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Research Progress in Integrative Chinese and Western Medicine Treatment and Molecular Mechanism of *Helicobacter Pylori*-Associated Chronic Atrophic Gastritis

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Abstract: Chronic atrophic gastritis (CAG) is a critical intermediate stage in the gastric mucosal inflammation-to-carcinogenesis cascade, with Helicobacter pylori (*H.pylori*) infection as its primary pathogenic driver. Confronted with rising antibiotic resistance of standard Western eradication regimens and limited efficacy in reversing advanced mucosal atrophy and intestinal metaplasia, this review systematically explores the pathogenic mechanisms of *H. pylori*-associated CAG and the diagnostic and therapeutic value of integrated traditional Chinese and Western medicine (ITCWM). We analyzed *H. pylori* molecular pathogenesis, summarized updated Western eradication regimens, interpreted the core of the 2025 Expert Consensus on CAG ITCWM diagnosis and treatment, and synthesized high-level clinical evidence of ITCWM. *H. pylori* mediates mucosal lesions via virulence factors that hijack signaling and drive epigenetic remodeling. High-dose dual therapy with a potassium-competitive acid blocker (P-CAB) provides an 89%–95% eradication rate and fewer adverse events. ITCWM enhances eradication success, while agents such as Weifuchun can reverse mucosal atrophy and low-grade dysplasia via multi-target actions. ITCWM provides an effective full-cycle management strategy for *H. pylori* -associated CAG, and its combination with regenerative medicine may further halt the gastric malignant transformation.

Keywords: *Helicobacter pylori*; Chronic atrophic gastritis; Combined treatment of traditional Chinese and Western medicine

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1. Introduction and epidemiological background

Chronic atrophic gastritis (CAG), a common digestive disorder, is marked by reduction and loss of intrinsic gastric mucosal glands and is frequently accompanied by intestinal metaplasia and dysplasia histopathologically. Worldwide, *H. pylori* infection is now recognized as the primary driver that initiates CAG, fuels progression, and culminates in carcinogenesis. Epidemiological data show approximately 50% global *H. pylori* prevalence; in high gastric cancer incidence regions, atrophic gastritis prevalence reaches 39.4% in *H. pylori* -positive populations, significantly higher than in negative cohorts [1]. The classic Correa cascade delineates gastric mucosal pathological evolution: normal mucosa →

chronic superficial gastritis → CAG → intestinal metaplasia → dysplasia → gastric cancer. As the core nodal stage of this cascade, CAG is acknowledged as the key intervention window to interrupt inflammation-to-cancer transformation and achieve pathological reversal [2]. Here is the revised, de-AI-ed text, with the letter count kept nearly identical and the academic tone maintained: Chronic atrophic gastritis (CAG) is a common digestive disorder marked by reduced and lost intrinsic gastric mucosal glands; intestinal metaplasia and dysplasia are frequent histopathological companions. Globally, *H. pylori* infection is now firmly established as the dominant driver behind CAG initiation, sustained progression, and eventual carcinogenesis. In response to these problems, the combination of traditional Chinese and Western medicine treatment provides a new strategy for the full cycle and precise management of CAG. This model, grounded in modern etiological control and endoscopic-pathological evaluation, integrates the overall syndrome differentiation of traditional Chinese medicine with multi-target Chinese medicine intervention, establishing a framework for eradicating pathogens, protecting mucosa, reversing pathology, and preventing canceration. Clinical data confirm that this model elevates eradication rates and mitigates antibiotic-associated adverse events, while achieving histologic reversal of precancerous lesions, an outcome that provides evidence-based support for interrupting the inflammation-to-carcinogenesis cascade [3].

2. Exploration of the molecular pathological mechanism of *Helicobacter pylori* in driving chronic atrophic gastritis

Understanding how *H. pylori* drives CAG pathogenesis lays the groundwork for developing precise therapeutic targets. Current evidence makes it clear that the gastric inflammation-to-carcinogenesis process relies on a complex regulatory network, spanning everything from virulence factor-induced tissue damage and immune dysregulation to aberrant signal transduction, epigenetic remodeling, and disrupted microecological balance. *Helicobacter pylori* use CagA and VacA as its core virulence factors to break down the gastric epithelial barrier, evade immune clearance, and hijack intracellular signaling networks. CagA is a major effector tied to precancerous lesions and enters host cells through the type IV secretion system (T4SS). Its C-terminal EPIYA motif gets tyrosine-phosphorylated by Src family kinases (SFKs), then binds and activates SHP-2, driving aberrant NF-κB, PI3K/Akt, and Wnt/β-catenin signaling. These events sustain chronic inflammation and damage epithelial cells [4]. At the same time, CagA can destroy p53, ATM / ATR, and other DNA damage response proteins, induce DNA mismatch repair (MMR) functional defects, and ultimately lead to microsatellite instability (MSI) -the latter is a genomic marker for the progression of gastric mucosal atrophy to dysplasia [5]. VacA enters host cells through endocytosis, which can induce cell vacuolar degeneration, mitochondrial dysfunction, and abnormal autophagy regulation. Autophagy is the core defense mechanism of the body against persistent infection of *Helicobacter pylori*, which can maintain the integrity of the cell genome. CagA and VacA work jointly in pathogenesis: both suppress expression of the key autophagy regulator Beclin-1 through epigenetic and transcriptional repression, thereby delaying autophagosome maturation and blocking autophagic flux [6]. Impaired autophagy causes accumulation of oxidative stress and DNA double-strand breaks, allowing precancerous cells to evade apoptosis and clonally expand, thereby driving the progression of precancerous lesions. Epigenetic regulation, which controls gene expression heritably without altering the DNA sequence, plays a central role in the Correa cascade. Persistent *H. pylori* infection activates the AKT-NF-κB pathway, increasing both expression and activity of DNA methyltransferase 1 (DNMT1) in gastric epithelial cells. This leads to hypermethylation of CpG islands in the promoters of tumor suppressor genes like MGMT, silencing their transcription. These epigenetic abnormalities disrupt the balance between epithelial proliferation and apoptosis and dismantle tumor-suppressive barriers, representing an early molecular mechanism that drives malignant progression of the gastric mucosa [7]. Moreover, CAG is regarded as an organ-specific inflammaging model. Low-grade chronic inflammation driven by *H. pylori* accelerates cellular senescence in the gastric mucosa. Senescent cells release senescence-associated secretory phenotype (SASP) factors, including pro-inflammatory cytokines and matrix metalloproteinases, which create a self-amplifying inflammatory loop. This exhausts the regenerative potential of gastric mucosal stem cells, driving the replacement of normal glands by fibrous tissue or spasmolytic polypeptide-expressing metaplasia (SPEM) [8].

3. Modern medical advancements in the eradication of *Helicobacter pylori* and chemoprevention

The Correa cascade represents the central pathological sequence from *H. pylori* -associated gastritis to gastric cancer. Standardized *H. pylori* eradication is broadly recommended as the most cost-effective primary prevention strategy for reducing gastric cancer incidence. Bismuth-containing quadruple therapy (BQT) was previously the standard first-line regimen [9,10]. However, with rising clarithromycin and levofloxacin resistance, conventional 14-day BQT eradication rates have dropped below 80% in some regions, accompanied by high pill burden and adverse events that compromise adherence. Potassium-competitive acid blocker (P-CAB)-based high-dose dual therapy (HDDT) has emerged as a breakthrough. P-CABs reversibly bind to the potassium site of gastric parietal cell H^+/K^+-ATPase, featuring faster onset, stronger and longer acid suppression, and CYP2C19-independent pharmacokinetics compared with proton pump inhibitors (PPIs). Stable intragastric pH above 6 drives *H. pylori* into active proliferation, increasing susceptibility to time-dependent antibiotics like amoxicillin. Multicenter randomized controlled trials (RCTs) in China confirm that 10-day and 14-day vonoprazan-amoxicillin dual therapy achieve 89–95% eradication rates in intention-to-treat, modified intention-to-treat and per-protocol analyses, with non-inferior efficacy to BQT [11]. Meta-analyses show HDDT has an 11.5% overall adverse event rate, 54% lower than BQT (RR = 0.46, $p < 0.001$), improving patient tolerability [12]. Accordingly, P-CAB-based HDDT is now recommended as first-line initial and rescue therapy in the latest Chinese consensus. In CAG patients with established intestinal metaplasia, eradicating *H. pylori* alone is not sufficient to reverse glandular atrophy or intestinal-type epithelial differentiation. Active chemoprevention and targeted optimization of the mucosal microenvironment are therefore needed alongside standard eradication treatment [2]. Rebamipide, a widely used mucosal protectant, downregulates local inflammatory mediators and boosts endogenous prostaglandin production, which in turn improves histological scores for antral atrophy and intestinal metaplasia [13]. For vitamin C, its ability to mitigate aberrant cell proliferation and apoptotic arrest stems from the upregulation of IGFBP7 and blockade of the HIF-1α/VEGF signaling pathway [14]. Folic acid serves as a core methyl donor in one-carbon metabolism; it reverses *H. pylori* -induced DNA hypermethylation and supports DNA repair. Findings from meta-analyses show that standardized folic acid supplementation slows and partially reverses the progression from atrophy to intestinal metaplasia, ultimately lowering gastric cancer risk [15].

4. Pathogenesis analysis of chronic atrophic gastritis in traditional Chinese medicine and the syndrome differentiation system in the 2025 expert consensus

In traditional Chinese medicine (TCM), CAG falls under the categories of epigastric fullness, epigastric pain, and epigastric upset, with a core pathogenesis of deficiency in the root and excess in the branch. First recorded in the ancient classic Huangdi Neijing, its external predisposing factors include *H. pylori* infection (categorized as an exogenous pathogenic toxin), improper diet, and emotional dysregulation, while spleen-stomach deficiency is the fundamental root. Deficiency patterns, mainly spleen Qi deficiency and stomach yin deficiency, persist throughout the disease course. The condition progresses from Qi stagnation and stagnated heat to dampness-heat accumulation, and further evolves into Qi deficiency with blood stasis and toxin injury to gastric collaterals with prolonged course. This deficiency-excess intermingled state corresponds to the glandular atrophy and inflammation-cancer transformation described in modern medicine. The 2025 Expert Consensus on CAG ITCWM standardizes clinical pathways and establishes a precision assessment system integrating TCM and modern medicine [3]. For modern medical diagnosis, it recommends OLGA (atrophy staging) and OLGIM (intestinal metaplasia staging) systems as severity assessment standards, adopts the Kimura-Takemoto classification for endoscopic atrophy evaluation, and establishes a quantitative gastric cancer risk scoring system to guide individualized treatment and surveillance. For syndrome differentiation, the consensus classifies CAG into six core TCM patterns based on clinical data and expert experience: liver-stomach Qi stagnation, liver-stomach stagnated heat, spleen-stomach dampness-heat, gastric collateral blood stasis, spleen-stomach deficiency, and stomach yin deficiency.

Each pattern is diagnosed by corresponding primary symptoms, characteristic tongue manifestations, and at least two secondary symptoms, with pulse findings as auxiliary reference [3].

5. Clinical evidence-based advantages of combining traditional Chinese and Western medicine in the treatment of Hp-related CAG

Against high *H. pylori* antibiotic resistance, the Second Beijing Consensus on ITCWM for Hp-related "Disease-Syndrome" Conditions states that integrating TCM syndrome differentiation into Western antibiotic regimens is a promising strategy to optimize eradication approaches [16]. Clinical evidence shows that adding Chinese herbal formulas (e.g., Banxia Xiexin Decoction, Lianpu Decoction) to conventional PPI-based triple therapy or BQT significantly improves eradication rates. Combined therapy shows non-inferior overall efficacy to standard BQT (effect ratio = 0.96, 95% CI: 0.89–1.03), with optimized regimens reaching RR = 2.58 for successful eradication. The most prominent advantage of herbal combination therapy is its toxicity-reducing effect, with 94% expert agreement. Herbal medicines mitigate gastrointestinal adverse reactions, modulate the host microenvironment, interfere with bacterial colonization, and downregulate virulence factors, reflecting TCM multi-target holistic regulation. This benefit enhances patient adherence and ensures full regimen completion. For rescue therapy, some herbal-augmented regimens achieve a 92— 1% per-protocol eradication rate with only 10-day antibiotic exposure, reducing antibiotic duration [16]. Weifuchun, the first NMPA-approved Chinese patent medicine for gastric precancerous lesions, consists of Red Ginseng, Isodonis Herba and stir-fried *Fructus Aurantii*, targeting CAG pathogenesis of spleen qi deficiency, qi stagnation-blood stasis and toxin accumulation [17]. A 2023 PLOS ONE meta-analysis including 15 RCTs (1488 patients) showed significantly higher overall clinical efficacy in the Weifuchun group than in controls (RR = 1.52, 95% CI: 1.41–1.63, $p < 0.00001$), with improved endoscopic appearance (RR = 1.42, $p < 0.0001$) and 2. 34-fold higher risk of histological regression of atrophy, metaplasia and dysplasia (RR = 2.34, 95% CI: 1.22–4.49, $p = 0.01$). Weifuchun also showed superior residual *H. pylori* eradication efficacy (RR = 1.26, $p = 0.02$), with no serious adverse events reported [18]. Moluodan, another agent for precancerous lesion regression, contains herbs including *Bulbus Lilii*, *Radix Ophiopogonis* and *Radix et Rhizoma Notoginseng*, indicated for CAG with stomach yin deficiency and gastric collateral blood stasis. A multicenter RCT found that after one-year intervention, Moluodan was non-inferior to folic acid in overall pathological improvement, with a significant advantage in reversing low-grade dysplasia [19]. It also achieved 37–83% symptom resolution rates for epigastric pain, fullness and belching, superior to controls. Other patent medicines such as Biling Weitong Granules also improve eradication rates and mucosal repair when combined with standard therapy [3].

6. Molecular pharmacological mechanism of traditional Chinese medicine compound and effective monomers in interfering with the Correa cascade reaction

What makes Chinese herbal medicine uniquely effective at reversing gastric atrophy and intestinal metaplasia, at its core, is its multi-target synergy rather than a narrow single-target mechanism. Packed with a diverse array of natural bioactive molecules, compound herbal formulas deliver network-level regulation and blockade of the gastric precancerous cascade across multiple layers, from epigenetics and cellular signaling to immunometabolism and microecology. Chronic local inflammation is the core driver behind glandular atrophy, and bioactive monomers from herbal medicine are particularly well suited to interrupt this inflammatory cascade through multi-target intervention. Lab experiments and network pharmacology analyses consistently show that Weifuchun's central mechanism against chronic atrophic gastritis lies in its strong ability to suppress activation of the NF-κB signaling pathway. This in turn sharply reduces levels of pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α, and cuts down abnormal accumulation of CD68-positive macrophages in the gastric mucosa. One key detail: Weifuchun stops the p65 subunit, the core component of NF-κB, from

binding to the promoter of CDX2, the key transcription factor that triggers intestinal metaplasia. By holding back CDX2 at the transcriptional level, it halts the abnormal intestinal-type differentiation of gastric mucosa. On top of that, Weifuchun protects gastric intrinsic glands from fibrosis and excessive apoptosis by modulating the IL-6/JAK1/STAT3 pathway and inhibiting the TGF-β/PI3K/Akt signaling axis [20]. Berberine, the main active alkaloid from *Coptis chinensis*, has broad anti-inflammatory and anti-tumor properties. In the *H. pylori* -infected microenvironment, berberine works on two fronts: it exerts direct antibacterial effects, and it interrupts the inflammation-driven cascade of cellular damage by blocking aberrant activation of the NF-κB and IRF8/IFN-γ pathways. At the same time, it activates IL-4-STAT6 signaling to push macrophage polarization toward the anti-inflammatory M2 phenotype. This reshapes the immune microenvironment disrupted by *H. pylori*, and shields the gastric mucosal epithelium from immune-mediated injury. This combined action from direct bacterial killing to immune modulation reflects the layered, sophisticated nature of its therapeutic mechanism [21].

7. Summary

Hp-related chronic atrophic gastritis is the core pathological hub in the chain of gastrointestinal inflammation-cancer transformation. This review discusses recent progress. This paper systematically reviews the research progress in this field in recent years, and points out that *Helicobacter pylori* (Hp) can hijack the host cell signaling pathway through virulence factors such as CagA and VacA, interfere with epigenetic modification, and destroy the regulatory network of autophagy and DNA damage repair, which is the core molecular mechanism of Hp-induced gastric mucosal gland atrophy and intestinal metaplasia. In modern medical treatment, high-dose dual therapy based on potassium-ion competitive acid blocker (P-CAB), represented by vonoprazen, can build a lasting and powerful acid-suppressing microenvironment in the stomach, solve the problem of high antibiotic resistance in traditional bismuth quadruple therapy, achieve more than 90 % Hp eradication rate, and significantly reduce treatment-related adverse reactions. The integrated traditional Chinese and Western medicine (ITCWM) paradigm provides a feasible way to get out of this clinical deadlock. Under the guidance of the Expert Consensus on Integrated Traditional Chinese and Western Medicine Diagnosis and Treatment of Chronic Atrophic Gastritis in 2025, an integrated evaluation model combining OLGA / OLGIM pathological staging, serological risk score, and six core TCM syndrome differentiation frameworks was constructed to make clinical intervention more refined. Evidence-based data confirm that adjuvant traditional Chinese medicine in the eradication stage can further improve the eradication effect and play a significant role in reducing toxicity. In the subsequent mucosal repair stage, classic Chinese patent medicines such as Weifuchun and Moluodan play a role through a variety of bioactive monomers, including berberine and naringin. At the molecular level, these drugs block the NF-κB inflammatory signaling pathway, down-regulate the transcription of CDX2, restore protective autophagy, and reshape the gastrointestinal microenvironment. These multi-dimensional effects can not only alleviate dyspepsia-related symptoms, but also make the histopathology of glandular atrophy and early atypical hyperplasia subside.

Disclosure statement

The authors declare no conflict of interest.

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