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Review Article

Overcoming Antibiotic Resistance in Helicobacter Pylori: The Promise of Non-Antibiotic Therapies

Junjie Rao[1], Canyu Zhan[1], Jie Yang[2*], Yurong Huang[3], Dongmei Chen[3], Sheng Wu[3], Gengqing Song[4*]

[1]Guizhou Medical University, Guiyang City, 550004, Guizhou Province China

[2]Department of Gastroenterology, the Affiliated Hospital of Guizhou Medical University, Guiyang City, 550004, Guizhou Province China

[3]Department of Gastroenterology, Liupanshui People's Hospital, Liupanshui City, 553000, Guizhou Province China

[4]Department of Gastroenterology and Hepatology, Metro health Medical Center, Case Western Reserve University, Cleveland, OH.

***Corresponding authors:** Jie Yang, Department of Gastroenterology, the Affiliated Hospital of Guizhou Medical University, Guiyang City, 550004, Guizhou Province China.

Gengqing Song, Department of Gastroenterology and Hepatology, Metro health Medical Center, Case Western Reserve University, Cleveland, OH.

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Abstract

Helicobacter pylori (H. pylori) infection, a widespread global health concern, has traditionally been tackled with combinations of antibiotics and proton pump inhibitors (PPIs). While effective, these treatment regimens are frequently costly, complex, and replete with side effects. The rising tide of antibiotic-resistant H. pylori strains further clouds the long-term reliability of such antibiotic-focused approaches, making it imperative to explore alternative strategies. This article illuminates the promising frontier of non-antibiotic treatments, featuring exciting prospects like probiotics, herbal extracts, certain foods, antimicrobial peptides, and traditional Chinese medicine. This burgeoning field presents a fresh opportunity to circumnavigate antibiotic resistance, optimize eradication rates, and revitalize our fight against H. pylori. Our comprehensive analysis of the latest strides in non-antibiotic treatments strives to spotlight effective, safe, and patient-centric approaches that could bolster our arsenal against H. pylori. By highlighting these new-age solutions, we hope to stimulate further research and catalyse the development of personalized, innovative treatments for H. pylori infections, redefining its management in a sustainable way.

Keywords: Helicobacter Pylori; Drug Resistance; Non-Antibiotic Treatment.

Abbreviations: H. Pylori: Helicobacter Pylori; Ppis: Proton Pump Inhibitors; AMO: Amoxicillin; CAM: Clarithromycin; MNZ: Metronidazole; LEV: Levofloxacin; TET: Tetracycline; FZD: Furazolidone; GSRS: Gastrointestinal Symptom Rating Scale; BBR**:** Berberine; Pal: Palmatine; GES-1 Cells: Gastric Mucosal Epithelium Cells; NAC: N-Acetylcysteine; ITT Analysis: Intention-To-Treat Analysis; PP Analysis: Per-Protocol Analysis; PAC: Procyanidins; EPS: Extracellular Polymers; RHL: Rhamnolipid; Amps: Antimicrobial Peptides; Pnps: Pexiganan And Its Nanoparticles ; TP: Tilapia Piscidin; TCM: Traditional Chinese Medicine.

Introduction

Currently, the primary treatment options for Helicobacter pylori (H. pylori) infection include classical triple therapy, bismuth quadruple therapy, non-bismuth quadruple therapy, and a new dual therapy involving high-dose, multi-frequency Amoxicillin (AMO) and proton pump inhibitors (PPIs). Antibiotics play a crucial role in these eradication strategies, with their effectiveness hinging on H. pylori's resistance to the specific antibiotics employed. However, the use of antibiotics contributes to escalating H. pylori resistance and diminished initial eradication rates. Present remedial treatments consist of empirically substituting more sensitive antibiotics or incorporating new ones, which leads to increased antibiotic consumption.

At present, H. pylori eradication therapy faces a growing trend of antibiotic resistance, encompassing single-drug, double-drug, and even multi-drug resistance. The multi-drug resistance rate of H. pylori is influenced by factors such as countries, regions, and host characteristics, resulting in varied resistance rates across different regions within the same country. The most prevalent form of multi-drug resistance involves triple resistance to Clarithromycin (CAM), Metronidazole (MNZ), and Levofloxacin (LEV) [1]. Past reports indicate primary CAM resistance rates of 16-20% in Europe, 23-44% in the Eastern Mediterranean, 30-38% in the Western Pacific, and 10% in the Americas and Southeast Asia. Dual resistance rates to primary CAM and MNZ are 19% in the Mediterranean region and below 10% in other regions [2-4].

Recent studies reveal that primary and secondary resistance rates to CAM, MNZ, and LEV exceed 15% in the World Health Organization region [5], while resistance rates to AMO are around 0-5% [6]. In China, resistance rates to CAM, MNZ, LEV, AMO, Tetracycline (TET), and Furazolidone (FZD) are 34%, 78%, 35%, 3%, 2%, and 1%, respectively [7]. Double, triple, and quadruple resistance rates are 29.03%, 11.71%, and 0.11%, respectively. Patterns of dual resistance primarily involve CAM and MNZ or LEV and MNZ, while triple resistance mainly features CAM, LEV, and MNZ resistance. Quadruple resistance may also include AMO resistance [8].

Given the high levels of antibiotic resistance in H. pylori eradication treatments, achieving successful eradication on the first attempt is increasingly challenging. It is imperative to proactively explore alternative treatment methods to effectively manage H. pylori infection and counter the rising rates of antibiotic resistance. Non-antibiotic treatment approaches for H. pylori infection present promising potential, as they do not induce antibiotic resistance and could enhance H. pylori eradication rates.

Materials and Methods

The purpose of this study was to review the literature on Helicobacter pylori infection or treatment to explore the broad prospects of non-antibiotic active substances against Helicobacter pylori infection. Eligible academic papers were published between 2011 and 2022, and their content must be based on the scientific consensus of the international conference. We searched for published academic papers on Google Academic, PubMed, the China National Knowledge Infrastructure Database and Wanfang database, containing the keywords «Helicobacter pylori or H. pylori,» «drug-resistant,» «non-antibiotic treatment.» These literatures were then collected and evaluated.

Non-antibiotic strategies for treating H pylori Infection

Probiotics

Previous in vitro and in vivo studies [9] have revealed that probiotics can inhibit H. pylori through various mechanisms. For example, inhibiting H. pylori growth with the secreting of short-chain fatty acids and antimicrobial substances. Additionally, probiotics can compete for binding sites or interfere with adhesion to hinder H. pylori colonization, and they can enhance the mucus barrier by increasing the expression of muc1, muc2, and muc3, upregulating tight junction proteins, and promoting mucus secretion [10-11].

Despite these findings, the use of probiotics in H. pylori treatment remains controversial. Gisbert JP et al. [12]. concluded that adding a probiotic does not provide any benefits when the efficacy of eradication therapy is greater than 80%. In contrast, the Maastricht VI/Florence consensus report argued that while probiotics may not directly eradicate H. pylori, they can improve the eradication rate by reducing therapy-related side effects [13]. Similarly, a Chinese consensus highlighted that certain probiotics can help alleviate adverse gastrointestinal reactions resulting from H. pylori eradication therapy [14].

A study discovered that Lactobacillus reuteri-DSM17648 can specifically coaggregation H. pylori without affecting other commensal intestinal bacteria. This interaction reduces the amount of H. pylori in the stomach through selective bacterial-bacterial cell interactions [15]. Subsequently, Martin Buckley et al. [16].

conducted a single-blind, placebo-controlled study involving H. pylori-positive patients experiencing mild dyspepsia with Pylopass™. Researchers evaluated the changes in H. pylori load using the 13C-UBT method and monitored symptom alterations through the Gastrointestinal Symptom Rating Scale (GSRS). The study concluded that the mean 13C-UBTδ value decreased by 22.5% during the Pylopass™ treatment phase, while it increased by 37.3% during the placebo phase. After 28 days of Pylopass™ supplementation, 62.5% of patients showed a trend toward reduced H. pylori load, and 66.7% of patients showed a trend toward decreased overall GSRS scores. These findings suggest that Lactobacillus reuteri-DSM17648 has the potential to inhibit H. pylori infection and may improve gastrointestinal symptoms associated with it. In our study, supplementing H. pylori-positive adult patients with inactive Lactobacillus reuteri-DSM17648 for four weeks before starting standard triple therapy did not improve H. pylori eradication rates compared to the control group. However, it did help enhance the gastrointestinal microecological environment and reduced the incidence of adverse events like bloating and diarrhoea, resulting in a significant reduction in GSRS scores [17].

However, probiotics are typically not used as standalone treatments for H. pylori infection; rather, they are often combined with eradication regimens. The eradication rate for probiotics alone is estimated at around 14% [18]. Some research [19] suggests that better eradication results are achieved when probiotics are used before and throughout eradication therapy, or for more than two weeks. Bismuth has been found to inhibit probiotics, so taking them at different times is recommended.

It is essential to acknowledge that using probiotics as adjuvants to antibiotics for H. pylori treatment requires a longer duration, and individual responses can vary. The effectiveness of probiotics should be assessed rationally, and further research is necessary to establish guidelines regarding the appropriate choice, timing, and circumstances for probiotic use in combination with antibiotic therapy.

Herbal extract

The intriguing properties of herbal extracts like Berberine (BBR), Palmatine (Pal), and Capsaicin offer a fresh perspective in our fight against H. pylori. These naturally derived compounds, celebrated for their varied pharmacological effects, could present promising alternative strategies, especially in response to the diminishing efficacy of conventional antibiotic protocols.

BBR is an isoquinoline alkaloid derived from traditional Chinese medicine Huang Lian and other Berberis plants, known for its numerous pharmacological properties, including anti-tumour, anti-inflammatory, hypoglycaemic, and hypolipidemic effects. Within the digestive system, BBR inhibits toxins and bacteria (including H. pylori), safeguards the intestinal epithelial barrier, and alleviates liver injury [20]. One way, BBR inhibits urease activity and interferes with urease maturation by targeting urease active site-sulfhydryl, thus exerting anti-H. pylori effect [21]. Additionally, it has been shown to reduce the expression of hefA mRNA and significantly decrease the minimum inhibitory concentration of AMO and TET against specific H. pylori strains when treated with BBR [22]. Furthermore, combining BBR with triple therapy enhances the H. pylori eradication rate and reduces the overall incidence of treatment-related adverse effects [23-24].

Pal, also an isoquinoline alkaloid found in Coptis, can alleviate gastric mucosal damage during H. pylori infection, inhibit H. pylori-induced inflammatory response in gastric mucosal epithelium (GES-1) cells, counteract H. pylori-induced morphological changes and cytotoxic activity in GES-1 cells, and suppress matrix metalloproteinase-10 (MMP-10) expression during infection, as well as ADAM17 cleavage of EGFR ligands [25]. Through these various mechanisms, Pal protects the gastrointestinal tract and mitigates H. pylori-induced chronic atrophic gastritis.

Capsaicin, found in chili peppers, has been studied for its potential anti-inflammatory effects in H. pylori-induced chronic gastritis. In an experimental model using Mongolian gerbils, those fed a capsaicin-containing diet exhibited reduced neutrophil infiltration in the gastric sinus and gastric body, as well as decreased formation of ectopic hyperplastic glands [26]. Additionally, a relevant in vitro study [27] observed that capsaicin demonstrated strong antibacterial activity against a standard H. pylori strain (NCTC 11916: resistant to MNZ with an MIC of 250μg/ml), with an MIC of 62.5μg/ml. When combined with MNZ, the MICs of both capsaicin and MNZ were significantly reduced, indicating a potential synergistic effect between capsaicin and the antibiotic MNZ. The study also showed that capsaicin exhibited inhibitory effects on H. pylori urease. However, current epidemiological studies in humans are insufficient to establish that capsaicin can effectively counteract H. pylori transmission. For example, Chinese regions known for their spicy cuisine, such as Guizhou and Hunan, do not exhibit lower H. pylori infection rates compared to areas with milder culinary preferences, like Shanghai and Jiangsu.

This exploration of herbal extracts, BBR, Pal, and Capsaicin, reveals promising prospects for H. pylori treatment. BBR, known for its versatile pharmacological properties, inhibits H. pylori and boosts eradication rates, making it a potential adjunct to quadruple therapy. Pal, displaying wide-spectrum antibacterial and anti-inflammatory actions, guards against H. pylori-induced chronic atrophic gastritis, yet requires more research for clinical applicability. Capsaicin exhibits anti-inflammatory and antibacterial potential against H. pylori, but its real-world effectiveness remains to be established. Despite their promise, further research is necessary to harness the full potential of these herbal extracts for H. pylori treatment.

N-acetylcysteine

N-acetylcysteine (NAC) is a medication known for its antioxidant and mucolytic properties. Research has shown that NAC can inhibit H. pylori growth in a concentration-dependent manner in vitro liquid cultures. In animal models, administering NAC for three days after a one-week infection period reduces H. pylori load, and giving NAC for six weeks after a one-week infection helps prevent gastritis development and decreases H. pylori colonization. [28].

In order to investigate the damaging effects of ROS and the protective role of NAC in H. pylori-related diseases, Xie et al. established an in vitro co-culture system using H. pylori-infected gastric epithelial cells and an in vivo Balb/c mouse model. The study found that H. pylori infection significantly increased ROS levels and caused DNA damage in GES-1 cells both in vitro and in vivo. NAC treatment effectively reduced ROS levels and prevented DNA damage in GES-1 cells and the gastric mucosa of Balb/c mice. Additionally, H. pylori infection triggered ROS-mediated activation of the PI3K/Akt pathway, which was inhibited by NAC treatment. As a result, it was concluded that elevated ROS levels are a critical mechanism in H. pylori pathogenesis, and NAC may be beneficial for treating H. pylori-associated gastric diseases related to oxidative DNA damage [29].

Despite the theoretical implications, a real-world clinical applications have yet to produce substantial evidence that NAC can greatly improve the eradication rate of H. pylori. For example, it was found in related clinical trial studies that the use of NAC as an adjuvant to sequential therapy resulted in a higher H. pylori eradication rate compared to sequential therapy alone. The eradication rates were 67.3% and 58.0% in intention-to-treat (ITT) analysis (P=0.336) and 80.5% and 70.0% in per-protocol (PP) analysis (P=0.274), respectively. But the results of the study were not statistically significant[30]. Similarly, a randomized controlled trial comparing clarithromycin-based triple therapy with or without NAC for H. pylori eradication reported ITT analysis eradication rates of 81.7% for combination therapy and 84.3% for triple therapy alone (P=0.36). PP analysis eradication rates were 85.7% and 88.0%, respectively (P=0.40), indicating that adjuvant NAC therapy was not superior to standard triple therapy [31]. And the result was also supported by the recent meta-analysis [32].Thus, future research on NAC treatment for H. pylori infection might consider investigating its potential as a pretreatment rather than as an adjuvant therapy before implementing current eradication protocols.

Natural foods with anti-H. pylori properties

Cranberry are rich in nutrients and numerous bioactive components with antioxidant properties, including phenolic acids, procyanidins (PAC), flavonoids, and organic acids [33]. They can exert antimicrobial effects in various forms, such as juice, powder concentrates, capsules, and tablets [33]. PACs in cranberries have an A-type double bond, which can prevent the adhesion of E. coli to urinary epithelial cells, oral bacteria to dental surfaces, and H. pylori to stomach cells. However, PACs do not kill bacteria like antibiotics; instead, they inhibit adhesion, the initial step in the infection process, reducing the risk of resistant strain development [34]. To explore the impact of daily cranberry consumption on H. pylori, Li et al. studied different doses of cranberry juice and powder [35]. Per PP analysis revealed the highest H. pylori eradication rates at week 2 and week 8 in the high PAC cranberry juice groups, at 13.8% (P=0.041) and 20.00% (P=0.012) respectively. Drinking high PAC cranberry juice (44 mg/240 mL) twice daily for 8 weeks reduced H. pylori infection by 20% compared to other doses and placebo ($P < 0.05$). However, there was no statistically significant difference in H. pylori negative rates among the groups consuming cranberry powder. The study concluded that drinking PAC-standardized cranberry juice twice daily may help suppress H. pylori infection [35]. The meta-analysis conducted by Ronak Nikbazm et al.[36] showed promising H. pylori eradication rates with cranberry juice, but not with cranberry powder capsules.

Ginger extract (GGE03) has been shown to significantly reduce the expression of H. pylori-induced pro-inflammatory cytokines and inhibit the NF-κB signalling pathway activated by H. pylori. This suggests that ginger extract may help inhibit the growth of H. pylori and reduce inflammation in gastric epithelial cells caused by the bacteria [37]. Similarly, Somi MH et al. also discovered that ginger extract might provide gastric protection and exhibit anti-H. pylori properties by resisting bacterial adhesion, inhibiting bacterial growth, and suppressing gastric acid secretion. The eradication rate for H. pylori-positive dyspepsia patients was 53.3% ($P = 0.019$) after four weeks of ginger supplementation [38]. However, the effectiveness of ginger alone for treating H. pylori has not been confirmed in clinical studies.

Allicin, the primary component in onion and garlic, has been found to possess anti-H. pylori infection activity [39]. Studies have shown that individuals who never or rarely consume raw garlic have a lower H. pylori infection rate than those who frequently or daily consume raw garlic (51.5% vs 55.4%, $P = 0.0310$) [40]. In a study comparing the effectiveness of allicin quadruple therapy (IDFA) and bismuth quadruple therapy (IDFB) for treating H. pylori infection, Zhang et al. observed no significant differences in eradication rates, safety, or compliance between the two regimens, whether used as first-line or second-line treatments. Both regimens achieved acceptably high eradication rates. In first-line treatment, ITT analysis showed eradication rates of 87.5% for IDFA and 86.3% for IDFB ($P = 0.815$), while PP analysis revealed rates of 91.9% and 91.8%, respectively ($P = 0.980$). In second-line treatment, ITT eradication rates were 83.3% for both IDFA and IDFB ($P = 1$), and PP eradication rates were 89.3% and 88.9%, respectively ($P = 1$). These findings suggest that allicin quadruple therapy may serve as a potential alternative to bismuth quadruple

therapy in the future [41]. However, this trial only compared allicin with colloidal bismuth tartrate, without considering other bismuth preparations like bismuth subsalicylate and colloidal bismuth subcitrate. Additionally, doxycycline and furazolidone were used in both regimens. Previous studies have indicated that drug resistance to tetracycline antibiotics and furazolidone in China is relatively low compared to other antibiotics, such as clarithromycin. Therefore, it remains unclear whether allicin combined with other bismuth agents and antibiotics would achieve similarly high H. pylori eradication rates. It is evident that more research is needed to explore the potential of allicin-based treatment for H. pylori infection.

Type of substance	Mechanism of action	References
Berberine	Inhibits urease activity Inhibits biofilm formation anti-inflammatory	[21,42,43]
Palmatine	Inhibits urease activity	[44]
Patchouli alcohol	Inhibits urease activity Inhibits bacterial efflux pump gene expression	[45,46]
Dihydrotanshinone	Inhibits energy metabolism Removes mature biofilm	[47]
Cranberry (formerly Cyanidin)	Inhibits bacterial adhesion	[34]
Garlic (Allicin)	Alters the permeability of bacterial cell membranes	[48]
Ginger	Inhibits NF-κB signaling pathway Anti-inflammatory Anti-bacterial adhesion Inhibits bacterial growth and gastric acid secretion	[37,38]
Chili (Capsaicin)	Anti-inflammatory Inhibits urease activity	[26,27]

Table 1: Food and herbal extracts against H. pylori and their antibacterial mechanisms

Vitamins and trace elements

Previous research has shown that vitamin D3 (VitD3) can inhibit H. pylori infection by increasing the expression of the vitamin D receptor (VDR) and cAMP in mouse models infected with H. pylori [49]. Later research [50] discovered a negative correlation between Vit D levels and H. pylori infection. Patients with Vit D levels below 20 ng/mL had a 31% ($P< 0.001$) higher detection rate of H. pylori positivity compared to those with levels at or above 20 ng/mL. Moreover, Vit D played a role in eradicating H. pylori. In a study by Mohamed S. EL Shahawy et al. [51], the H. pylori eradication rate was significantly higher in the clarithromycin-based triple therapy group with added VitD3 (88.23% in PP analysis and 80% in ITT analysis) compared to the group without VitD3 (74.19% in PP analysis and 61.33% in ITT analysis).

Lei Jing et al. found through their study that H. pylori infection leads to changes in pepsinogen and gastrin levels, which subsequently increase the risk of gastric cancer. Gastric mucosa atrophy causes serum pepsinogen I (PG I) levels to decrease, while pepsinogen II (PG II) levels remain relatively stable or increase slightly. However, folic acid can inhibit gastric mucosa carcinogenesis by influencing gastrin and pepsinogen levels. Maintaining folic acid doses at 20-30 mg/day and treatment duration of 3-6 months positively impacts the pathological changes in gastric precancerous lesions [52].

Azhar Hussain et al. found a correlation between a high H. pylori infection rate and low levels of vitamin C (ascorbic acid) in gastric juice and serum. For H. pylori infection, vitamin C serves as a biological antioxidant to eliminate free radicals and functions as an immune enhancer to activate the immune system for prevention. Additionally, vitamin C acts as a cofactor in synthesizing type IV collagen in the gastric mucosa's lamina propria. Strengthened collagen in the subepithelial lamina propria reduces or inhibits H. pylori penetration into the deeper layers of the gastric wall. High concentrations of vitamin C can decrease the nickel centre of urease and inhibit its activity, thereby playing a role in treating H. pylori infection. Furthermore, vitamin C promotes the synthesis of prostaglandins, providing a protective effect on the gastric mucosa [53].

Zinc, an essential trace element for the human body, offers protective effects on mucous membranes and exhibits antibacterial properties. Huang et al. synthesized a small molecule, zinc linolenic

acid (ZnLla), which displayed significant antibacterial activity in vitro against both standard and clinically resistant strains of H. pylori with MIC values of 4-8 g/ml. Importantly, no resistance was observed during successive passages. The study also revealed that, compared to the previously standard triple therapy, ZnLla monotherapy or dual therapy (ZnLla combined with a proton pump inhibitor or PPI) demonstrated equivalent efficacy in reducing bacterial load in the stomachs of drug-resistant H. pylori-infected mice. Moreover, ZnLla exhibited minimal effects on the toxicity of normal tissues and the diversity and composition of intestinal flora in mice [54]. Hany G. Attia et al. found that AMO and zinc oxide nanoparticles displayed a synergistic effect against H. pylori infection [55]. Additionally, it has been shown that zinc acetate inhibits H. pylori growth and increases the susceptibility of H. pylori to LEV [56]. However, further research or data from large clinical studies are needed to investigate the mechanisms involved in improving H. pylori eradication rates with zinc preparations. Questions remain regarding whether combining standard triple or bismuth quadruple therapy can achieve better clinical outcomes and the safety of zinc preparations in terms of type selection and application.

Maotai-flavor liquor

Maotai liquor, a type of sauce-flavoured white wine, contains various high-boiling point compounds such as polyols, organic acids, aldehydes, ketones, esters, aromatic compounds, and amino acids [57]. Wang et al. observed that the rate of H. pylori infection was higher in drinkers compared to non-drinkers, which might align with popular assumptions [40]. However, other studies have indicated that the risk of H. pylori infection is significantly lower in alcohol drinkers than in non-drinkers. People who consumed wine or mixed alcoholic beverages exhibited a lower risk of H. pylori infection compared to beer drinkers. In individuals over 40 years of age, alcohol drinkers had a lower risk of H. pylori infection than non-drinkers, while among those under 40 years of age, alcohol consumption was not associated with the risk of H. pylori infection [58]. Furthermore, there may be gender differences in the association between alcohol consumption and H. pylori infection. In the male test group, the prevalence of H. pylori infection was higher in drinkers than in non-drinkers (63.9% vs. 54.1%), while in the female test group, the prevalence of H. pylori infection was lower in drinkers than in non-drinkers (10.8% vs. 56.4%). Consequently, alcohol consumption was a risk factor for men and a protective factor for women [59]. Thus, the relationship between alcohol consumption and the risk of H. pylori infection remains inconclusive.

During the exploration of various active ingredients in soy-based white wine and their potential mechanisms to inhibit H. pylori-induced damage to GES-1 cells, our researchers discovered that certain compounds, including aldehydes (ALD-22: 2-thiophenecarboxaldehyde), alcohols (AA-29: phenylethanol, MIC of 105.2ug/ml), ketones (KC-1: geranylacetone, MIC of 123.2ug/ml), and organic acids (OAC-18: 2,3-dimethyl-2-pentenoic acid, MIC 119.3ug/ml), not only impeded the growth and proliferation of H. pylori but also suppressed the secretion of inflammatory cytokines and oxidative stress in H. pylori-infected GES-1 cells. Specifically, AA-29, KC-1, and OAC-18 hindered H. pylori urease activity by downregulating the transcription of structural and auxiliary genes of urease. For instance, AA-29 significantly reduced the transcription of ureA, ureH, and nixA genes, while OAC-18 inhibited the transcription of ureA, ureB, ureE, and nixA genes, and KC-1 suppressed the expression of ureA, ureB, ureE, ureI, and nixA genes. Additionally, ALD-22, AA-29, and OAC-18 exerted inhibitory effects on H. pylori damage to GES-1 cells by attenuating the transcription of H. pylori-related virulence genes Bab A, Vac A, and Cag A, as well as the expression of Vac A and Cag A proteins [60-63].

However, alcohol consumption should be avoided while taking antibiotics to prevent disulfiram-like reactions. Moreover, alcohol consumption increases the risk of other diseases, and no relevant studies in China have reported that alcohol consumption reduces the rate of H. pylori infection. Although liquor can inhibit H. pylori growth through various mechanisms, alcohol consumption is not recommended as a means to reduce H. pylori infection.

Anti-biofilm method

H. pylori colonizes the gastric mucosa by secreting proteins, polysaccharides, extracellular DNA (eDNA), and producing extracellular polymers (EPS). These components combine and adhere to one another, ultimately forming biofilms [64]. Bacteria within biofilm structures exhibit greater resistance to harsh external environments compared to planktonic bacteria [65] with biofilm-embedded bacteria being 10-1000 times more resistant to antibiotic [66]. It is believed that EPS plays a significant role in the antibiotic resistance of H. pylori biofilms. One reason for this is that antibiotics typically target the interior of the bacterium, while EPS is situated in the outermost layer of the biofilm and surrounds the bacteria. This arrangement prevents direct interaction between human immune cells and H. pylori, and reduces the penetration of antibiotics [67]. Another contributing factor is the opposing charges of EPS and antibiotics; the former has a negative charge and the latter has a positive charge, making the EPS component of the biofilm a natural charge barrier that restricts the penetration of antibiotics [68]. Other related mechanisms include overexpression of bacterial efflux pump genes and the formation of globular H. pylori [69].

Rhamnolipid (RHL), a glycolipid biosurfactant, not only disrupts biofilm structure but also potentially inhibits bacterial adhesion. In a study by Chen et al. [70] found that combining RHL with antibiotics in conventional triple therapy significantly improved the eradication of H. pylori biofilms. The most effective combination, which included RHL, AMO, and PPI, had an eradication rate of over 95% and the lowest bacterial viability in the biofilm. Furthermore, RHL combined with antibiotics can inhibit the formation of H. pylori biofilms below the MIC, reducing the risk of recurrent infection. The study suggests that RHL has significant clinical potential as an antibiotic adjuvant in treating H. pylori biofilms. However, the efficacy of RHL-containing combinations requires further validation in animal models or human trials.

Antimicrobial peptides (AMPs)

The current resistance rate of H. pylori to certain antibiotics remains low, but future resistance issues may arise due to the widespread use of antibiotics. Recent studies suggest that AMPs could serve as a potential alternative to antibiotics in H. pylori eradication treatment. AMPs are a class of biologically active small molecule proteins that play a crucial role in the body's first line of defense against pathogens. They function by disrupting bacterial cell membranes, modulating immune responses, and regulating inflammation [71]. Most AMPs share common characteristics, such as the ability to kill drug-resistant strains, α-helical structure, cation city, high positive charge, and isoelectric point [72]. Due to their effectiveness against a broad range of drug-resistant bacteria and their reduced likelihood of developing resistance, AMPs have garnered significant research interest in recent years for their potential role in H. pylori treatment and related mechanisms.

Pexiganan

Pexiganan, a 22-amino acid AMP derived from the African clawed toad, has a molecular weight of 2.4 kDa and demonstrates potent bactericidal activity against both Gram-positive and Gram-negative bacteria, such as Staphylococcus aureus and Escherichia coli. Previous studies have reported the in vitro and in vivo activity of Pexiganan and its nanoparticles (PNPs) against H. pylori. Two clinical isolates of H. pylori (gastric ulcer strain and gastric cancer strain) and a standard strain (ATCC 43504) exhibited susceptibility to both Pexiganan and PNPs, with a minimum inhibitory concentration (MIC) of 4 μ g/m L. Pexiganan and PNPs eliminated over 106 CFU/mL of H. pylori within 20 minutes at four times the MIC. The MIC of MNZ, clarithromycin (CAM), and AMO gradually increased after 15 consecutive generations of the strains, with 36-fold, 15-fold, and 6-fold increases in the 15th generation, respectively. In contrast, the MICs of Pexiganan and PNPs against H. pylori remained relatively stable, similar to the initial values. These results suggest that Pexiganan and PNPs are effective against certain antibiotic-resistant H. pylori infections. Repeated oral administration of Pexiganan and PNPs in rat and mouse models of H. pylori infection demonstrated that PNPs adhered more firmly to the gastric mucosa, remaining in the stomach for extended periods and clearing H. pylori more effectively. In conclusion, Pexiganan is a promising agent for combating H. pylori infection [73].

Tilapia piscidin (TP)

Huang and colleagues investigated the MICs of five thiopeptides (TPs) against various H. pylori strains, including 43504, 700392, 43629, and multi-drug-resistant strain CI-HP-028b. They found that TP1, TP3, TP4, and TP5 inhibited H. pylori growth, except for TP2, with TP4 being the most potent. All four H. pylori strains were susceptible to TP4 (MIC: 1.5-3 μg/mL), which inhibited 99.9% of H. pylori at twice the MIC. Additionally, the researchers compared the time-based bactericidal activity of TP4 and conventional antibiotics against the multi-drug-resistant strain CI-HP-028b (resistant to both MNZ and CAM. TP4 reduced H. pylori counts by more than three-fold within six hours. Among the antibiotics, MNZ initially reduced bacterial counts but gradually lost activity, CAM continued to decrease bacterial levels, but the time required for a 90% reduction exceeded 24 hours, and only AMO caused 90% of H. pylori deaths within 24 hours. These findings suggest that TP4 is more effective against multi-drug-resistant bacteria than conventional antibiotics. When combined with AMO, CAM, and MNZ, TP4 demonstrated synergistic effects, reducing the MIC of AMO by a quarter and those of MNZ and CAM by half. In conclusion, TP4 may serve as an effective and safe mono-therapeutic agent for treating multi-drug-resistant H. pylori infections [74].

Bacteriocin PLNC 8

Bacteriocin PLNC8, secreted by Lactobacillus plantarum, has been shown to exhibit inhibitory effects on most Gram-positive bacteria and some Gram-negative bacteria [75]. Diffusion experiments demonstrated that bacteriocin PLNC8 could produce a 6-8 mm zone of inhibition against H. pylori ZJC03. The agar dilution method determined its MIC to be 80 μ M, indicating that bacteriocin PLNC8 effectively inhibits H. pylori ZJC03 growth and has significant anti-H. pylori ZJC03 potential. When treated with varying concentrations of PLNC8, the urease activity of H. pylori ZJC03 decreased as the PLNC8 concentration increased, ranging from 98.58 ± 0.86% to 25.68 ± 1.36%. This suggests a negative correlation between the urease activity of H. pylori and

the PLNC8 concentration. Furthermore, PLNC8 reduced the ATP levels and hydrogen peroxide sensitivity of H. pylori ZJC03, thereby disrupting its ability to modify the host environment [76].

AMPs are a promising class of anti-H. pylori substances due to their strong antibacterial efficacy and low risk of drug resistance. However, most previous studies on AMPs have been limited to animal experiments or in vitro studies, and the extraction, purification, and preparation of AMPs remain a significant challenge for clinical practice. Nonetheless, overcoming these obstacles could lead to significant advancements in the treatment of antibiotic-resistant H. pylori infections, making AMPs a valuable option in the era of antibiotic resistance.

Antibacterial peptide	Mechanism of action	References
Pexiganan	Attacks cell membrane Binds to lipopolysaccharide (LPS)	[72]
Tilapia piscidin	Induces H. pylori to form membrane micelles, thereby causing Depolarizes and extravasates cellular components and bacterial death Prevents bacterial immune escape	[74]
Epinecidin‐1	Ruptures H. pylori cell membrane Results in membrane lysis and death	[72,76]
Cathelicidins	Breaks the biofilm Forms pores in the cell membrane	[77]
PGLa‐AM1	Inhibits the growth of H. pylori with an MIC of 1 μg/mL	[78]
Bacteriocin PLNC8	Inhibits urease activity	[76]
Cbf-K16	Increases the permeability of bacterial cell membranes Inhibits bacterial adhesion and expression of cytotoxin-related genes	[79]

Table 2: Anti-H. pylori peptides and their antibacterial mechanisms

Unique advantages of Traditional Chinese Medicine in treating H. pylori infection

Traditional Chinese medicine (TCM) has a rich history and offers unique treatment options for gastrointestinal diseases, including H. pylori infection. TCM views H. pylori as belonging to the damp-heat pathogenic category, which is often associated with lifestyle factors such as a spicy and oily diet. TCM also recognizes that the body's deficiency and pathogenic factors can make one susceptible to H. pylori. According to TCM syndrome differentiation, H. pylori infection can be categorized into five types: spleen-stomach deficiency, spleen-stomach damp-heat, stomach-yin deficiency, liver-stomach disharmony, and stomach collateral blood stasis. Although the H. pylori infection occurs in the stomach, TCM recognizes that the disease occurs in the spleen, with the pathogenic factors being external invasion of pathogenic Qi, insufficient healthy Qi, and imbalance of Qi movement. The main treatment approach, therefore, focuses on clearing away heat and toxic materials, eliminating dampness with fragrance, and invigorating the spleen and Qi to restore balance and health [80-81].

Numerous experiments have demonstrated that a wide range of Chinese herbal monomers, formulas, and patent medicines have proven effective in inhibiting or killing H. pylori. Among them, the research is more in-depth may be Banxia Xiexin decoction, which is a herbal formula consisting of pinellia ternata, scutellaria, coptis chinensis, ginseng, rhizoma zingiberis, glycyrrhiza, and fructus jujube. Studies have demonstrated that this decoction can exert its therapeutic effects by inhibiting the Toll-like receptor (TLR)/NF-κB signalling pathway [82], regulating the TGF-β/Smad signalling pathway by inhibiting the expression of TGFβ1 and Smad3, and increasing the expression of Smad7[83]. Lin et al. found that patients with peptic ulcer or H. pylori-associated chronic gastritis who received Banxia Xiexin Decoction alone had a slightly higher cure rate and effective rate compared to the conventional treatment group. In addition, the clearance rate of H. pylori 1 month after treatment with Banxia Xiexin Decoction was slightly higher at 84.2%, compared to the triple therapy group (78.5%) and quadruple therapy groups (83.7%) [84]. Combining

Banxia Xiexin Decoction with triple therapy has been shown to significantly increase the H. pylori eradication rate up to 90% ($\chi 2 = 5.96$，$P<0.05$), which is notably higher than the triple therapy group. Furthermore, patients in the combination therapy group have reported a significant improvement in their quality-of-life scores, as well as a reduction in TCM symptom scores and adverse reactions compared to those who received triple therapy alone [85].

Hu et al. conducted a study showing that H. pylori infection can decrease the survival rate of human GES-1 cells and increase apoptosis levels, which can lead to gastric-related diseases. After intervention with Huangqi Jianzhong Decoction, the activity of GES-1 cells was significantly increased, and the expression of H. pylori-related virulence factors, such as BabA2, was reduced, demonstrating the decoction's anti-H. pylori effect [86]. Further studies in China revealed that the combination of Huangqi Jianzhong Decoction with acupuncture and moxibustion significantly reduced inflammatory reactions and regulated pepsinogen levels in the treatment of H. pylori-associated atrophic gastritis with spleen and stomach deficiency cold, thus significantly improving the eradication rate of H. pylori [87].

According to Jia [88] et al. Jinghua Weikang capsule has shown potent antibacterial activity against drug-resistant H. pylori strains, with MIC ranging between 64-1024 μ g/ml. Furthermore, treatment with 0.5 MIC Jinghua Weikang Capsule was able to reverse the resistance of 26,695-16R to MNZ, reducing its MIC from 64 μ g/ml to 6 μ g/ml. This effect was attributed to Jinghua Weikang capsule's ability to inhibit the adhesin/efflux pump-biofilm pathway. In combination with triple or quadruple therapy, Jinghua Weikang capsule can significantly increase the H. pylori eradication rate after four weeks of treatment, outperforming pure triple or quadruple therapy [89].

In addition to the previously mentioned therapies, TCM offers other effective treatments for H. pylori-positive patients with precancerous lesions of gastric cancer. For instance, the combination of Shengyang Yiwei Decoction and quadruple therapy can significantly alleviate patients' clinical symptoms, improve the H. pylori eradication rate, and reduce CRP and tumour marker levels, while also potentially delaying or reversing gastric mucosal lesions [90]. Studies have shown that the combination of Weisu Granule and Weifuchun Tablet is another effective TCM therapy for patients with atrophic gastritis. Studies have shown that this combination significantly increases the levels of G-17, PG-I, and PG-II in the serum of patients, reduces the levels of inflammatory factors, TCM syndrome scores, and gastric mucosa pathological scores, and improves the H. pylori negative conversion rate [91]. Additionally, several other traditional Chinese medicines have also demonstrated anti-H. pylori activity, which can be found in (Table 3).

While TCM has been shown to have many advantages, such as high eradication rates, low drug resistance, and low toxicity in the treatment of H. pylori, there are also limitations that need to be addressed. These include the complex composition of TCM, difficulty in extracting active ingredients, and a lack of fully elucidated inhibition mechanisms. As such, additional experimental and clinical studies are necessary to promote its application. Moreover, most of the studies on the treatment of H. pylori infection by TCM have been published in Chinese, with insufficient international communication and dissemination, and its effectiveness and specific mechanism of action need to be further confirmed in depth and detail by more researchers through basic and clinical studies.

Chinese Medicine	Pharmacological effects	Efficacy of combined Chinese and Western medicine treatment
Evodiamine	Down-regulates gene expression of H. pylori replication and transcriptional machinery; Down-regulates urease; Reduces of translocation of Cag A and Vac A proteins to AGS cells; Inhibits the activation of signaling proteins such as NF-κB and MAPK pathways[92].	-
Phillygenin	Causes leakage of ATP and inhibits biofilm formation (MIC of 16-32 μg/ml); Against H. pylori in acidic environment[93].	-
Zuojin Pills	Promotes GES-1 cell proliferation and ameliorates H. pylori-induced gastric epithelial cell injury; Down-regulates inflammatory response; Inhibits JMJD2B/COX-2/VEGF axis and HMGB1/NF-κB signaling pathway[94].	-
Jinghua Weikang capsule	Inhibit the inflammatory response and regulate the NF-κB signaling pathway; Reduces gastrointestinal inflammation and ulcers[95].	The combination of bismuth-containing quadruple therapy with Jinghua Weikang capsule significantly increased the eradication rate of H. pylori (93.85%) and significantly improved patients' symptoms such as indigestion[96].
Sanhuang XiexinTang plus	-	The eradication rate of H. pylori with the combination of standard triple therapy with Sanhuang XiexinTang plus and standard quadruple therapy containing bismuth was comparable, but the symptom improvement rate was elevated compared with standard quadruple therapy containing bismuth[97].
Chaihu Shugan Powder	-	Bismuth quadruple therapy combined with Chaihu Shugan Powder for gastric ulcer with high H. pylori eradication rate can reduce the TCM symptom score, improve serological indexes, and reduce the recurrence rate of gastric ulcer and H. pylori infection rate[98].
Huanglianjiedu Decoction	-	Bismuth quadruple therapy combined with Huanglianjiedu Decoction improved the cure rate of H. pylori infection (98.33%), reduced the reinfection rate within 2 years (6.67%), and increased CD3+, CD4+, and NK cell levels thus improving the cellular immune function of patients [99].

Table 3: Traditional Chinese Medicine for H. pylori infection

Conclusion

The search for safe, efficient, sustainable, and affordable treatments for H. pylori infection continues to evolve, with a focus on non-antibiotic substances that offer multi-component, multi-target antibacterial effects. These substances are less likely to induce drug resistance and cause adverse effects and side effects, while also improving inflammatory response and promoting mucosal repair. Promising avenues of exploration include probiotics, plant extracts, certain foods, AMPs, and TCM, as well as the integration of non-antibiotic therapies to address the limitations of current antibiotic-focused eradication protocols. Although there are still challenges to be overcome in their translational application, it is worth conducting more in-depth basic research or large-scale, randomized, double-blind clinical studies to gather data for their development and application, and to reverse the declining trend of H. pylori eradication efficacy. By exploring and implementing these non-antibiotic treatments, we can improve the health outcomes of those affected by H. pylori infection and reduce the global burden of related diseases.

Author Contributions

Dongmei Chen, Sheng Wu contributed to study conception and design. Canyu Zhan and Yurong Huang contributed to literature search and collation. Junjie Rao contributed to the literature collation and writing-original draft. Jie Yang contributed to the Supervision and critical revision of the work for important intellectual content. Gengqing Song contributed to conceptualization, project supervision, writing and editing manuscript. All authors have read and agreed to the published version of the manuscript.

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