receptor antagonists, antacids, anticholinergics, sucralfate, bismuth salts, and antimicrobials—may be suboptimal in offering relief and cause a number of side effects, e.g., impotence, arrhythmias, hematopoietic changes, hypersensitivity, and gynecomastia[63,64]. These limitations resulted in the need for more research on natural, plant-derived alternatives with gastroprotective agents. A number of plant extracts have shown useful antioxidant, anti-inflammatory, and antimicrobial activities and thus are potential candidates for treatment of ulcers[64].

The medicinal activity of the plants is primarily because of their production of secondary metabolites, including alkaloids, flavonoids, terpenoids, tannins, and phenolic compounds. These renewable and structurally diverse bioactive phytochemicals are the intrinsic defense mechanisms of the plants against disease and environmental stress[65]. Most importantly, they also show significant potential for development into pharmacologically active agents.

The surging wave of drug-resistant organisms has also intensified interest in herbal remedies. Resistance has also made pharmaceutical companies rethink their strategy in drug discovery, promoting the identification of new antimicrobial drugs derived from therapeutic plants66. Although synthetic antibiotics remain the prevailing choice, the infectious disease burden has increased in the last thirty years globally, especially with the rise of zoonotic diseases. Approximately 60% of these infections are thought to be zoonotic in etiology, Helicobacter *pylori*, a major cause of peptic ulcer, chronic gastritis, and gastric cancer, being a classic case in point[67].

One of the aims of this review has been to discover medicinal plants that possess both antibacterial and antioxidant activity against H. *pylori* and peptic ulcer disease. Resistance in H. *pylori* strains has, however, also extended to plant-derived therapies, lowering the efficacy of some phytotherapeutics. It is thus recommended that active constituents from the most potent extracts be isolated and characterized to develop more specific anti-H. *pylori* therapies[68].

It should be noted that herbal preparations often contain a complex mixture of bioactive constituents, some of which may produce toxic or undesirable effects as well as desired ones. Hence, regulatory control is necessary to ensure safety, efficacy, and quality of herbal drugs. In addition, more education of patients and clinicians regarding the correct use of phytotherapy is urgently required. Additional randomized controlled trials need to be done to define the therapeutic utility of these agents in peptic ulcer and other gastrointestinal diseases[69].

Lastly, the integration of modern principles of pharmacology and traditional systems of medicine such as Ayurveda may lead to the discovery of more effective, less toxic antiulcer drugs from medicinal plants[70].

Table 3: Overview of Herbal Antiulcer Agents and H. *pylori* Eradication Strategies

Herbal Plant	Family	Botanical Name	Mechanism of Action	Pharmacological Effects	Side Effects	References
Korean Red Ginseng	Araliaceae	*Panax ginseng*	Inhibits *H. pylori*-induced 5-lipoxygenase (5-LOX) activity; downregulates IL-8 and 5-LOX mRNA expression	Anti-inflammatory; enhances *H. pylori* eradication; reduces gastric inflammation and DNA oxidative damage	Possible interactions with conventional drugs	70,71
Garlic	Amaryllidaceae	*Allium sativum*	Antioxidant enzyme induction; inhibits lipoprotein oxidation and *H. pylori*-associated gastric inflammation; exact mechanisms under investigation	Antioxidant; reduces *H. pylori*-induced gastric inflammation (in vivo and in vitro)	Drug interactions (especially anticoagulants); may cause gastrointestinal upset	72
Turmeric	Zingiberaceae	*Curcuma longa*	Inhibits *H. pylori*-induced 5-LOX pathway	Antioxidant; anti-inflammatory	Not well established	73
Ginger (Common)	Zingiberaceae	*Zingiber officinalis*	Inhibits prostaglandin E2 (PGE2) and parietal cell H+, K+-ATPase enzyme	Antioxidant; anti-inflammatory; gastroprotective	Nausea, vomiting (especially in pregnancy), heartburn; may interact with anticoagulants and analgesics	74,75,76
Ginger (Bitter)	Zingiberaceae	*Zingiber zerumbet*	Enhances endogenous glutathione (GSH); reduces lipid peroxidation; involves	Antioxidant; antiproliferative; anti-inflammatory;	Like common ginger, may include GI distress; potential drug interactions	76,77

			gastroprotective actions (zerumbone); additional mechanisms under exploration	antisecretory; ulcer reduction		
Green Tea Polyphenols	Theaceae	*Camellia sinensis*	Suppresses TNF-α gene expression; inhibits *H. pylori* urease enzyme	Antioxidant; improves intestinal flora; modulates immune function	Possible drug interactions; dizziness, diarrhoea, headaches, insomnia; risk of iron deficiency with long-term use	78,79

THE EFFECT ON *H. PYLORI* ERADICATION

The failure of conventional therapy to eradicate *Helicobacter pylori* (H. *pylori*) infection is attributed to several key reasons. The most significant factor is the low bioavailability of the antibiotics, mainly because of the protective function of the gastric mucus layer that hinders effective penetration of the drug to the gastric epithelium[71]. Moreover, there are only a limited number of antibiotics stable enough to effectively work across the broad pH scale of the stomach from acidic to neutral[80]. It is also added by the reality of antibiotic-resistant microorganisms, commonly as co-infections of a mixture of different H. *pylori* strains, that also lower the effectiveness of treatment[81]. Patient failure to comply with treatment, diet, and lifestyle are other such challenges to treatment that can cause a serious adverse effect on outcomes of treatment[47].

The recent past has seen an upsurge in research work on the anti-H. *pylori* activity of medicinal plants. They have characterized their mechanisms of action as generally by inhibiting major bacterial enzymes—e.g., dihydrofolate reductase, DNA gyrase, myeloperoxidase, N-acetyltransferase, and urease—and interfering with bacterial adhesion to gastric mucosa. The high redox potential and hydrophilic or hydrophobic nature of certain phytoconstituents have also been suggested to contribute towards antibacterial action.

Chronic H. *pylori* infection induces gastric inflammation, which is an important determinant in the development of gastric cancer, atrophic gastritis, and superficial gastritis. Natural products have been reported to exert anti-inflammatory effects primarily through nuclear factor-kappa B (NF-κB) inhibition, mitogen-activated protein kinase (MAPK) signaling activation, and prevention of oxidative stress. These mechanisms have the potential to suppress the inflammatory cascade and restrict the occurrence of gastric mucosal injury.

Though the leading cause of gastric carcinogenesis, H. *pylori* itself is not a carcinogen. As such, eradication of infection may not be sufficient to avoid H. *pylori*-associated gastric cancers[82]. However, some medicinal herbs have been reported to express chemopreventive properties by suppressing key pro-inflammatory and apoptosis signaling pathways. Illustratively:

•Garlic (*Allium sativum*) and ginger (*Zingiber officinalis*) possess anti-inflammatory and antioxidant activities

•Korean red ginseng is reported to modulate immune functions and inhibit gastric mucosal inflammation.

•Cistus laurifolius inhibits cytokine production and NF-κB DNA binding, inhibiting mutagenesis and inducing apoptosis cell death.

These plants may suppress gastric inflammation collectively, inhibit precancerous alterations, and inhibit gastric cancer growth.

Despite these promising findings, there are a number of significant issues prior to phytoceuticals being accepted as mainstream treatments for H. *pylori* infection. These include standardization of herbal preparations, clarification of pharmacokinetics and pharmacodynamics, and large-scale clinical trials to establish safety and efficacy[83].

HERBAL AGENTS IN *H. PYLORI* MANAGEMENT

Korean Red Ginseng

Korean red ginseng (KRG) has been a focus of extensive interest due to its anti-inflammatory and anti-H. *pylori* activities. KRG exerts its effects via multiple molecular pathways, especially inhibiting the c-Jun transcription factor, NF-κB DNA binding, and H. *pylori*-induced generation of pro-inflammatory 5(S)-hydroxyeicosatetraenoic acid (5-HETE). Combined, these mechanisms are accountable for the inhibition of 5-lipoxygenase (5-LOX) activity and therefore prevention of the progression of H. *pylori*-induced gastric carcinogenesis.

KRG has also been shown to down-regulate 5-LOX mRNA expression and enzyme activity, thereby limiting leukotriene-induced inflammation. In addition, it may exert protective effects by inhibiting COX-2 and iNOS expression, and MAPK activation. It also inhibits TLR-4-mediated activation of inflammatory transcription factors triggered by H. *pylori* lipopolysaccharide. All these activities have an additive effect to down-regulate pro-inflammatory signaling cascades, thus reducing gastric mucosal damage[84,85].

In vitro studies by Kim et al. [84]showed that KRG prevented H. *pylori*-induced cytotoxicity. Clinical evidence also supports these results, with KRG supplementation found to enhance H. *pylori* eradication rates, reduce gastric inflammation, and prevent oxidative DNA damage and apoptosis, supporting its use as an adjuvant therapy for H. *pylori*[85].

Allium sativum (Garlic)

Allium sativum has also been widely used for their therapeutic and antimicrobial properties, which are primarily attributed to its organosulfur compounds, especially S-allyl-L-cysteine (SAC), SAC sulfoxides, and γ-glutamyl-S-allyl-L-cysteine. The bioactive constituents vary in different preparations because crude garlic is likely to be transformed into inert forms, so different extract preparations were standardized with different chemical compositions and biological activities[86].

Garlic extract has also been found to have excellent antioxidant activity by scavenging ROS, inhibition of lipoprotein oxidation, and induction of antioxidant enzyme activity under oxidative stress. It was found to exhibit anti-inflammatory activity by inhibiting H. *pylori*-induced gastric inflammation in vivo and exhibits apoptotic and tumorigenic inhibitory activities by cell cycle arrest and inhibition of cellular proliferation[87,88].

Moreover, it has been proven in vitro that the like compounds allicin, allyl-methyl, and acetonic allyl thiosulfinate in *Allium sativum* suppressed the growth of H. *pylori*, demonstrating its application as a natural anti-bacterial medication in gastric well-being[89].

FLAVONOID-BASED AND GINGER-DERIVED PHYTOTHERAPEUTICS IN *H. PYLORI* INFECTION

Cistus laurifolius

Flavonoids, an important group of secondary metabolites in the human diet, play a role in cell function and have a wide range of biological activities, including antioxidant, anti-inflammatory, and antimicrobial activity. Due to the unavailability of some flavonoids and their very high cost, synthetic pathways—e.g., methoxylation and bromination of flavanones—have been investigated to prepare compounds like 3′-demethoxysudachitin, a flavone with reported antibacterial activity against H. *pylori*[83,90].

Chloroform extracts of Cistus laurifolius have also been found to show excellent in vitro anti-H. *pylori* activities. Sudachitin and 3′-demethoxysudachitin are the most active antibacterial flavonoids present as isolated forms and reflect flavonoids' tremendous potential for being adjunct or alternative medicines in the traditional treatment of H. *pylori*. Additional studies by Nakagawa et al. have documented additional flavonoid compounds, e.g., (2S)-4′,7-dihydroxy-8-methylflavan, as very strong inhibitors of H. *pylori*[92].

In addition, certain isoflavones have been shown to harbor different antimicrobial activities and flavonoids with conventional antibiotics like metronidazole possessing synergistic therapeutic efficacies[91]. Such observations justify evidence to the therapeutic application of flavonoid-containing plant extracts like Cistus laurifolius in integrative treatment protocols against H. *pylori* in the background of growing antibiotic resistance phenomenon[43,77].

Zingiber officinalis (Ginger)

Zingiber officinalis or ginger is a spice and, in addition to that, it is an enormously valuable medicinal crop that exhibits anticancer, anti-inflammatory, and anti-ulcer activity, respectively, as noted. Its corresponding bioactive phenolic compound is 6-gingerol. It was documented to suppress the synthesis of prostaglandin E2 (PGE2), reduce oxidative stress, suppress parietal cell H+,K+-ATPase action, and lower gastric acid production and antiulcer effect[74,75].

Gingerol and zingerone, the two major phenolics of ginger, are endogenous proton pump inhibitors with a protective action against H. *pylori* ulcers. However, despite their efficacy, ginger extracts are limited by pharmacokinetic issues, including poor solubility in gastric juice and rapid intestinal absorption, which may limit their local therapeutic action in the stomach[94].

Jiang et al. substantiated in research that Z. officinalis has significant antioxidant activity against gastric ulcer models, though issues continue to lie with bioavailability in gastrointestinal transit[94].

Zingiber zerumbet

Zingiber zerumbet, a ginger plant, also shows strong gastroprotective activity, primarily due to zerumbone, its primary bioactive compound. With zerumbone pre-treatment, when given with an ethanol-induced gastric ulcer model in rats, it significantly postponed the occurrence of ulcer area, the efficacy being comparable to omeprazole. Particularly, zerumbone at 5 and 10 mg/kg body weight decreased ulcers by 75.59% and 88.75%, respectively, while omeprazole at 20 mg/kg decreased ulcers by 76.77%[95].

These observations indicate that zerumbone is significantly anti-ulcerogenically highly active, though its action against ethanol-induced ulcers still to be demystified. Its efficacy against various models of ulcers and putative molecular mechanisms involved need further research.

CAMELLIA SINENSIS, CURCUMA LONGA, AND ARTEMISIA ASIATICA: EMERGING HERBAL AGENTS FOR GASTROPROTECTION AND *H. PYLORI* ERADICATION

*Camellia sinensis (*Green Tea Polyphenols)

Camellia sinensis or green tea, is globally one of the most consumed beverages. The key chemopreventive and gastroprotective effects are mediated through the high content of polyphenols in the tea, that is most potent in epigallocatechin gallate (EGCG). They possess strong antioxidant, anti-inflammatory, and apoptosis-modulating effects and the ability to modulate intestinal microbiota composition. Inhibition of tumor necrosis factor-alpha (TNF-α) expression plays a dominant role that has an essential role in inflammation[96].

Significantly, *Camellia sinensis* has demonstrated anti-H. *pylori* activity. Green tea polyphenols inhibited the urease enzyme—a principal virulence factor for H. *pylori* colonization—preventing adhesion of bacteria to gastric

epithelial cells[97]. Additional research suggests green tea extracts inhibit H. *pylori* colonization by enhancing cell vacuolation and disrupting the VacA mechanism and urea transport, proposing in vivo anti-H. *pylori* efficacy[98].

The gastroprotective action of a 50% ethanolic extract has been examined in a model of rat gastric ulcers by Rao et al. (2008). Oral administration of the extract at the doses of 50, 100, and 200 mg/kg body weight for five consecutive days caused notable inhibition of ulcers induced by ethanol, pylorus ligation, and cold-restraint stress in a dose-dependent fashion. Its protective effect was correlated with the reduction of lipid peroxidation, inhibition of H+/K+-ATPase, and rise in the activity of antioxidant enzymes, particularly superoxide dismutase, which indicates its significant role in protection against oxidative damage to the gastric mucosa[99].

Curcuma longa and Artemisia asiatica

Few anti-inflammatory and antioxidant medicinal plants have been investigated as adjunct medications for H. *pylori* diseases and gastroesophageal reflux disease (GERD). They are Artemisia asiatica and Curcuma longa (turmeric), of which special interest has been taken.

Curcuma longa is also abundant in curcumin, a polyphenol with established anti-inflammatory, antioxidant, and antiulcer activities. Curcuma longa may guard against gastric mucus integrity, suppress gastric acid secretion, and suppress proinflammatory gene expression such as ICAM-1 and cytokine-induced neutrophil chemoattractant-2-beta (CINC-2β)[100]. Despite being well prevented from acute acid reflux esophagitis (RE) in rat models, Curcuma longa failed against chronic RE. Specific interest, co-treatment with DMSO markedly reduced esophagitis ulcer index, exhibiting synergistic antioxidant. Especially, curcumin enhanced lansoprazole in stimulating histopathological abnormalities to greater extent, witness to greater histological curcumin safety[102].

Artemisia asiatica and its bioactive fraction DA-9601 also demonstrated potential gastroprotection. Pretreatment with DA-9601 led to significant reduction in ulcer volume and thickness of the esophageal wall in preclinical models, and was better compared to that of ranitidine, a proven H2-receptor antagonist[101]. The findings confirm the therapeutic potential of Artemisia asiatica against gastric and esophageal mucosal injury.

HERB–DRUG INTERACTIONS: CLINICAL CONSIDERATIONS IN CO-ADMINISTRATION WITH HERBAL REMEDIES

Concomitant administration of drug and herbal supplement combinations is becoming more popular worldwide, and interest in potential herb–drug interactions is growing. Herb–drug interactions can be either pharmacodynamic(PD) or pharmacokinetic(PK).

Pharmacokinetic interactions are controlled through alterations in drug absorption, distribution, metabolism, or excretion and usually lead to variations in plasma drug levels and therapeutic action. Pharmacodynamic interactions, in contrast, alter clinical drug effects but not concentration, either by inhibiting or potentiating their action[78].

Herb–Drug Interactions of Common Significance:

•*Allium sativum* (Garlic):

- Described to reduce plasma levels of drugs transported by P-glycoprotein (P-gp) like digoxin, doxorubicin, rosuvastatin, and verapamil[103].
- Interacts with warfarin, which can increase the risk of bleeding due to its antiplatelet action, although there are no large clinical trials[104].
- Used cautiously in anticoagulated patients or in patients with bleeding disorders because it inhibits platelet aggregation.

•*Zingiber officinalis* (Ginger):

- May have a prolongation of bleeding time through the inhibition of thromboxane synthetase action, although this was not shown by clinical trials.
- Ginger, like garlic, is antiplatelet and can lead to increased risk of bleeding, particularly when combined with anticoagulants[105].

•*Ginkgo biloba*:

- Has flavonoids with antiplatelet effect but has no considerable impact on human blood coagulation factors[104].
- Combination with NSAIDs may increase risk of bleeding[106].

•*Panax ginseng* (Korean Red Ginseng):

- Inhibits cytochrome P450 3A4 (CYP3A4), with possible reduction in plasma drug levels and drug action of statins, calcium channel blockers, and antidepressants[107].
- Has been implicated in unwanted CNS effects (e.g., headache, tremors, manic reaction) when administered with monoamine oxidase inhibitors (e.g., phenelzine).
- Has been shown to exhibit activity as a hypoglycemia agent, which can add to the antidiabetic effect of drugs[108].

• *Camellia sinensis* (Green Tea Extract):

- Simvastatin plasma levels were increased, indicating inhibition of its metabolism[109].
- Inhibits organic anion transporting polypeptides (OATPs), OATP1A1 and OATP1A2, which can affect fluoroquinolone, beta-blocker, and imatinib absorption and transport[78].

Clinical Drug Interactions with Antiulcer Agents:

•The frequently prescribed antiulcer medication cimetidine is involved in multiple drug interactions as it inhibits cytochrome P450 enzymes, primarily CYP1A2 and CYP3A4.

- There have been documented clinically important interactions with warfarin, phenytoin, diazepam, chlormethiazole, propranolol, and lidocaine[110,111].
- Cimetidine also has the ability to enhance the effect of green tea, as it inhibits CYP1A2, thus reducing caffeine metabolism and possibly increasing CNS stimulation[112].

CONCLUSIONS

Concurrent application of herbal medicines with conventional anti-ulcer drugs offers immense scope for synergistic therapeutic advantage in the treatment of *Helicobacter pylori* (H. *pylori*) infection and gastric ulcer disease. Natural products have shown polypharmacology with multiple mechanisms of action like direct bactericidal action, anti-inflammatory action, inhibition of virulence factors (e.g., urease and VacA), antioxidant action, and gastroprotection by inducing mucosal defense and regulation of acid secretion. These findings put herbal medicine in a beneficial adjunctive role in the science of gastrointestinal medicine.

Considering these positive experimental findings, the current literature is limited by a lack of adequate large-scale, well-designed human clinical trials. Most data currently available have come from in vitro and animal studies, which, although useful, cannot be directly translated to man. Therefore, rigorous clinical trials with proper sample sizes and standardized regimens are the crying need to determine the efficacy, safety, optimal dose, and long-term effects of herbal preparations in human subjects. Furthermore, hard-core studies on pharmacokinetic and pharmacodynamic profiles are needed to determine the bioavailability, metabolism, and interaction potential of these plant compounds.

Another equally important area is regulation and standardization of herbal preparations. Unsteadiness in plant material due to unsteadiness in geographical origin, harvesting, processing, and extraction solvents can significantly impact reproducibility and therapeutic homogeneity. Institutionalization of quality control procedures, Good Manufacturing Practices (GMP), and licencing will facilitate safety, purity, and therapeutic homogeneity of herbal products. Randomized controlled trials (RCTs) shall be made compulsory to establish efficacy evidence before release of such products for clinical usage.

In addition, mounting numbers of reports of herb–drug interactions point to an urgent need for systematic pharmacovigilance. Most of the medicinal herbs, including *Allium sativum, Zingiber officinalis, Panax ginseng, and Camellia sinensis*, have demonstrated interactions with traditional drugs through the modulation of cytochrome P450 enzymes, P-glycoprotein transporters, platelet function, or metabolic pathways, and this may result in decreased drug efficacy or increased toxicity. For example, Panax ginseng was found to have an effect on the metabolism of antidepressants and calcium channel blockers, while *Allium sativum* may contribute to the risk of bleeding upon co-administration with anticoagulants. These are especially significant risks for the polypharmacy patients, for example, cardiovascular diseases, cancer, or diabetes.

To neutralize such threats, physicians, pharmacists, and other health care providers must be well educated about potential herb–drug interactions and actively inquire about the use of herbal products. Continuing education programs, clinical decision support systems, and pharmacological databases must be constructed so that they will aid in safe prescribing and patient education.

In conclusion, while the herbal remedies do hold tremendous potential to act as adjuncts or alternatives in treating H. *pylori*-induced gastric disorders, their integration into mainstream medicine needs to be reliant on rigorous scientific evaluation, robust clinical data, and rigorous regulatory oversight. The future shall see interdisciplinarity among scientists, doctors, pharmacologists, and the regulatory authorities in order to fully unlock the therapeutic potential of these drugs of natural origin while providing public health assurance.

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