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Review

Chinese Medicine-Derived Bioactive Compounds and Chronic Atrophic Gastritis: Therapeutic Potential and Mechanisms

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Abstract

Chronic atrophic gastritis (CAG) is a well-established precancerous condition linked to the development of gastric adenocarcinoma the development of global incidence and disease burden. Traditional Chinese medicine (TCM) has a long clinical history of managing gastrointestinal disorders using standardized herbal formulations. Accumulating preclinical and clinical evidence supports the therapeutic efficacy of bioactive compounds derived from TCM, including berberine, paeoniflorin, luteolin, and rutaecarpine, in ameliorating CAG. This review offers a systematic synthesis of current evidence on the multimodal mechanisms of action of these medicines, including modulation of immune-inflammatory responses, regulation of programmed cell death pathways (e.g., apoptosis, ferroptosis, and pyroptosis), disruption of the *Helicobacter pylori*–favoring gastric microenvironment, and enhancement of gastric mucosal repair via antioxidant and cytoprotective signaling. Thus, by integrating mechanistic insights with translational relevance, this review offers a scientific foundation for evidence-informed clinical deployment of these TCM-derived compounds and informs the rational design of novel, mechanism-based therapeutics for CAG.

Keywords: medicine; Chinese traditional; bioactive compounds; gastritis; atrophic; pharmacological mechanism; *Helicobacter pylori*

1. Introduction

Chronic atrophic gastritis (CAG) is a persistent inflammatory condition characterized by the reduction or complete loss of intrinsic glands in the gastric mucosa. It is typically regarded as a precancerous state that predisposes individuals to gastric cancer (GC) [1]. Rather than an isolated or idiopathic pathological alteration, CAG represents the ultimate consequence of chronic inflammation resulting from prolonged and multifactorial damage to the gastric mucosa. CAG forms a critical link in the inflammatory-oncogenic cascade through which chronic inflammation progresses to GC, thereby significantly elevating the risk of eventual GC onset [2,3]. The global epidemiology of this condition exhibits considerable regional and age-related variations. In individuals aged over 70, the prevalence of CAG can reach as high as 47.8%, underscoring its relevance as a major public health concern [4,5]. In Asian nations, particularly China and Japan, the higher prevalence of CAG may be associated with *Helicobacter pylori* (Hp) infection and specific dietary habits [6,7].

The etiology of CAG is complex and multifactorial. Key pathogenic factors with relatively well-defined pathological pathways include Hp infection [8] and autoimmune mechanisms [9]. Hp infection significantly increases the risk of CAG [10,11], and the World Health Organization (WHO) classifies it as a Group I carcinogen [8]. Through its virulence factors and the persistent activation of signaling pathways such as the nuclear factor κB (NF-κB) and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathways, Hp induces chronic inflammation, ultimately resulting in glandular atrophy and intestinal metaplasia [12,13]. However, Hp eradication therapy has limited efficacy in reversing the extensive atrophy or intestinal metaplasia after it has already occurred [14]. Another important subtype of CAG is autoimmune atrophic gastritis (AAG), which accounts for approximately 5–10% of all cases [9,15]. The prevalence of this disease in the general population is relatively low, ranging from 0.3% to 2.7%, and it is more common in females and is often associated with other autoimmune diseases [15,16]. Progressive loss of parietal cells leads to defects in gastric acid and intrinsic factor secretion [9,17], which may subsequently result in systemic symptoms such as pernicious anemia, iron deficiency, and neurological disorders [17,18].

In addition to Hp infection and autoimmune mechanisms, a range of environmental and genetic factors contribute to the onset and progression of CAG. Prolonged use of proton pump inhibitors (PPIs) may impair mucosal repair by altering the gastric acid-base environment [14,19]. Duodenogastric reflux of bile acids can directly damage the epithelial barrier [9]. In addition, adverse habits, such as a high-salt diet, have been shown to exacerbate inflammatory responses [20]. With respect to genetic susceptibility, polymorphisms in the genes encoding interleukin-1β

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(IL-1β) and tumor necrosis factor-α (TNF-α) may independently regulate the intensity of the mucosal inflammatory response to injury [21]. These various factors ultimately converge on a central pathological process: the failure of the mechanisms governing the repair and regeneration of the gastric mucosal epithelium. At the molecular level, this is primarily manifested as a defect in the maintenance functions of gastric stem cells, accompanied by a network-level disruption of several key signaling pathways. For example, abnormalities in the Wingless-type MMTV integration site family (Wnt)/β-catenin pathway affect stem cell fate determination and proliferation [13,22], while impairment of the epidermal growth factor (EGF)/EGF receptor (EGFR) pathway weakens the ability to repair mucosal damage promptly [9]. Abnormal interactions among these pathways collectively form the complex molecular foundation for glandular atrophy and regenerative disorders in CAG.

Clinically, approximately 30–40% of CAG patients remain asymptomatic [16]. Among those who do exhibit symptoms, the most common manifestations include digestive disturbances such as upper abdominal discomfort, postprandial abdominal distension, and early satiety. The severity of these symptoms often correlates with the degree of mucosal atrophy [23]. In some cases, patients present with precancerous lesions or GC as their initial symptom. Epidemiological data indicate that patients with moderate atrophy have a 2.22-fold increased risk of developing GC [24]. Among CAG patients, approximately 1.44% eventually progress to GC [2], and the annual risk of developing type I gastric neuroendocrine tumors (g-NENs) in AAG patients is approximately 2.8% [15]. Currently, Western medicine primarily focuses on managing CAG by addressing the underlying cause (such as eradicating Hp) and providing symptomatic treatment (e.g., supplementing vitamin B12 and folic acid). However, the efficacy of these strategies as a means of reversing mucosal atrophy and intestinal metaplasia remains limited, and long-term medication may be associated with adverse reactions [14,19]. Therefore, there is a pressing need for the development of novel therapeutic strategies capable of directly intervening in and reversing these precancerous pathological conditions.

Traditional Chinese Medicine (TCM) offers unique potential value as a means of addressing the unmet need in the CAG space. Research aimed at clarifying how TCM preparations function has increasingly focused on the activities of isolated active components from TCM preparations known as TCM monomers. Numerous studies have confirmed the critical role of these monomers in the treatment of gastritis. For instance, flavonoids such as quercetin (QUE) and luteolin (LUT) exert potent anti-inflammatory and antioxidant effects by regulating pathways such as the TGF-β1/Smads and AGE-RAGE signaling pathways [25,26], while tanshinone improves the microcirculation of the gastric mucosa [27], berberine (BBR) derived from *Coptis chinensis* has been shown to inhibit Hp, regulate the gut microbiota, and promote mucosal repair [28], and herbal monomers like Baicalin (BA) exhibit significant antioxidant activity [29]. Some individual TCM monomers can also reverse specific metabolic disorders observed in CAG model systems [19,30]. Collectively, these findings suggest that, although the molecular targets and pathways affected by different monomers may vary, they systematically target multiple core pathological processes of CAG, including inflammation, oxidative stress, microcirculation disorders, dysbiosis, and metabolic abnormalities.

Research progress has led to a shift in the focus of recent studies from the initial verification of drug efficacy to the precise analysis of the molecular mechanisms underlying the actions of individual components of TCM preparations and the collaborative development of novel delivery strategies. Despite the growing and diverse library of TCM monomers and an abundance of data, there remains a lack of a systematic summary of the pharmacological activities of these compounds, an integrative evaluation of their molecular mechanisms of action, or a comprehensive review of advanced strategies for their effective administration. This absence of systematic knowledge has, to some extent, hindered the in-depth exploration and efficient translation of the full therapeutic potential of individual TCM components. In light of this gap, this article aims to provide a comprehensive and systematic review of research progress focused on the potential of individual TCM monomers for the management of CAG over the past two decades.

To ensure a comprehensive and objective synthesis of current evidence, a systematic literature search was conducted across electronic databases including PubMed, Web of Science, Embase, and China National Knowledge Infrastructure (CNKI) from January 2006 to May 2026. The search MeSH terms included ("Chronic Atrophic Gastritis" OR "Gastric Precancerous Lesions" OR "Intestinal Metaplasia") AND ("Traditional Chinese Medicine" OR "Bioactive Compound" OR "Monomer" OR "Flavonoids" OR "Alkaloids"). Inclusion criteria focused on peer-reviewed research analyzing molecular mechanisms, pharmacokinetics, or the clinical efficacy of isolated TCM monomers. Document types were restricted to original research and mechanism-focused reviews published in English or Chinese.

2. The Main Mechanism of TCM Monomers in Treating CAG

The pathogenesis of CAG is not a linear progression driven by isolated pathways, but rather a closely synchronized pathological outcome driven by a combination of oxidative stress, inflammation, and programmed cell death (PCD). Specifically, long-term mucosal damage leads to excessive accumulation of reactive oxygen species (ROS), which directly act as upstream messengers, activating the NF-κB and Janus Kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) pathways, thereby

initiating a chronic immune-inflammatory cascade. Conversely, overactivated inflammatory cytokines exacerbate mitochondrial dysfunction, establishing a vicious positive feedback loop characterized by extensive oxidative damage. Crucially, this cellular stress environment determines the mode of programmed cellular death induced, which can include apoptosis mediated by the JAK/STAT or AP-1 pathways that inhibit the Bcl-2 family, pyroptosis initiated when ROS activate the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, triggering caspase-1-mediated gasdermin D (GSDMD) cleavage, and ferroptosis, which occurs when severe oxidative stress leads to lipid peroxidation, causing the nuclear factor erythroid 2-related factor 2 (Nrf2)/glutathione peroxidase 4 (GPX4) antioxidant defense system to be overly suppressed in parallel with the accumulation of an unstable intracellular iron pool. By acting on interconnected regulatory networks, TCM monomers can disrupt the self-amplifying feedback cycles that cause these forms of cellular death and damage.

The following sections of this review detail the tightly interconnected mechanisms that govern CAG pathogenesis. The effects of individual TCM monomers within this broader discussion are not confined to any single mechanism, instead adhering to the principles of network pharmacology such that they allow for multidimensional, coordinated regulation of the core network, which includes inflammation, immunity, cell death, oxidative stress, and barrier repair.

2.1 Anti-Inflammatory and Immune Regulation

The progression of CAG from chronic inflammation to atrophy and intestinal metaplasia is fundamentally driven by the disruption of local immune homeostasis in the gastric mucosa and the persistence of unrestrained chronic inflammation. This process is initiated by pathogen-associated molecular patterns or endogenous danger signals released due to tissue damage, which are recognized by Toll-like receptors (TLRs) on the surface of innate immune cells [18,31]. Once these receptors are activated, they transmit signals through key adaptor proteins, such as myeloid differentiation factor 88 (MyD88), leading to the strong activation of the core transcription factor NF-κB. This, in turn, initiates the transcription of genes for pro-inflammatory mediators, including IL-1β, IL-6, IL-8, and TNF-α [18,32]. In parallel with these processes, NLRP3 inflammasome assembly and activation take place within the cell, catalyzing the caspase-1-mediated cleavage of pro-IL-1β and pro-IL-18, thus enabling their maturation and large-scale release [33]. The NF-κB and NLRP3 pathways form a positive feedback loop that collectively drives the continuous and elevated expression of various pro-inflammatory cytokines (such as TNF-α, IL-1β, IL-6) and chemokines in the gastric mucosa [32,33,34].

These inflammatory cytokines establish the fundamental microenvironment that drives inflammation and immune dysregulation in CAG. In addition to sustaining the activated state of innate immune cells through autocrine mechanisms, they also transmit inflammatory signals to adaptive immune cells by activating the MAPK and JAK/STAT signaling pathways, profoundly influencing their functions and differentiation [34,35]. IL-12 induces CD4+ T cells to differentiate into Th1 cells, which primarily secrete interferon-γ (IFN-γ), while IL-6, IL-1β, and IL-23 collaboratively promote the differentiation of Th17 cells, which secrete IL-17 [31,36]. Conversely, the functions of regulatory T cells (Tregs), which possess immunosuppressive and anti-inflammatory properties, are inhibited under these conditions. This unbalanced immune polarization, characterized by an excessive Th1/Th17 response and a relative insufficiency of Treg function, represents a key immunological mechanism underlying chronic inflammation and ongoing tissue destruction [37,38]. Activated Th1 and Th17 cells, along with their effector molecules (IFN-γ, IL-17), further recruit and activate additional myeloid immune cells, establishing a chronic inflammatory lesion dominated by lymphocytes and plasma cells. This, in turn, directly interferes with the normal functions of gastric mucosal epithelial cells and disrupts homeostatic balance within the local microenvironment, thereby serving as a direct effector that promotes the pathological remodeling that results in gastric gland atrophy and intestinal metaplasia. This immune-inflammatory axis spanning from TLR/NF-κB/NLRP3 to JAK/STAT/MAPK-mediated signal transduction and ultimately to immune outcomes determined by the Th1/Th17/Treg balance drives the development of CAG. The regulation of this multifaceted process is a core pharmacological basis for the therapeutic effects of numerous TCM formulations and their active components [35,38,39,40].

The core process of CAG pathogenesis, characterized by chronic inflammation and immune imbalance, has been extensively studied at the molecular level, with multiple studies revealing the specific mechanisms through which herbal monomers exert therapeutic effects by modulating key signaling pathways. BBR, the main active alkaloid in TCM formulations such as Coptis, has demonstrated anti-inflammatory and immunoregulatory effects that it exerts through multiple mechanisms. BBR can activate the IL-4/STAT6 signaling axis, promoting the polarization of macrophages from the pro-inflammatory M1 phenotype (expressing high levels of TNF-α, inducible nitric oxide synthase (iNOS)) to the anti-inflammatory and reparative M2 phenotype (expressing high levels of IL-10, TGF-β), thereby reshaping the immune microenvironment of the gastric mucosa [41]. Furthermore, the BBR derivative palmatine (PAL) can inhibit STAT1 phosphorylation and the expression of its downstream chemokine target C-X-C motif chemokine ligand 10 (CXCL10), thereby blocking the cascading amplification of the inflammatory IL-17 and TNF-α/NF-κB pathways, abrogating the inflam-

matory response at its source [39]. With respect to the TGF-β1/PI3K/Akt pathway, BBR has been shown to down-regulate transforming growth factor-β1 (TGF-β1), p-Akt, and p-mTOR at the protein level, in addition to upregulating the autophagy markers microtubule-associated protein 1 light chain 3-II (LC3-II) and Beclin-1. This dual effect inhibits excessive inflammatory signal transduction while also enhancing cellular autophagy, promoting intracellular stability [42]. BBR also exerts anti-inflammatory effects by regulating the MAPK signaling pathway and correcting associated metabolic abnormalities [43]. Network pharmacology studies and supporting experimental validation have shown that the anti-CAG effects of astragaloside IV (AS-IV), which is the key active component found in Astragalus, are associated with its ability to significantly down-regulate the secretion of key pro-inflammatory cytokines (IL-6, IL-8, IL-1β, and TNF-α) in N-methyl-N′-nitro-N-nitrosoguanidine (MNNG)-induced human gastric mucosal epithelial cells, with this effect being mediated through its effects on multiple targets. Its effects are related to the regulation of signaling pathways such as the "proteoglycan in tumors" pathway, thus demonstrating clear multi-target anti-inflammatory properties [44]. Kaempferol (KAE), a key component of Chaihu Liujun Decoction, has a protective effect closely associated with the activation of the Hedgehog (Hh) signaling pathway. It can significantly upregulate Sonic hedgehog (Shh), patched-1 receptor (Ptch1), and glioma-associated oncogene homolog 1 (Gli1) at the protein and mRNA levels in gastric tissues. The activation of this pathway directly promotes the proliferation and differentiation of glandular cells and indirectly decreases the levels of pro-inflammatory factors such as IL-1β and IL-6 [45]. The anti-inflammatory mechanism through which atractylenolide I (ATL-I) functions is centered on the classical NF-κB pathway, as it inhibits the nuclear translocation and activation of the NF-κB p65 subunit, reducing the expression of its downstream inflammatory mediator cyclooxygenase-2 (COX-2) and the production of IL-8 [46]. The citrus-derived polymethoxy flavonoid compound nobiletin (Nob) has also been the focus of intensive study for its gastroprotective anti-inflammatory effects in CAG. In an MNNG-induced CAG rat model, Nob demonstrated a dose-dependent ability to alleviate gastric histological damage and inhibit the excessive production of inflammatory cytokines. Through combined metabolomics and network pharmacology analyses, the target of Nob in this context was narrowed down to two key pro-inflammatory enzymes in the arachidonic acid metabolism pathway: arachidonic acid 5-lipoxygenase (ALOX5) and COX-2. Further *in vitro* experiments confirmed that Nob can mitigate damage to gastric epithelial cells and mitochondrial dysfunction induced by MNNG through the inhibition of ALOX5 and prostaglandin endoperoxide synthase 2 (PTGS2) expression. In addition to directly blocking the generation of potent inflammatory mediators such as prostaglandins and leukotrienes, this mechanism is also closely associated with the regulation of upstream inflammatory factors such as NF-κB [47]. The associated signaling pathways are detailed in Fig. 1, while corresponding information regarding TCM monomers is presented in Table 1 (Ref. [39,41,42,44,45,46,47]).

2.2 Molecular Mechanisms of Programmed Cell Death

The core pathogenesis of CAG lies in the progressive loss of gastric mucosal glands and persistent chronic inflammation. This process is controlled by a complex regulatory network, with the disruption of gastric mucosal epithelial cell homeostasis as a central step. This disruption is primarily characterized by an imbalance between abnormal cell proliferation and apoptosis, along with the abnormal activation of multiple regulatory pathways that influence forms of cell death, including apoptosis, pyroptosis, and ferroptosis. These pathways interact with one another and collectively form the pathological core that drives gastric mucosal atrophy and the development of precancerous lesions. The signaling pathways involved in this process are detailed in Fig. 2, while corresponding details regarding TCM monomers are presented in Table 2 (Ref. [25,27,29,39,48,49,50,51,52,53,54,55]).

2.2.1 Cell Proliferation and Apoptosis

Under normal conditions, the renewal of the gastric mucosal epithelium relies on a precise balance between the proliferation of basal stem cells and the apoptosis of surface cells. However, in CAG, this balance is disrupted, establishing a chronic inflammatory environment that can induce excessive pro-apoptotic signaling activity. Hp infection has been shown to upregulate the expression of the apoptosis regulator PUMA, which is transcribed by the TLR2/NF-κB pathway. This, in turn, upregulates the expression of the pro-apoptotic protein p53, leading to an increase in the apoptotic death of gastric epithelial cells. This mechanism is considered crucial for the development of gastritis [56]. In response to continuous damage and cell loss under these conditions, compensatory proliferative activity is initiated; however, this proliferation is often dysregulated. In cellular experimental studies, markers associated with cell proliferation, such as proliferating cell nuclear antigen (PCNA), are expressed at higher levels, while the pro-apoptotic proteins such as p53 and caspase-3 are also significantly upregulated [57]. This uncoordinated state leads to the progressive atrophy of the gastric gland structure but may also allow cells with damaged DNA to evade apoptotic death, thus providing a foundation for abnormal clonal proliferation and carcinogenesis.

Individual TCM monomers have been shown to disrupt these apoptotic signaling pathways, thereby protecting the gastric mucosa. Although these compounds act through different mechanisms, their effects ultimately converge on the core process of apoptosis execution. BBR, for instance,

Table 1. Summary of information on Chinese herbal monomers with anti-inflammatory and immune regulation activities.

Name	Main source	Research design	Dosage of administration	Molecular mechanism	References
Berberine	The dried rhizome of the plant belonging to the Ranunculaceae family, *Coptis chinensis Franch.*	*In vivo* experiments (Sprague-Dawley rats were orally inoculated with 1.5 × 10^8 CFU/mL of *H. pylori* for 8 weeks)	14 mg/kg/d; 28 mg/kg/d	BBR decreased TNF-α and downregulated NOS2 expression, which increased IL-4, STAT6, and IL-10 levels and activated the IL-4-STAT6 signaling pathway.	[41]
		In vivo experiments (SD rats freely ingested MNNG (170 μg/mL) + alternate hunger and satiety + intragastric administration of MNNG (170 μg/mL, 1 mL/100 g body weight) every other day for 10 weeks)	14 mg/kg/d; 28 mg/kg/d, last for 4 weeks	BBR can inhibit the expression of inflammatory factors IL-8, TNF-α, and IL-1β, down-regulate the TGF-β1/PI3K/Akt/mTOR signaling pathway, and up-regulate PTEN as well as autophagy-related proteins LC3-II and Beclin-1. It exerts its therapeutic effect by regulating the PI3K/Akt/mTOR axis mediated by TGF-β1 and activating protective autophagy.	[42]
Palmatine	The dried vine stems of the plant *Fibraurea recisa Pierre* from the Menispermaceae family	*In vivo* experiments (C57BL/6J mice freely ingested MNNG (170 μg/mL) for 3 weeks)	45 mg/kg; 90 mg/kg; 180 mg/kg, last for 8 weeks	PAL inhibits the phosphorylation of STAT1 and the expression of its downstream target gene CXCL10, thereby suppressing the expression of key inflammatory proteins such as IL-17, TNF-α, and p-p65 (NF-κB), as well as the oxidative stress response. Ultimately, it plays a role in improving chronic atrophic gastritis induced by MNNG.	[39]
Astragaloside IV	The dried roots of the leguminous plant Mongolian Astragalus (*Astragalus membranaceus* (Fisch.) Bunge)	*In vitro* experiment (Induction of human gastric mucosal epithelial cells with 80 μmol/L MNNG)	20 μmol/L	Astragaloside IV can reduce the secretion of inflammatory factors such as IL-6, IL-8, IL-1β, and TNF-α.	[44]
Kaempferol	The dried root and rhizome of the ginger plant (*Alpinia officinarum Hance*)	*In vivo* experiments (Wistar rats exposed to 0.1% ammonia water and 20 mmol/L sodium deoxycholate solution with alternate food deprivation and refeeding, for a duration of 16 weeks)	50 mg/kg per day, for a duration of 4 weeks	Kaempferol exerts its therapeutic effect on CAG by regulating the hedgehog signaling pathway and reducing the levels of IL-6 and IL-1β.	[45]
Atractylenolide I	The dried rhizome of the plant of the Asteraceae (Compositae) family (*Atractylodes macrocephala Koidz.*)	*In vivo* experiments (intragastric administration of 0.2% sodium deoxycholate solution in SD rats + 50 °C hot saline administration + abnormal hunger and satiety)	10 mg/kg/d; 20 mg/kg/d; 40 mg/kg/d, last for 8 weeks	Atractylenolide I exerts anti-inflammatory effects by upregulating the expression of HSP70 protein and inhibiting the expression of key inflammatory proteins such as IL-8, NF-κB and COX-2, thereby ultimately improving chronic atrophic gastritis.	[46]
Nobiletin	The dried and mature rind of the citrus plant *Citrus reticulata Blanco* and its cultivated varieties	*In vivo* experiments (200 mg/L MNNG was freely consumed by SD rats + alternate periods of hunger and feeding, for a duration of 10 weeks)	6.25 mg/kg; 12.5 mg/kg; 25 mg/kg, last for 6 weeks	Nobiletin can inhibit MNNG-induced damage to gastric epithelial cells and mitochondrial dysfunction by suppressing 5-lipoxygenase (ALOX5) and prostaglandin-endoperoxide synthase 2 (PTGS2) in the body.	[47]

SD, Sprague-Dawley (rat strain); CFU, colony-forming units; NOS2, nitric oxide synthase 2; STAT1, signal transducer and activator of transcription 1; STAT6, signal transducer and activator of transcription 6; HSP70, heat shock protein 70; Wistar, Wistar rat strain; C57BL/6, C57BL/6 mouse strain.

Table 2. Summary table of herbal monomers for cell programmed death.

Name	Main source	Research design	Dosage of administration	Molecular mechanism	References
Paeoniflorin	The dried roots of the plant in the Ranunculaceae family (*Paeonia lactiflora Pall.*)	*In vivo* experiments (SD rats, 2% sodium salicylate solution 2 mL + MNNG 180 μg/mL + alternate hunger and satiety, for 12 weeks)	5 mg/kg/d; 15 mg/kg/d; 30 mg/kg/d, last for 8 weeks	Paeoniflorin can alleviate the inflammatory damage and cell apoptosis caused by CAG by up-regulating the anti-apoptotic protein Bcl-2 and down-regulating the pro-apoptotic protein Bax as well as the activity of the IL-6/STAT3 pathway.	[48]
Hesperidin	The dried and mature rind of the citrus plant *Citrus reticulata Blanco* and its cultivated varieties	*In vivo* experiments (SD rats, 2% sodium salicylate solution 2 mL + MNNG 180 μg/mL + alternate hunger and satiety, for 12 weeks)	7 mg/kg/d; 14 mg/kg/d; 28 mg/kg/d, last for 4 weeks	Hesperidin activates the Keap1/Nrf2/ARE signaling pathway, upregulates the expression of downstream protective proteins Nrf2, HO-1 and NQO1, and downregulates the expression of Keap1. Thus, it alleviates oxidative stress and inflammatory damage in CAG rats and exerts a protective effect on the gastric mucosa.	[49]
Formononetin	The dried roots of the leguminous plant Mongolian Astragalus (*Astragalus membranaceus* (Fisch.) Bge. var. mongholicus (Bge.) Hsiao)	*In vitro* experiments (MNNG) were used to induce the establishment of a CAG cell model in human gastric epithelial cells (GES-1)	5 μM; 10 μM; 20 μM	FMN reduced NCOA 1, c-Jun, and the inhibitor of activator protein-1 (AP-1), T-5224, enhanced the effects of FMN on the survival rate, inflammatory response, and apoptosis of GES-1 cells triggered by MNNG.	[50]
Tanshinone IIA	The dried roots and rhizomes of the plant of the Labiatae family, *Salvia miltiorrhiza Bge.*	*In vivo* experiments (Wistar rats, MNNG (0.04 g/mL) + ranitidine 0.03 g/kg by gavage + alternate hunger and satiety, for 20 weeks)	5 mg/kg/day, for a duration of 12 weeks	Tanshinone IIA can alleviate inflammatory responses and cell apoptosis by inhibiting the activation of the JAK2/STAT3 signaling pathway (down-regulating p-JAK2 and p-STAT3), blocking the nuclear translocation of NF-κB p65, down-regulating Bax, and activating the expression of Caspase-3 and Caspase-9. Thus, it can improve the structural and functional damage of the gastric mucosa in CAG rats.	[27]
Baicalin	The dried roots of the plant of the Labiatae family, *Scutellaria baicalensis Georgi*	*In vivo* experiments (C57BL/6N mice, MNNG at 100 μg/mL administered by gavage + alternate fasting and feeding, for 16 weeks)	10 mg/kg/d, for 4 weeks	Baicalin can significantly improve the gastric mucosal injury in CAG model mice by down-regulating JAK1/STAT3. It has a certain positive effect on the repair of gastric mucosa. The mechanism may be related to the down-regulation of the mRNA and protein expressions of JAK1 and STAT3.	[29]
Jatrorrhizine	The dried rhizome of the plant belonging to the Ranunculaceae family, *Coptis chinensis Franch.*	*In vivo* experiments (SD rats freely consumed MNNG at 170 μg/mL + received MNNG at 170 μg/mL by gavage twice a day, for a total of 16 weeks)	20 mg/kg/d; 40 mg/kg/d, for 4 weeks	The jatrorrhizine treatment for CAG is mainly related to the inhibition of pyroptosis and apoptosis-related factors.	[51]

Table 2. Continued.

Name	Main source	Research design	Dosage of administration	Molecular mechanism	References
Ginsenoside Rg1	The dried roots and rhizomes of the Panax ginseng plant from the genus Panax	*In vivo* experiments (SD rats, free drinking of MNNG at 150 μg/mL + free diet with 0.03% ranitidine + alternate hunger and satiety, for 24 weeks)	10 mg/kg/d; 20 mg/kg/d, for 4 weeks	Ginsenoside Rg1 can down-regulate the nuclear translocation of phosphorylated NF-κB p65, the activation of NLRP3 inflammasome and the cleavage of GSDMD through the NF-κB/NLRP3/GSDMD pathway. This significantly improves the gastric mucosal damage in the CAG model. Its repair effect is closely related to the inhibition of pyroptosis of gastric epithelial cells mediated by this pathway.	[52]
Luteolin	The dried flower buds or the newly opened flowers of the plant of the Lonicera genus (*Lonicera japonica Thunb.*)	*In vivo* experiments (SD rats, intragastric administration of MNNG at 170 μg/mL + free drinking of MNNG at 170 μg/mL, for 16 weeks)	80 mg/kg/d, for 12 weeks	Luteolin inhibits the AGE-RAGE signaling pathway, reduces the inflammatory response in gastric tissues, lowers the concentrations of MDA and Fe^{2+}, down-regulates the expressions of ACSL4 and NOX1, and up-regulates the expression of FIH1 and GPX4 ferroptosis-related proteins, thereby inhibiting ferroptosis in gastric tissue cells and having a therapeutic effect on CAG.	[25]
Galangin	The dried rhizomes of the plant belonging to the genus Alpinia of the ginger family, namely high-quality ginger (*Alpinia officinarum Hance*)	*In vivo* experiments (Wistar rats were intragastrically administered a 2% sodium salicylate + 30% ethanol mixture + subjected to forced exercise + alternate hunger and satiety, for a duration of 10 weeks)	0.3 mg/kg/d; 1.2 mg/kg/d, for 4 weeks	Galangin exerts its protective effect on the gastric mucosa by regulating the iron metabolism pathway mediated by the Runx3 transcription factor, down-regulating TFR1 and DMT1, and up-regulating FTL, FTH and GPX4. This helps to restore iron homeostasis, reduce oxidative stress and mitigate mitochondrial damage in the CAG model, thereby promoting gastric mucosal health.	[53]
Costunolide	The dried roots of the plant *Aucklandia lappa Decne.*, belonging to the Compositae family	*In vivo* experiments (SD rats, freely drinking MNNG at 170 μg/mL and 10% ethanol + MNNG 1 mL/100 g/2 days + alternate hunger and satiety, for 8 weeks)	10 mg/kg/d; 20 mg/kg/d, for 4 weeks	COS activates the Nrf2 signaling pathway, upregulates antioxidant proteins such as SOD, GSH, and HO-1, and downregulates oxidative damage products such as ROS and MDA, as well as DNA damage and apoptosis markers such as γH2AX and PARP1. Thus, it inhibits oxidative stress, repairs DNA damage, and reduces cell apoptosis, exerting therapeutic effects on CAG.	[54]
Evodiamine	The dried near-mature fruits of the plant belonging to the Rutaceae family, *Evodia rutaecarpa* (Juss.) Benth.	*In vivo* experiments (SD rats, freely drinking 0.1% ammonia water and 20 mmol/L sodium deoxycholate solution + alternate hunger and satiety, for 10 weeks)	10 mg/kg/d; 20 mg/kg/d, for 4 weeks	Evodiamine, through the MAPK signaling pathway, upregulates ZO-1, E-cadherin, Claudin-4, Occludin, MTL, PP, PGI, PGIII, IL-10; and downregulates SS, GAS-17, IL-6, TNF-α. It repairs the mucosal barrier, regulates inflammation and gastrointestinal function, and improves metabolic disorders.	[55]
Palmatine	The dried stem of the yellow vine (Fibraurea recisa)	*In vivo* experiments (C57BL/6J mice freely ingested MNNG (170 μg/mL) for 3 weeks)	45 mg/kg; 90 mg/kg; 180 mg/kg, for 8 weeks	PAL inhibits the STAT1/CXCL10 signaling pathway, thereby regulating key inflammatory pathways such as IL-17, TNF, and NF-κB. Eventually, it exerts the effect of suppressing oxidative stress and inflammatory responses, thereby alleviating CAG induced by MNNG.	[39]

SD, Sprague-Dawley (rat strain); Wistar, Wistar rat strain; C57BL/6, C57BL/6 mouse strain; GES-1, human gastric epithelial cell line; Keap1, Kelch-like ECH-associated protein 1; ARE, antioxidant response element; NCOA1, nuclear receptor coactivator 1; c-Jun, a component of the AP-1 transcription factor; γH2AX, phosphorylated histone H2AX; PARP1, poly(ADP-ribose) polymerase 1; ZO-1, zonula occludens-1; E-cadherin, epithelial cadherin; Claudin-4, claudin-4; Occludin, occludin.

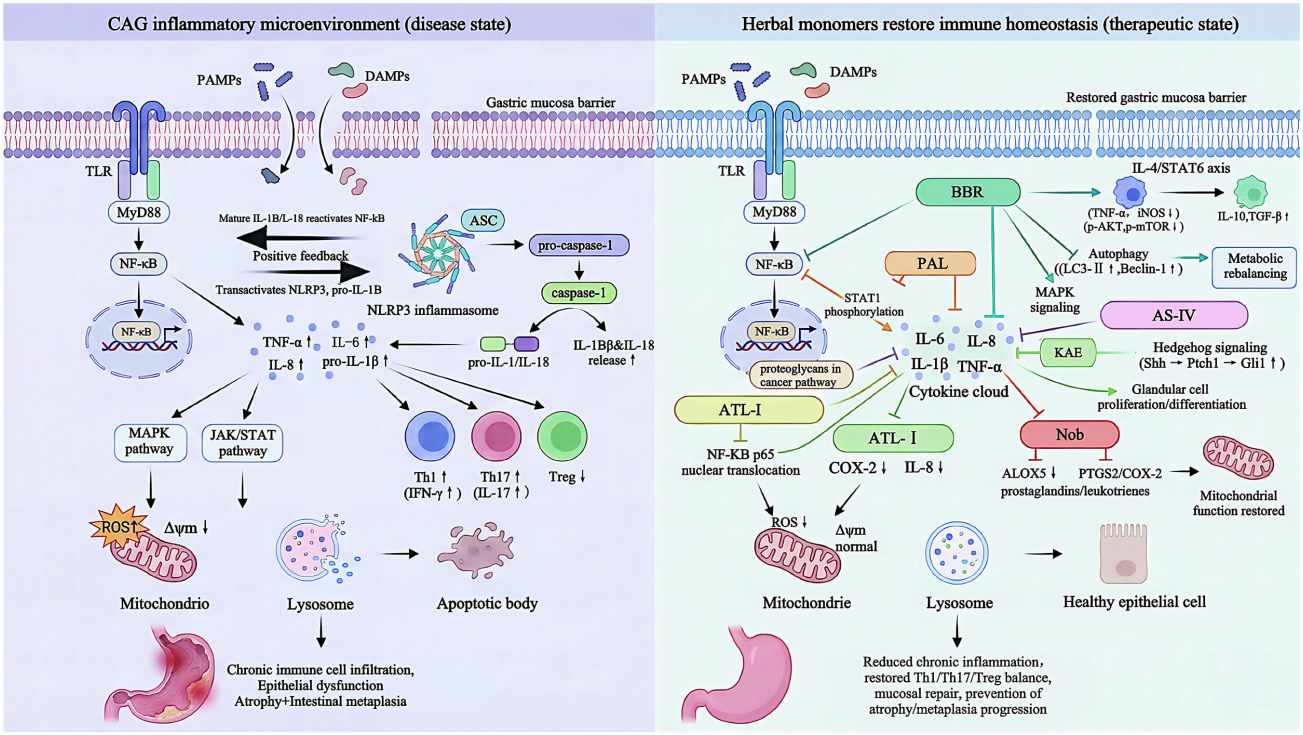


Fig. 1. Mechanism diagram of Chinese medicine-derived bioactive compounds regulating core signaling pathways to intervene in the CAG immune inflammatory microenvironment. CAG, chronic atrophic gastritis; ALOX5, arachidonate 5-lipoxygenase; ASC, apoptosis-associated speck-like protein containing a CARD; DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; PTGS2, prostaglandin-endoperoxide synthase 2; STAT6, signal transducer and activator of transcription 6; Th1, T helper type 1 cell; Th17, T helper type 17 cell; Treg, regulatory T cell; Δψm, mitochondrial membrane potential.

has been found to influence the apoptosis process by regulating MAPK signaling activity linked to cell fate determination [43], although the supporting evidence is primarily based on predictive network pharmacology analysis, such that it requires further experimental validation. Paeoniflorin (PF) inhibits the activation of the IL-6/STAT3 pathway, reducing the nuclear translocation of phosphorylated STAT3 (p-STAT3). This, in turn, upregulates the expression of the anti-apoptotic protein B-cell lymphoma-2 (Bcl-2) and downregulates the expression of the pro-apoptotic protein Bax, significantly reducing the apoptosis index of gastric mucosal cells in rat model systems [48]. Hesperidin (HES) has also been shown to activate the antioxidant response, regulating the Keap1/Nrf2/ARE pathway by promoting the nuclear translocation of the transcription factor Nrf2, thereby upregulating the expression of downstream cell-protecting proteins such as heme oxygenase-1 (HO-1) and NAD(P)H:quinone oxidoreductase 1 (NQO1). This process is accompanied by a significant reduction in the rate of gastric mucosal cell apoptosis and a restoration of an anti-apoptotic Bcl-2/Bax protein ratio, as confirmed by evidence from both *in vivo* and *in vitro* studies [49]. In addition to these pathways, the transcription factor AP-1 serves as another core hub for cellular stress and apoptosis regulation, and is also an important target for the action of TCM monomers. Network pharmacology predictions combined with experimental verification have revealed that formononetin (FMN) can inhibit the activity of the AP-1 signaling axis by downregulating the expression of nuclear receptor co-activator 1 (NCOA1) and AP-1. In GES-1 cells damaged by MNNG exposure, FMN significantly reverses the observed decline in cell viability, the release of inflammatory factors, and the increase in cellular apoptosis. The AP-1-specific inhibitor T-5224 can further enhance the protective effects of FMN, confirming that FMN, by regulating the NCOA1/AP-1 signaling axis, exerts dual anti-inflammatory and anti-apoptotic effects, which are crucial for alleviating gastric epithelial cell damage [50], with the use of a pharmacological inhibitor in this study offering strong target validation. In the JAK/STAT pathway, Tanshinone IIA inhibits the phosphorylation of JAK2 and STAT3 (p-JAK2, p-STAT3) and blocks the nuclear translocation of NF-κB p65. As a result, it upregulates the expression of Bcl-2 while downregulating Bax, activated caspase-3 (C-Cas-3), and activated caspase-9 (C-Cas-9), thereby inhibiting apoptosis through multiple pathways [27]. Similarly, baicalin (BA) has been shown to downregulate JAK1 and STAT3 at the mRNA and protein levels in the gastric mucosa of CAG model animals, thereby inhibiting apoptosis [29].

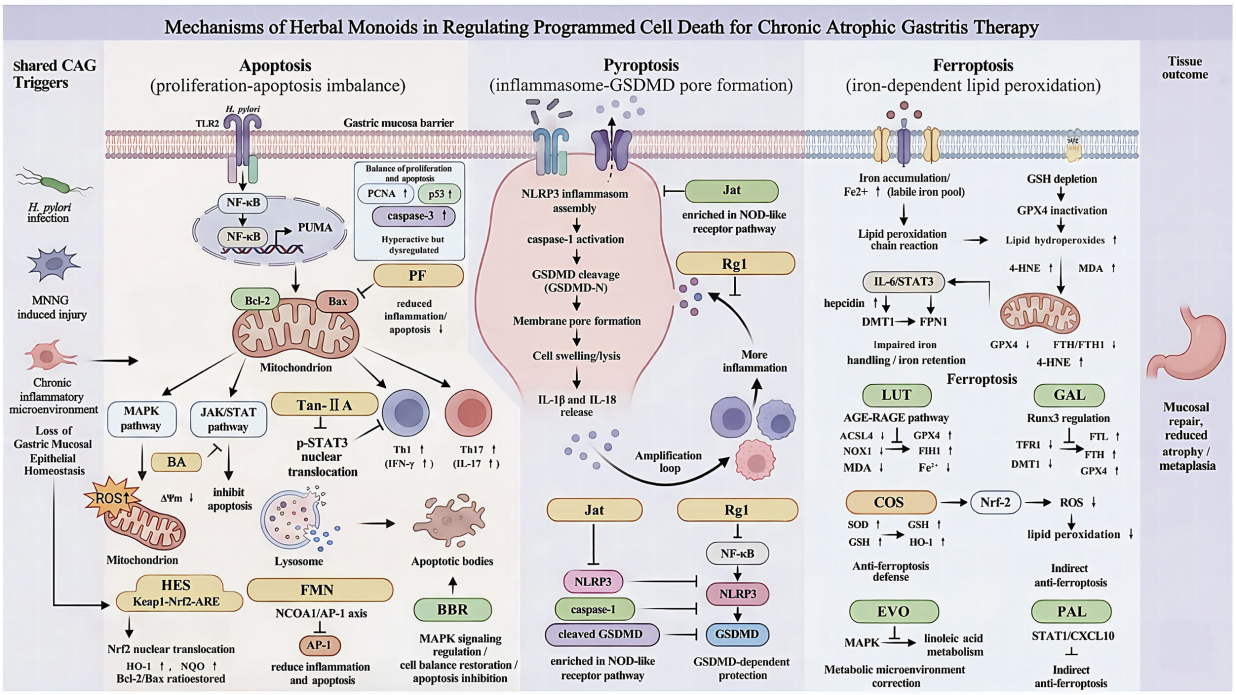


Fig. 2. The core pathways of programmed cell death regulated by single components of traditional Chinese medicine in CAG cells. 4-HNE, 4-hydroxynonenal; ARE, antioxidant response element; CXCL10, C-X-C motif chemokine ligand 10; DMT1, divalent metal transporter 1; FPN1, ferroportin 1; FTH, ferritin heavy chain; GSDMD-N, N-terminal fragment of gasdermin D; Keap1, Kelch-like ECH-associated protein 1; NCOA1, nuclear receptor coactivator 1; NQO, NAD(P)H:quinone oxidoreductase; PUMA, p53 upregulated modulator of apoptosis; STAT1, signal transducer and activator of transcription 1; Tan-IIA, tanshinone IIA; TFR1, transferrin receptor 1; Th1, T helper type 1 cell; Th17, T helper type 17 cell; TLR2, toll-like receptor 2; ΔΨm, mitochondrial membrane potential.

In summary, although the upstream intervention targets of these TCM monomers are distributed across multiple signaling networks, including JAK/STAT, IL-6/STAT3, Nrf2, and AP-1, their downstream effects converge on the regulation of the balance between Bcl-2 family proteins and the ultimate inhibition of the Caspase cascade. This multi-target, convergent pharmacological characteristic collectively reverses the abnormal apoptosis of gastric mucosal epithelial cells, providing a solid pharmacological theoretical foundation for intervening in the atrophic process of CAG from the perspective of cell apoptosis.

2.2.2 Cell Pyroptosis

Pyroptosis is a form of programmed cell necrosis mediated by proteins from the gasdermin family characterized by the release of large amounts of pro-inflammatory factors that is closely linked to the chronic inflammatory state that characterizes CAG. The classical pyroptosis activation pathway involves the assembly of the NLRP3 inflammasome, which then activates caspase-1. The resulting cleavage of GSDMD leads to the formation of pores in the cell membrane, causing cell swelling, rupture, and the release of inflammatory factors such as IL-1β and IL-18. Studies have shown that in the MNNG-induced CAG models and cell-based systems, significant increases are evident in the expression of GSDMD, along with the upstream proteins NLRP3 and caspase-1 [51,52]. In addition to directly leading to the death of gastric epithelial cells, pyroptosis also releases potent inflammatory signals that further recruit and activate immune cells, forming a positive feedback loop that drives the continuous worsening of chronic inflammation and exacerbates the pathological progression of CAG.

Jatrorrhizine (JAT) and ginsenoside Rg1 (G-Rg1) have been shown to exert protective effects on the gastric mucosa by inhibiting pyroptosis-related signaling pathways. Jatrorrhizine can effectively downregulate the expression of the pro-GSDMD protein and caspase-1 in the gastric tissues of MNNG-induced CAG model rats. KEGG pathway enrichment results suggest that this effect is primarily associated with the Nod-like receptor-related pyroptosis pathway, and molecular docking analyses have confirmed the ability of JAT to directly interact with key effector molecules, such as IL-1β and caspase-3 downstream of pyroptosis [51]. G-Rg1 has been shown to primarily inhibit pyroptosis by regulating the NF-κB/NLRP3/GSDMD signaling axis. In both *in vitro* and *in vivo* CAG models, G-Rg1 inhibits the activation of NF-κB, thereby downregulating the activation of the NLRP3 inflammasome and ultimately reducing the formation of its substrate GSDMD. This, in turn, improves the morphological characteristics and membrane integrity of cells undergoing pyroptosis. More importantly, experiments involving overexpression and knock-

down of GSDMD in human GES-1 gastric mucosal epithelial cells have confirmed that GSDMD is an indispensable target required for the Rg1-mediated inhibition of pyroptosis, providing robust evidence of target validation [52].

In summary, although JAT and G-Rg1 primarily target the NLRP3 pathway and the upstream NF-κB pathway, respectively, their effects ultimately converge on the inhibition of GSDMD-associated membrane perforation, which is the final step in the cascade of pyroptosis execution. Both compounds inhibit the inflammatory pyroptotic death of gastric mucosal epithelial cells by directly reducing abnormal cell death and also interrupting the continuous inflammatory amplification loop driven by this pyroptotic death. These results offer a new pharmacological perspective and experimental foundation for treating CAG through the inhibition of pyroptosis.

2.2.3 Ferroptosis

Ferroptosis is an iron-dependent, lipid peroxide-associated form of cell death that plays a significant role in the pathogenesis of CAG [58,59,60]. The occurrence of ferroptosis in CAG is closely associated with local iron metabolism disorders and the collapse of the antioxidant defense system. Significant iron deposition has been detected in the gastric tissues of both CAG patients and model animals. Concurrently, the expressions of key negative regulators of ferroptosis, such as glutathione peroxidase 4 (GPX4) and ferritin heavy chain (FTH), decrease, while the level of the lipid peroxidation product 4-hydroxynonenal (4-HNE) increases, consistent with the induction of ferroptosis [60]. There are many factors that likely explain these findings. First, CAG pathogenesis is associated with an imbalance in local iron homeostasis in the stomach. High levels of hepcidin expression in gastric wall cells are mediated through the IL-6/STAT3 signaling pathway, leading to the inhibition of the intestinal iron absorption-related proteins divalent metal transporter 1 (DMT1) and ferroportin 1 (FPN1), potentially reducing intestinal iron absorption. These processes may also lead to iron retention or dysregulation in the stomach, providing the necessary substrate for ferroptosis [60]. Second, the antioxidant defense system is impaired in CAG, as the activity of GPX4, which is responsible for removing lipid peroxides, depends on reduced glutathione (GSH). In the CAG microenvironment, which is characterized by oxidative stress, the synthesis or regeneration of GSH may be blocked, leading to the inactivation of GPX4 and its inability to effectively inhibit lipid peroxidation chain reactions [61,62]. Ferroptosis can also interact with other forms of cell death, such as apoptosis. The lipid free radicals produced during ferroptosis can activate inflammatory pathways, forming a synergistic damage network that exacerbates the destruction of the gastric mucosa [63,64,65].

Various individual components of TCM preparations can establish a multi-level defensive interventional network by targeting different molecular pathways to inhibit ferroptosis. LUT, for instance, inhibits ferroptosis by targeting the AGE-RAGE signaling pathway. It downregulates the expression of lipid peroxidation-driven factors such as acyl-CoA synthetase long-chain family member 4 (ACSL4) and NADPH oxidase 1 (NOX1) in *in vivo* models, while upregulating key ferroptosis inhibitory proteins, including factor inhibiting HIF-1 (FIH1) and GPX4. This leads to a significant reduction in the levels of lipid peroxidation end products, including malondialdehyde (MDA) and Fe^{2+}, in gastric tissues, thereby inhibiting ferroptosis [25]. Furthermore, galangin (GAL) has been found to directly regulate iron metabolism to inhibit ferroptosis through an underlying mechanism closely related to the transcription factor Runt-related transcription factor 3 (Runx3). By targeting iron metabolism regulatory pathways, GAL downregulates the expression of iron uptake-related proteins, including transferrin receptor 1 (TFR1) and DMT1, while upregulating the expression of iron storage-related proteins, such as ferritin light chain (FTL), FTH, and the key ferroptosis inhibitor GPX4. As a result, the level of Fe^{2+} in the unstable intracellular labile iron pool (LIP) and the risk of lipid peroxidation are significantly reduced, exemplifying the regulation of iron homeostasis at the pathway, protein, and ionic levels to inhibit ferroptosis [53]. In addition to these direct regulatory effects, *in vivo* antioxidant enzyme assays have shown that costunolide (COS) activates the key antioxidant response regulator Nrf2, leading to the upregulation of downstream protective proteins such as superoxide dismutase (SOD), GSH, and HO-1, reducing the production of ROS and MDA [54]. Since the function of GPX4 depends on GSH, and Nrf2 directly regulates multiple genes related to iron metabolism and antioxidant defense, this pathway provides a crucial global antioxidant defense foundation essential for effectively resisting ferroptosis. Both evodiamine (EVO) and PAL exert their effects indirectly by improving the upstream microenvironment. EVO improves metabolic disorders in gastric tissues by inhibiting the MAPK signaling pathway and regulating fatty acid metabolism [55], whereas PAL reduces oxidative stress by inhibiting the STAT1/CXCL10 axis [39]. These two interventions indirectly eliminate the critical microenvironment necessary to trigger ferroptosis by correcting the upstream metabolic and oxidative stress imbalances that drive lipid peroxidation, establishing supportive *in vivo* metabolic and inflammatory profiles.

In summary, these individual components function in a synergistic manner, directly regulating iron-dependent cell death execution proteins (such as ACSL4 and GPX4) and enhancing core antioxidant defense mechanisms (through Nrf2), while also remediating the abnormal metabolic and oxidative microenvironment that promotes ferroptotic induction. Together, these effects establish a unified defensive system that restores the balance between lipid peroxidation and cell protection in the

CAG-associated gastric mucosa, thereby mitigating ferroptotic activity in gastric epithelial cells. These interventional strategies offer a robust pharmacological foundation for efforts centered on preventing and treating CAG by targeting ferroptosis.

2.3 Antioxidant Activity and Protection of the Gastric Mucosal Barrier

During the process of CAG pathogenesis, oxidative stress serves as a central driver of damage to the gastric mucosal barrier. This process is characterized by an imbalance between excessive ROS production and the body's antioxidant defense system. This imbalance directly targets cellular components and activates downstream inflammatory networks, collectively leading to the progressive atrophy of gastric mucosal glands. In patients with Hp-related multifocal atrophic gastritis (MAG), the levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), which is a key marker of oxidative DNA damage, have been shown to be significantly elevated and positively correlated with IL-10 levels. This finding directly highlights the coexistence of oxidative damage and chronic inflammation as well as their contribution to genomic instability. In contrast, 8-OHdG levels in patients with AAG are significantly lower, suggesting that the risk of cancer induced by oxidative stress varies across different etiologies of CAG [66]. This implies that interventional strategies for different subtypes of CAG may need to be tailored accordingly. From the perspective of disease progression, as CAG progresses to GC, the plasma levels of lipid peroxidation products such as MDA and diene conjugates (DCs) progressively increase, while the activity of endogenous antioxidant enzymes such as SOD and catalase (CAT) exhibits characteristic changes, consistent with the intensification of oxidative damage as the disease grows more severe [67].

At the molecular level, oxidative stress and chronic inflammation form a vicious cycle. Mitochondrial dysfunction and other factors leading to excessive ROS production can initiate deleterious signaling through the ROS-Nrf2-HO-1-NF-κB axis. While this signaling activity can trigger a compensatory antioxidant response by activating the transcription factor Nrf2 and downstream proteins, such as HO-1, it also continuously drives pro-inflammatory signaling through the NF-κB, exacerbating inflammatory damage to the gastric mucosa [68]. Of the pathways involved in this process, the close, mutually reinforcing interaction between oxidative stress and ferroptosis is particularly crucial. In this core pathological axis, oxidative stress acts as the upstream driving force, directly establishing the necessary conditions for ferroptosis by causing excessive ROS accumulation, depleting antioxidant substances like GSH, and triggering lipid peroxidation. This process culminates in dysregulated iron metabolism, extensive lipid peroxide accumulation, and the collapse of GPX4 and other key defensive systems [58].

Effectively addressing these core pathological processes necessitates a multi-target approach capable of simultaneously enhancing antioxidant defenses and inhibiting inflammation, thereby disrupting this vicious cycle. The mechanisms of action for a range of active substances and combinations thereof have been found to converge on this common target through effects on different molecular pathways. For instance, active substances such as COS can significantly increase the expression of SOD, GSH, and HO-1 in the gastric mucosa by directly activating the Nrf2 signaling pathway while also reducing MDA and ROS levels, thereby inhibiting oxidative stress and DNA damage [54]. Crucially, interventions targeting the oxidative stress-ferroptosis axis have been found to exert multi-dimensional synergistic protective effects. For instance, LUT-mediated targeting of the AGE-RAGE signaling pathway alleviates inflammation while also significantly reducing the concentrations of MDA and Fe^{2+} in gastric tissues. It also simultaneously downregulates the expression of the positive regulators of ferroptosis, such as ACSL4 and NOX1, and elevates the levels of the negative regulators, including hypoxia-inducible FIH1 and GPX4. Through these effects, it directly blocks the ferroptotic process at multiple levels [25]. In conjunction with these effects, certain plant-derived compounds, such as lycopene, specifically enhance upstream antioxidant defenses. Lycopene significantly upregulates the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and its downstream effectors, including HO-1 and NQO1, in the gastric tissues of CAG model mice, in addition to increasing SOD, CAT, and GPX4 activity. These effects systematically eliminate ROS, reduce MDA production, and weaken the foundation for ferroptotic induction [69]. Similarly, Rhein (Rhe) exerts anti-inflammatory and antioxidant effects by activating Nrf2 and inhibiting the mitogen-activated protein kinase (MAPK) signaling pathway [40]. Allicin (AL) affords similar benefits by inhibiting the activation of the JAK2/STAT3 pathway, which in turn reduces MDA levels, enhances SOD and CAT activity, and alleviates the inflammatory response [70]. QUE achieves these effects by regulating the transforming growth factor-β1/Smads (TGF-β1/Smads) signaling pathway and activating the Nrf2 pathway, thereby improving gastric secretory function and protecting gastric epithelial cells from oxidative damage in addition to maintaining mucosal integrity [26]. Although the initial targets of these individual components vary, they ultimately converge on the enhancement of overall antioxidant capacity, reductions in levels of oxidative damage products, direct or indirect stabilization of GPX4 function, remediation of dysregulated iron metabolism, and coordinated stabilization and repair of the gastric mucosal barrier. The underlying mechanisms are illustrated in Fig. 3, while supporting details regarding the Chinese herbal monomers involved in these processes are presented in Table 3 (Ref. [25,26,40,70]).

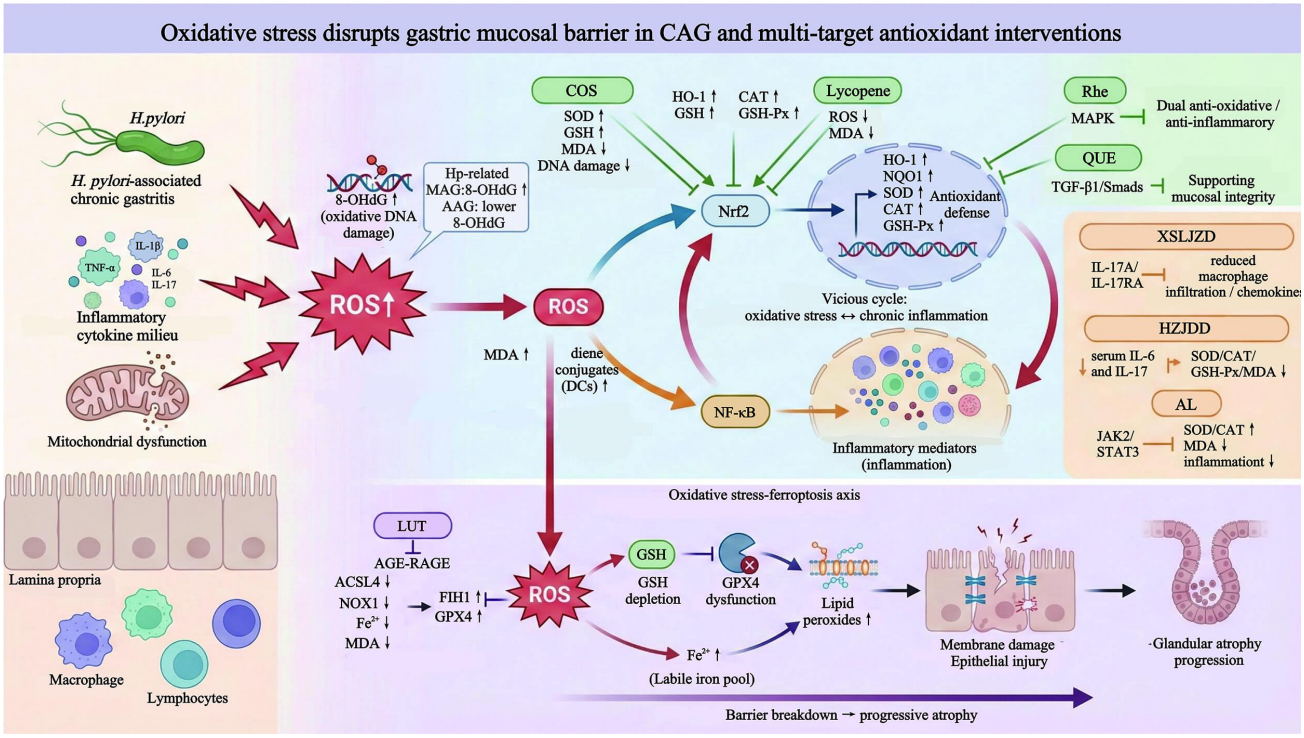


Fig. 3. Molecular mechanism of oxidative stress-induced CAG gastric mucosal injury and schematic diagram of multi-target intervention by traditional Chinese medicine. 8-OHdG, 8-hydroxy-2'-deoxyguanosine; AAG, autoimmune atrophic gastritis; GSH-Px, glutathione peroxidase; HZJDT, Hua-Zhuo-Jie-Du Decoction; IL-17A, interleukin-17A; IL-17RA, interleukin-17 receptor A; MAG, multifocal atrophic gastritis; NQO1, NAD(P)H:quinone oxidoreductase 1; XSLJZD, Xiang-Sha-Liu-Jun-Zi Decoction.

2.4 Hp Eradication and Microenvironmental Improvement

Hp infection is a central driving factor in the onset and progression of CAG. It initiates and sustains a complex, damaging microenvironment, promoting the transition of the gastric mucosa from an inflammatory state to atrophy and eventually to precancerous lesion development. Effective inhibition or eradication of Hp has been established as an important approach to eliminating this pathological microenvironment and halting disease progression.

When highly virulent type I Hp colonizes the gastric mucosa through the effects of factors such as heparanase, these bacteria secrete virulence factors, including CagA and VacA, which directly damage epithelial cells and continuously activate signaling pathways such as NF-κB, leading to the release of large amounts of pro-inflammatory cytokines including IL-8 and TNF-α, triggering and sustaining chronic inflammation [26,55,71]. This persistent inflammatory state not only directly damages the gastric glands, resulting in atrophy of the gastric mucosa and intestinal metaplasia, but also profoundly reshapes both local and distant microbial ecosystems. Infection significantly reduces the alpha diversity of the microbial community in the stomach and specifically enriches certain oral-derived bacterial groups. At the same time, altering gastric acid secretion affects the composition of the intestinal microbiota, leading to dysbiosis spanning from the stomach to the intestine [72,73]. More importantly, the chronic inflammation induced by Hp, combined with oxidative stress, causes DNA damage and cellular senescence in gastric mucosal cells. Although these senescent cells cease proliferating, they drive the further deterioration of the local microenvironment by secreting a series of inflammatory factors, creating conditions conducive to carcinogenesis [31,55]. Clinical studies have confirmed that the density of Hp infection is positively correlated with the activity of gastritis and the severity of atrophy. Moreover, precancerous changes such as gastric mucosal atrophy and intestinal metaplasia have been observed even in infected children and adolescents, highlighting the need for early intervention [74,75,76]. In conclusion, Hp infection plays a decisive role in promoting gastric mucosal atrophy and carcinogenesis through a cascade of events involving inflammation, microbiota disruption, cellular aging, and positive feedback regulation.

In light of this complex and interwoven pathological network, eradicating Hp is fundamental to improving the microenvironment of the gastric mucosa. Standard quadruple therapy, combined with TCM treatment, offers enhanced efficacy in this setting. For example, formulas aimed at tonifying the spleen and unblocking the meridians, or methods involving tonifying the spleen, clearing heat, and promoting diuresis, when used alongside Western medicine, can increase the rate of Hp clearance while also more effectively downregulating pro-inflammatory factors

Table 3. Summary table of antioxidant defense Chinese herbal monomers.

Name	Main source	Research design	Dosage of administration	Molecular mechanism	References
Luteolin	The dried flower buds or the newly opened flowers of the plant of the Lonicera genus (*Lonicera japonica Thunb.*)	*In vivo* experiments (SD rats, intragastric administration of MNNG at 170 μg/mL + free drinking of MNNG at 170 μg/mL, for 16 weeks)	80 mg/kg/d, for 12 weeks	Luteolin inhibits the AGE-RAGE signaling pathway, reduces the inflammatory response in gastric tissues, lowers the concentrations of MDA and Fe2+, CAG down-regulates the expressions of ACSL4 and NOX1, and up-regulates the expressions of FIH1 and GPX4 ferroptosis -related proteins, thereby inhibiting ferroptosis in gastric tissue cells and having a therapeutic effect on CAG.	[25]
Rhein	The dried roots and rhizomes of plants belonging to the Polygonaceae family, such as palm leaf rhubarb (*Rheum palmatum L.*), Tangut rhubarb (*Rheum tanguticum Maxim. ex Balf.*), or medicinal rhubarb (*Rheum officinale Baill.*)	*In vivo* experiments (C57BL/6N mice, 108 CFU/mL Hp was gavaged (4 times/week) + high-salt diet, for a total of 24 weeks)	100 mg/kg/d, for 8 weeks	Rhein exerts anti-inflammatory and antioxidant effects in CAG by activating the nuclear factor erythroid 2-related factor 2 and inhibiting the mitogen-activated protein kinase signaling pathway.	[40]
Allicin	The fresh bulb of the plant in the lily family, garlic (*Allium sativum L.*)	*In vivo* experiment (0.04 g/mL MNNG freely consumed + 0.03 g/kg ranitidine + alternate hunger and satiety, lasting for 20 weeks)	10 mg/kg/d, for 12 weeks	Allicin inhibits the activation of the JAK2/STAT3 signaling pathway, downregulates p-JAK2 and p-STAT3, and upregulates HMGB1. This inhibits inflammatory responses and oxidative stress damage.	[70]
Quercetin	The dried flower buds of the leguminous plant *Sophora japonica L.*	*In vivo* experiments (Wistar rats, 20 mmol/L sodium deoxycholate solution + 0.1% ammonia water + alternate hunger and satiety, for 90 days)	10 mg/kg/d; 25 mg/kg/d, for 30 days	Quercetin can alleviate gastric mucosal inflammation in CAG rats. Its effect may be mediated through the inhibition of the TGF-β1/Smads signaling pathway.	[26]

SD, Sprague-Dawley (rat strain); C57BL/6, C57BL/6 mouse strain; Wistar, Wistar rat strain; CFU, colony-forming units; HMGB1, high mobility group box 1.

such as CXCL5 in the gastric mucosa. Additionally, these therapies upregulate the expression of tumor suppressor genes such as Runx3, improve the levels of serum gastrin and pepsinogen, and thus, eliminate the pathogen while promoting the repair and functional recovery of the gastric mucosa [77]. Basic research has confirmed that Hp infection leads to an increase in the frequency of Runx3 promoter methylation in the gastric mucosa, thereby suppressing its protein-level expression. However, after successful eradication of Hp, both mRNA and protein expressions of Runx3 can be substantially restored [78]. Clinical efficacy analyses have further confirmed that, in patients in whom Hp had been successfully eradicated, the rate of improvement in gastric mucosal pathology was significantly higher, and the ratio of serum pepsinogen I to pepsinogen II (PGI/PGII) was significantly increased, indicating the partial recovery of gastric mucosal secretion functionality [79].

At the molecular level, various TCM monomers can target specific signaling pathways activated by Hp, thereby synergistically enhancing the efficacy of eradication-focused treatment efforts. The therapeutic effect of BBR stems from its specific inhibition of the IRF8-IFN-γ signal-

ing pathway. In *in vitro* and *in vivo* models of Hp infection, BBR intervention significantly downregulates the mRNA-level expression of a series of IFN-stimulated genes (ISGs) downstream of this axis, including Ifit3, Upp1, USP18, and Nlrc5. It also reduces the levels of key proteins, including IRF1 and Ifit1, thereby effectively alleviating immune pathological damage caused by the excessive activation of the type I IFN response [28]. JAT simultaneously targets two key pro-inflammatory hubs, as it inhibits the activation of the NF-κB signaling pathway, reducing the transcription of downstream inflammatory factors, while also inhibiting the assembly and activation of the NLRP3 inflammasome, blocking the caspase-1-mediated maturation and release of cytokines such as IL-1β. In animal models, JAT has been shown to directly reduce the Hp bacterial load in the gastric mucosa and to improve associated histopathological scores [80]. The core mechanism through which rutaecarpine (RUT) functions centers on the regulation of local immunity in the gastric mucosa, as it promotes M1-to-M2 macrophage repolarization. RUT has been shown to mediate a dose-dependent reduction in the mRNA-level expression of M1 markers such as iNOS and CD86, while increasing the expression of M2 markers, including arginase-1 (Arg-1) and CD206. This effect is directly related to its inhibition of the phosphorylation of IκBα and the NF-κB p65 subunit, thereby blocking NF-κB pathway activation [81]. EVO exerts its beneficial effects through the modulation of growth factor-related pathways, as it significantly reduces the expression of EGFR, MAPK, and ERK at the mRNA and protein levels in the gastric mucosa, thereby inhibiting the excessive production of various chemokines (IL-8, CXCL1) driven by this pathway. This not only improves inflammatory infiltration but also restores gastric mucosal blood flow and gastrointestinal motility [66].

In summary, although the specific targets on which these TCM monomers act vary, their effects converge on key mechanisms such as the inhibition of excessive immune responses, the disruption of core inflammatory pathways, the phenotypic regulation of immune cells, and the enhancement of mucosal self-repair. They inhibit inflammation and regulate immunity across multiple dimensions at the molecular level, complementing the oncogene silencing and functional restoration effects achieved through Hp eradication. Together, these monomers constitute a systematic and mechanism-driven treatment strategy for addressing the Hp-related malignant microenvironment present within the gastric mucosa. The signaling pathways and TCM monomers discussed above are illustrated in Fig. 4, and corresponding information regarding these monomers is presented in Table 4 (Ref. [28,66,80,81]).

2.5 Reversal of Intestinal Epithelial Hyperplasia and Dysplasia

Intestinal metaplasia and dysplasia are key precancerous pathological steps that characterize the Correa cascade reaction in CAG, setting the stage for GC development. Their occurrence and development are characterized by clear pathological definitions, risk stratification, and molecular mechanisms. Intestinal metaplasia is defined as the replacement of intrinsic gastric mucosal glands with glands exhibiting goblet-cell-like intestinal epithelial phenotypes. The histological presence of such metaplasia can serve as a diagnostic marker for CAG and is an important indicator for GC risk stratification [10,32]. However, intestinal metaplasia exhibits significant heterogeneity. Among its subtypes, incomplete intestinal metaplasia (especially type III) carries a notably higher risk of malignancy compared to complete intestinal metaplasia. One meta-analysis found that the combined relative risk of progressing to GC or dysplasia was as high as 4.48 [82], and that this high-risk subtype is closely associated with specific molecular expression profiles. For example, in the lesion area, the cell adhesion molecules CEACAM5 and TROP2 are specifically expressed at high levels, mirroring the atypical hyperplasia and molecular characteristics seen in GC. These findings provide potential molecular markers for identifying high-risk patients [83]. The core mechanism driving this malignant transformation involves persistent inflammation and abnormal microenvironmental stimulation. Hp infection promotes lesion progression by inducing specific antibody responses and the release of inflammatory factors [55,84]. In individuals affected by bile reflux, deoxycholic acid has been shown to directly drive the proliferation of gastric epithelial cells, enhance anti-apoptotic responses, and upregulate the expression of genes related to intestinal metaplasia by activating the STAT3 signaling pathway and increasing the activity of the transcription factor KLF5. Additionally, this reflux process disrupts the microbial and bile acid metabolic balance in the stomach, thereby creating a microenvironment conducive to carcinogenesis [85]. Furthermore, during the progression from intestinal metaplasia to dysplasia and eventually to GC, genomic characteristics undergo dynamic evolution. For instance, mutations in genes such as *TP53* occur in precancerous lesions and persist through the cancer stage [86]. In summary, the risks associated with intestinal epithelial metaplasia and dysplasia are highly heterogeneous. Incomplete metaplasia, the expression of specific molecular markers, and the continuous activation of key pathways such as the STAT3 signaling axis together constitute critical nodes involved in the progression from a reversible precancerous state to irreversible oncogenesis, making them promising targets for therapeutic intervention.

Given the heterogeneity of precancerous lesions and their multi-pathway activation characteristics, developing interventional methods that can precisely regulate these key signaling events through multiple targets is crucial for achieving pathological reversal. Various TCM monomers have shown promise in this context. For instance, AS-IV exerts its effects by interfering with abnormal glycolytic ac-

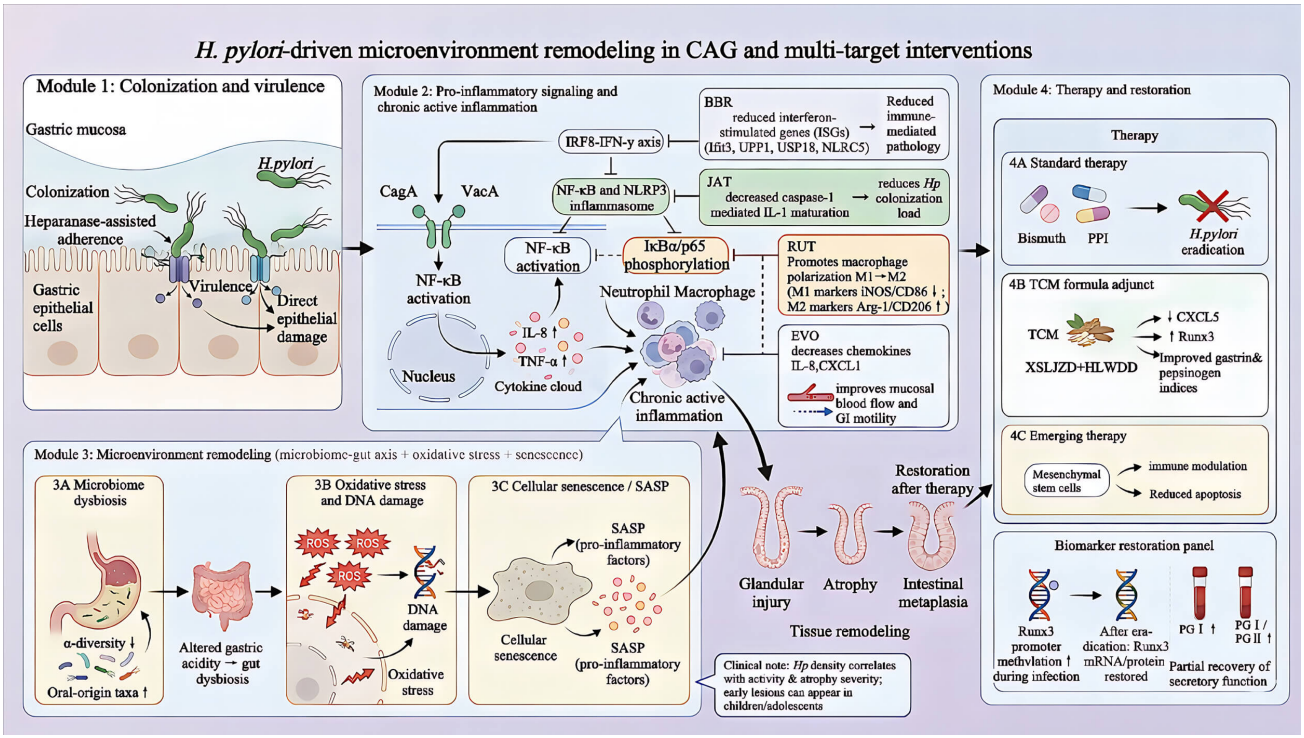


Fig. 4. The core pathological network of the malignant microenvironment driving CAG by Hp. Hp, Helicobacter pylori; CagA, cytotoxin-associated gene A; CXCL1, C-X-C motif chemokine ligand 1; CXCL5, C-X-C motif chemokine ligand 5; GI, gastrointestinal; HLWDD, Huang-Lian-Wen-Dan Decoction; IκBα, inhibitor of nuclear factor kappa-B alpha; M1, classically activated macrophage; M2, alternatively activated macrophage; PPI, proton pump inhibitor; SASP, senescence-associated secretory phenotype; VacA, vacuolating cytotoxin A; XSLJZD, Xiang-Sha-Liu-Jun-Zi Decoction.

tivity. In an MNNG-induced precancerous lesion model, AS-IV has been shown to significantly downregulate the protein levels of key rate-limiting enzymes in glycolysis, including lactate dehydrogenase A (LDHA), the monocarboxylate transporters MCT1 and MCT4, HIF-1α, and membrane-associated CD147. AS-IV also promotes the upregulation of p53 and its downstream glycolysis-inhibiting factor TP53-induced glycolysis and apoptosis regulatory factor (TIGAR), in addition to increasing miRNA-34a expression levels. Through these effects, it achieves the multitarget metabolic reprogramming of lesion cells and reverses dysplasia [87]. Epigallocatechin gallate (EGCG), in contrast, targets the pro-survival PI3K/Akt/mTOR pathway by reducing p-PI3K, p-Akt, and p-mTOR levels while increasing the expression of the negative regulatory factor PTEN and activated Caspase-3, which is responsible for apoptotic execution. This induces apoptosis in diseased cells, thereby alleviating gastric mucosal atrophy and dysplasia [88]. Similarly, 6-Gingerol (6-Gin) has been shown, through network pharmacology and experimental studies, to inhibit the PI3K/Akt pathway, thereby inhibiting cellular proliferation and invasion while promoting apoptosis [89]. Naringenin (NAR) has further been found to inhibit the microsomal triglyceride transfer protein/apoB (MTTP/APOB) axis, thereby improving pathological changes in a model of intestinal metaplasia [90]. Furthermore, erianin (ERI) significantly downregulates proteins such as HRAS, p-AKT, MDM2, and Cyclin D1 by inhibiting the HRAS-PI3K-AKT pathway, while upregulating the cell cycle inhibitory protein p21 [91]. The combination of ursolic acid (UA) and oleanolic acid (OA) inhibits malignant transformation by regulating the PI3K/Akt/NF-κB p65/NLRP3 pathway [38], whereas physochloside D inhibits apoptosis and intestinal epithelial metaplasia by regulating the JAK2/STAT3 pathway [92].

In summary, although these TCM monomers originate from different sources, their effects converge on the precise regulation of the core characteristics of precancerous lesions. By correcting metabolic abnormalities, blocking survival-promoting signals, and regulating specific target axes, they achieve the multi-dimensional downregulation of oncogenic proteins together with the upregulation of tumor suppressor factors. This multi-target interventional strategy addresses the precancerous pathological process that defines intestinal epithelial metaplasia and dysplasia in the context of CAG at multiple levels. However, a critical evaluation of the current evidence warrants caution in interpreting these findings as evidence of the definitive “reversal” of advanced lesions. While the presented evidence demonstrates that compounds like AS-IV

Table 4. Summary table of Chinese herbal monomers targeting the signal pathways of Hp infection for improving the gastric mucosal microenvironment.

Name	Main source	Research design	Dosage of administration	Molecular mechanism	References
Berberine	The dried rhizomes of the plant belonging to the Ranunculaceae family, *Coptis chinensis Franch.*	*In vivo* experiments (in SD rats, induced by 1.5×10^8 CFU/mL H. pylori for 8 weeks)	14 mg/kg/d; 28 mg/kg/d	Berberine inhibits the IRF8-IFN-γ signaling transduction axis, down-regulating the protein expression of the key transcription factor IRF1 and a series of interferon-stimulated gene products downstream of this pathway, including Ifit1, Ifit3, Upp1, USP18 and Nlrc5, thereby improving CAG.	[28]
Jatrorrhizine	The dried rhizomes of the plant belonging to the Ranunculaceae family, *Coptis chinensis Franch.*	*In vivo* experiments (in SD rats, induced by 1.5×10^8 CFU/mL *H. pylori* for 8 weeks)	50 mg/kg/d, for 8 weeks	Jatrorrhizine inhibits the activation of two signaling pathways, namely NF-κB and NLRP3 inflammasome, thereby down-regulating the abnormally elevated phosphorylation levels of NF-κB p65, PI3K, and p38 MAPK, as well as the protein expressions of NLRP3, caspase-1, IL-1β, and IL-18, in the gastric inflammation model induced by Hp This improves CAG in rats.	[80]
Rutaecarpine	Dried near-mature fruit of *Evodia rutaecarpa* (Juss.) Benth. (Rutaceae)	*In vivo* experiments (SD rats, *H. pylori* 1.2×10^{12} CFU/mL, after 28 days, given 0.83% deoxycholic acid sodium and 0.05% ammonia for free drinking, for a duration of 8 weeks)	5, 10, and 20 mg/kg/d	Rutaecarpine inhibits the activation of the NF-κB signaling pathway (manifested by the downregulation of phosphorylated protein levels of p-p65 and p-IκBα), thereby reducing the expression of pro-inflammatory macrophage (M1 type) related factors TNF-α, IL-6, iNOS, and CD86, and increasing the expression of anti-inflammatory macrophage (M2 type) related markers Arg-1 and CD206, thereby improving chronic gastritis induced by Hp.	[81]
Evodiamine	The dried near-mature fruits of the plant belonging to the Rutaceae family, *Evodia rutaecarpa* (Juss.) Benth.	*In vivo* experiments (SD rats, 1.5×10^8 CFU/mL *H. pylori*, gavage on days 1, 3, 5, 7, for 8 weeks)	20 mg/kg/d, for 30 days	Evodiamine downregulates the expression of proinflammatory factors IL-1β and IL-8 by inhibiting the EGFR/MAPK/ERK signaling pathway, while upregulating gastrointestinal hormones GAS and G-17 and repair factors GMBF and SS. This results in a comprehensive improvement of gastric mucosal atrophy, inflammation, and motility disorders.	[66]

SD, Sprague-Dawley (rat strain); CFU, colony-forming units; IRF1, interferon regulatory factor 1; Ifit1, interferon-induced protein with tetratricopeptide repeats 1; Ifit3, interferon-induced protein with tetratricopeptide repeats 3; Upp1, uridine phosphorylase 1; USP18, ubiquitin-specific peptidase 18; Nlrc5, NLR family CARD domain-containing protein 5; CD86, cluster of differentiation 86; CD206, cluster of differentiation 206; GAS, gastrin; G-17, gastrin-17.

and EGCG can suppress markers of malignant transformation and alter glycolytic phenotypes in MNNG models, the definitive clinical "reversibility" of advanced intestinal metaplasia remains a subject of intense gastroenterological debate. Histologically, complete intestinal metaplasia has been widely regarded as a "point of no return" in the Correa cascade, where genomic instability (e.g., early *TP53* mutations) and irreversible epigenetic rewiring have already taken place. The observed "reversal" in preclinical studies often reflects the clearing of surrounding active inflammation, the reduction of dysplastic cell proliferation, or the structural rejuvenation of early-stage, incomplete metaplastic lesions rather than a complete phenotypic erasure of mature goblet cell structures. Therefore, a balanced perspective suggests that TCM monomers function primarily as chemopreventive stabilizers that halt

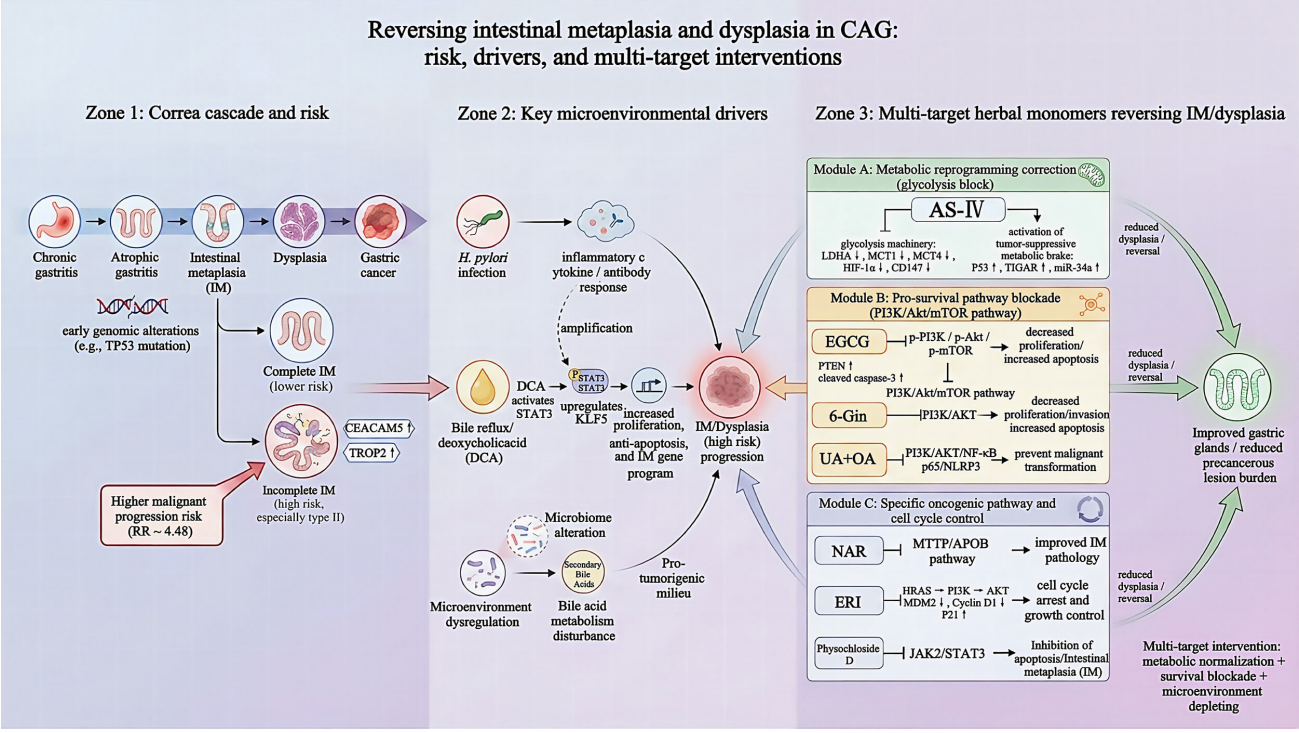


Fig. 5. Relevant signaling pathways and targets related to the precancerous lesions of CAG. CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; KLF5, Krüppel-like factor 5; RR, relative risk; TROP2, trophoblast cell-surface antigen 2.

progression and lower the risk of malignancy, rather than fully reversing established, advanced mucosal transformations. The signaling pathways and TCM monomers discussed above are illustrated in Fig. 5, and corresponding information regarding these monomers is presented in Table 5 (Ref. [38,87,88,89,90,91,92]).

3. Conclusions

Increasing evidence suggests that the pathological process of CAG cannot be fully explained by the traditional inflammation-driven model. Although chronic inflammation is the core initiating factor for CAG occurrence and progression, its persistent presence triggers a series of interrelated pathological processes, including oxidative stress, dysregulated programmed cell death, aberrant immune activity, and disruption of gastric mucosal barrier function. These pathological processes are not independent; rather, they form a tightly interwoven and mutually interactive pathological network, continuously exacerbating gastric mucosal damage and promoting the development of precancerous lesions such as intestinal metaplasia and dysplasia. Within this regulatory network, chronic inflammation triggered by Hp infection or autoimmune reactions readily promotes the excessive generation of ROS, leading to oxidative stress that directly damages cellular structures in addition to activating the NLRP3 inflammasome [93], inducing pyroptosis, while also promoting ferroptosis through lipid peroxidation. These programmed cell death mechanisms further trigger the release of damage-associated molecular patterns, amplifying local inflammatory responses and immune dysregulation, while simultaneously disrupting tight junction proteins of the gastric mucosa and weakening its barrier function. In this persistent pathological microenvironment, gastric epithelial cells are forced to initiate abnormal repair and compensatory proliferation, ultimately driving the occurrence of metaplasia and dysplasia. Therefore, CAG should be regarded as a dynamic, imbalanced system maintained by multiple pathological modules through positive feedback mechanisms, rather than a linear progressive process driven by a single inflammatory pathway.

Recent studies have consistently shown that individual TCM monomers can exert therapeutic effects in CAG by coordinating and regulating multiple key signaling modules. Among these, astragalus polysaccharides have been demonstrated to inhibit the excessive activation of the JAK1/STAT3 signaling pathway in a dose-dependent manner. Specifically, they reduce p-JAK1 and p-STAT3 levels in the gastric mucosa, effectively lowering the concentrations of IL-6 and TNF-α in the serum while improving overall inflammatory status. The NLRP3-mediated pathway of pyroptotic induction is another important regulatory module [94]. Crucially, the role of NLRP3 signaling in CAG is highly context-dependent. On one hand, studies have shown that certain TCM combinations can induce pyroptosis in abnormal gastric epithelial cells by upregulating key molecules such as NLRP3, Caspase-1, and GSDMD, thereby eliminating potential abnormal cells [52].

Table 5. Summary of herbal monomers for reversing intestinal metaplasia and dysplasia.

Name	Main source	Research design	Dosage of administration	Molecular mechanism	References
Astragaloside IV	Dried root of the leguminous plant Mongolian Astragalus (*Astragalus membranaceus* var. *mongholicus*) or Membranous Astragalus (*Astragalus membranaceus*)	*In vivo* experiment (SD rats, 200 mg/L MNNG ad libitum drinking + alternate feeding and fasting, for 16 weeks)	50 mg/kg/d; 100 mg/kg/d, for 10 weeks	Astragaloside IV (AS-IV) significantly reversed MNNG-induced precancerous gastric lesions (PLGC) in rats by modulating glycolysis-related pathways. Specifically, it upregulates the expression of p53, TIGAR, and miRNA-34a while downregulating the expression of LDHA, MCT1, MCT4, HIF-1α, and CD147 at the gene and/or protein level, thereby correcting abnormal glycolytic processes.	[87]
Epigallocatechin gallate	Leaves of the tea plant (*Camellia sinensis*)	*In vivo* experiment (Wistar rats, 100 μg/mL MNNG + free water access + twice-weekly gavage of 2 mL 2% sodium salicylate, for 17 weeks)	50 mg/kg/d, for 4 weeks	Epigallocatechin gallate exerts therapeutic effects on gastric precancerous lesions by inhibiting the PI3K/Akt/mTOR signaling pathway, thereby upregulating the expression of the pro-apoptotic protein caspase-3.	[88]
6-Gingerol	Fresh or dried rhizome of ginger (*Zingiber officinale*)	*In vitro* experiment (Establishing a PLGC cell model using MNNG-induced GES-1 cells)	100 μmol/L	6-Gingerol downregulates PI3K and p-Akt expression in a dose-dependent manner by inhibiting the PI3K/Akt signaling pathway, thereby suppressing cell proliferation, invasion, and metastasis while promoting apoptosis.	[89]
Naringenin	The peel or flowers of citrus plants such as the pomelo (*Citrus maxima*) belonging to the Rutaceae family	*In vivo* experiment (SD rats, 0.02 mol/L MNNG solution, 0.5 mL/100 g/day, administered for 20 weeks)	50 mg/kg/d, for 8 weeks	Naringenin suppresses intestinal metaplasia (IM) progression by improving pathological alterations in an IM model through downregulation of MTTP and APOB protein expression.	[90]
Erianin	The whole plant or pseudobulbs of Eria (*Eria* spp.)	*In vitro* experiment (MNNG-induced GES-1 cell line to establish a PLGC model)	80 nmol/L	Erianin inhibits the HRAS-PI3K-AKT signaling pathway, thereby downregulating the expression of HRAS, PI3K, AKT, p-AKT, MDM2, p-Gsk3β, and downstream Cyclin D1 proteins within the pathway. Simultaneously, it upregulates the expression of the cell cycle suppressor protein p21, thereby regulating the cell cycle and exerting an anti-gastric precancerous lesion (PLGC) effect.	[91]

Table 5. Continued.

Name	Main source	Research design	Dosage of administration	Molecular mechanism	References
Ursolic acid and oleanolic acid	Dried root of *Actinidia chinensis Planch.* (Chinese gooseberry)	*In vitro* experiment (MNNG-induced GES-1 cell line to establish a PLGC model)	30 μmol/L	Ursolic acid/oleanolic acid directly binds to and inhibits the PI3K/Akt signaling pathway, thereby downregulating the phosphorylation levels of PI3K and AKT within this pathway, as well as the expression of pro-inflammatory and pro-fibrotic proteins downstream of the pathway, including NF-κB p65, NLRP3, N-cadherin, vimentin, and α-SMA. Concurrently, they promote apoptosis by upregulating the pro-apoptotic protein Bax and downregulating the anti-apoptotic protein Bcl-2.	[38]
Physochloside D	The whole plant or entire herb of *Physochlaina physaloides* (Solanaceae)	*In vivo* experiment (SD rats, 10% ethanol + MNNG (170 μg/mL) ad libitum drinking + 1 mL/100 g MNNG gavage once every 2 days + alternate fasting and feeding, for 8 weeks)	10 mg/kg/d; 20 mg/kg/d; 40 mg/kg/d, for 2 weeks	By inhibiting the activation of the JAK2/STAT3 signaling pathway, the protein expression of p-JAK2, p-STAT3, and their downstream effector molecules Snail and HMGB1 was downregulated. Among these, STAT3 is likely a direct target of this inhibition, thereby suppressing apoptosis and intestinal metaplasia.	[92]

SD, Sprague-Dawley (rat strain); Wistar, Wistar rat strain; PLGC, precancerous lesions of gastric cancer; GSK3β, glycogen synthase kinase 3 beta; α-SMA, alpha-smooth muscle actin; HMGB1, high mobility group box 1.

On the other hand, separate studies have suggested that the TCM monomer galangin can alleviate gastric mucosal inflammation by inhibiting the over-activation of the NLRP3 inflammasome [53]. These seemingly contradictory results may stem from differences in disease stage, cell type, and treatment goals. The Nrf2-mediated antioxidant-ferroptosis pathway is another key regulatory axis [95]. As oxidative stress is one of the core pathological drivers of CAG, interventions targeting redox homeostasis hold significant therapeutic promise [96]. In the early stages of this disease, activating the Nrf2 signaling pathway may protect the gastric mucosa; however, studies in GC and precancerous lesion models have shown that inhibiting the Nrf2/GPX4 axis can effectively induce ferroptosis in abnormal cells [97]. This suggests that along the continuous spectrum of CAG progression toward precancerous and malignant stages, oxidative stress-related pathways may exhibit dual and stage-dependent regulatory significance [54]. The PI3K/Akt signaling pathway is another key target of TCM monomer-based intervention in CAG, as it plays a crucial role in regulating the balance between cell proliferation and apoptosis and is closely related to abnormal epithelial repair and precancerous progression [98]. Network pharmacology analyses have consistently identified PI3K/Akt as one of the most prominent signaling pathways involved in the TCM-based treatment of CAG and related pathologies [99]. For example, BBR can simultaneously regulate the inflammatory response and epithelial cell survival through multiple upstream and downstream effectors, demonstrating the multifunctional regulatory characteristics that characterize TCM monomers [28].

These synergistic multi-target interventions regulate entire signaling networks, effectively reversing the imbalanced "disease state" back to a more stable condition. The individual components of TCM preparations can jointly regulate core pathological processes such as inflammation, oxidative stress, apoptosis, and autophagy through the integrated action of multiple components, pathways, and targets. This approach provides a more systematic and disease-complexity-appropriate treatment strategy for reversing the precancerous process of CAG [100]. Active polysaccharide components, such as astragalus polysaccharides and dendrobium polysaccharides, effectively demonstrate the unique potential of TCM-based approaches to regulating network homeostasis. The target of dendrobium polysaccharides is the Wnt/β-catenin pathway. These polysaccharides downregulate the gene and protein levels of the pathway ligand Wnt2β, the core transcription factor β-catenin, and their downstream targets, including proliferating cell nuclear antigen (PCNA) and the cell cycle regulator CyclinD1. This inhibition effectively impedes the progression of precancerous lesions, offering a new direction for intervening in abnormal cell proliferation and differentiation [101].

In addition to classical signaling pathways, recent research into the mechanisms of CAG has expanded to explore deeper cellular processes. Gastric gland atrophy is the core pathological feature of CAG, reflecting the impairment of gastric epithelial regeneration [4]. Recent reports have found that active peptides isolated from the TCM formula "Kangfuxin" can stabilize the EGF-EGFR complex and activate downstream ERK/STAT1 signaling to trigger gastric stem cell activity, thereby promoting gastric mucosal regeneration in animal models and patient-derived gastric organoids [1]. This finding provides direct biological evidence for the ability of TCM compounds to reverse atrophy, exerting regenerative effects rather than simply mediating injury repair. Mitochondrial quality control is also considered an important mechanistic basis for the antioxidant effects of TCM. Mitochondria are not only a major source of ROS but also a key target of oxidative stress [102]. Research has shown that the Hua-Zhuo-Jie-Du Decoction can enhance mitochondrial autophagy by activating the Sirt3/Foxo3a/Parkin pathway, promoting the clearance of dysfunctional mitochondria. This restores cellular energy homeostasis and alleviates oxidative damage [103]. The antioxidant effects of individual TCM monomers may thus be more dependent on the precise regulation of mitochondrial quality rather than the simple removal of free radicals. Importantly, the therapeutic effects of individual TCM components are not limited to the local area of the stomach [104]. Increasing evidence indicates that TCM preparations can alleviate the inflammatory response in the stomach at the systemic level by regulating the structure of the intestinal microbiota and the associated immune microenvironment. By reshaping intestinal microecology and promoting the production of beneficial metabolites, TCM preparations may exert distant regulatory effects through the gut microbiota-gastric axis, providing a systems biology-based explanation for its multi-target synergy [53,105].

4. Future Perspectives

Despite the continuous advancement of relevant research, the clinical application of single TCM components to the treatment of CAG still faces multiple challenges. First, it is essential to prioritize the selection of monomers from among numerous candidates, focusing on those with clear mechanistic innovation and transformative potential, such as BBR [106], curcumin [107], and LUT [108], which have already accumulated substantial human pharmacokinetic and safety data in other disease areas. Second, significant pharmaceutical bottlenecks, including low oral bioavailability, poor stability in the gastric environment, and the lack of gastric mucosal targeting, limit the efficacy of single TCM components. Therefore, it is crucial that new delivery systems capable of enhancing local exposure and treatment efficiency be developed [109]. Novel systems that improve delivery efficiency and achieve precise release at affected sites remain a key challenge for

translational research efforts to overcome [110,111]. Third, it remains essential to establish a clinical evaluation system aligned with the standards of modern pharmacological research. This includes systematic safety assessments, composite biomarkers that can reflect gastric mucosal regeneration and network regulation, and a rational clinical research design tailored to the different stages of CAG.

In addition to the aforementioned drug development and clinical evaluation challenges, the unique pharmacokinetic (PK) properties of TCM monomers present additional translational barriers. For example, although BBR has been clearly shown to modulate the PI3K/Akt pathway via multiple targets, its low solubility, poor intestinal permeability, and efflux mediated by P-glycoprotein (P-gp) result in extremely low oral bioavailability [112], necessitating advanced delivery systems to achieve therapeutically relevant concentrations. Similarly, flavonoids such as LUT and QUE undergo extensive first-pass metabolism in the gut and liver through glucuronidation and sulfation, significantly shortening the plasma half-life of their parent compounds; however, their conjugated metabolites may persist *in vivo* and retain some pharmacological activity [112].

With respect to toxicological safety, most TCM monomers exhibit favorable cytoprotective effects within therapeutic dose ranges. However, their toxicity is dose- and route-dependent, requiring close monitoring. Notably, although AS-IV has been widely reported to possess hepatoprotective and cardioprotective activities, the long-term safety of its high-dose administration—particularly via intravenous routes—remains to be systematically evaluated [113].

Furthermore, when these bioactive monomers are used in combination with conventional Western medications, herb-drug interactions (HDIs) pose significant clinical challenges [114]. For instance, quercetin (QUE) is a competitive inhibitor of CYP3A4, which could elevate plasma concentrations of co-administered CYP3A4 substrates, including the antibiotic clarithromycin and certain proton pump inhibitors [115]. Although direct clinical evidence for these specific combinations remains limited, the potential for HDIs should be carefully considered, especially in polypharmacy settings or when integrating TCM monomers into established treatment regimens [114,116].

In the current literature, most mechanistic insights stem from chemically induced animal models of CAG generated primarily using MNNG or sodium deoxycholate in combination with irregular fasting. Although these models can successfully reproduce significant histological endpoints such as glandular atrophy and compensatory mucosal thinning, they have structural limitations in their ability to simulate the etiology of human CAG. In patients, the progression of CAG is a gradual, decades-long pathological process primarily driven by persistent Hp virulence interactions or genetic autoimmune destruction targeting parietal cells [117]. Chemical models, in contrast, trigger sudden and widespread DNA alkylation and chemical damage, which may overly simplify the complex and immunopolarized microenvironment observed in clinical patients [118]. Notably, the occurrence of GC induced by MNNG does not follow the classic sequence of atrophy-intestinal metaplasia-dysplasia observed in the human Correa cascade reaction; instead, chemical carcinogens typically directly induce oncogenic transformation, bypassing the clinically significant precancerous stages that define human GC development [119,120]. Moreover, no Hp infection model can fully simulate the entire spectrum of human disease, and the gastric inflammation patterns induced in animals are mostly lymphocytic, lacking the neutrophil infiltration commonly seen in adult Hp infection [121]. These fundamental differences between animal models and human pathology highlight the importance of caution when interpreting preclinical research results. There thus remains a significant clinical evidence gap. Although the activity of TCM compounds such as Moluodan has been supported through randomized controlled trials (RCTs) [122], studies on individual monomers such as LUT, isoflavones, and erianin remain lacking in CAG owing to an absence of large-scale, double-blind human trials. For example, isoflavones (formononetin) have only been evaluated in the MNNG-induced GES-1 cell model, and no clinical studies have reported their protective effect on human CAG [50]. Similarly, although erianin is considered a promising drug for the treatment of gastric precancerous lesions, current evidence is still restricted to *in vitro* MNNG-induced cell models [123]. The clinical validation of these single components mostly stems from indirect inference based on the safe application of these compounds in other inflammatory or metabolic diseases. BBR, however, is a notable exception, as some small-scale clinical studies have demonstrated its therapeutic benefits for CAG patients [124], though these studies were hampered by limited sample sizes and insufficient methodological rigor. Future translational research must prioritize validation in human-derived gastric organoids and phase I/II clinical pilot studies to bridge the gap between preclinical prospects and clinical practice.

In this context, gastric organoid technologies offer an important tool for bridging mechanistic research and clinical translation. Gastric organoids derived from patients can effectively simulate the three-dimensional structure of the gastric mucosa, disease heterogeneity, and individualized drug responses, demonstrating significant advantages in GC research. To effectively integrate cutting-edge organoid technologies into future TCM-focused CAG research, it is essential that a clear path from theory to empirical evidence be established. Gastric organoids, especially those derived from patients, have become a crucial bridge between basic research and clinical translation due to their ability to simulate the structure of the gastric mucosa and retain individual disease characteristics and heterogeneity [125]. Their value as tools for modeling tumor microenvironments, drug re-

sponses, and personalized medicine in GC has been firmly established [126,127,128,129]. These organoids have been successfully applied to mechanistic studies of the functions of TCM preparations in gastric inflammatory diseases. For example, one recent study used a lipopolysaccharide-induced model of murine gastric inflammation to precisely screen and confirm the anti-inflammatory and antioxidant effects of multiple individual components present in the TCM preparation known as Jinhong Tablets, establishing a clear material basis for its efficacy as a means of treating chronic gastritis [130]. This offers a useful model for researching the treatment of CAG with TCM. Future research should thus focus on establishing a closed-loop path consisting of clinical sample-based organoid modeling, multi-omics analysis, and mechanistic verification. First, drawing on successful experiences from the broader field of GC research, a CAG patient-derived organoid library should be established to preserve disease heterogeneity [131,132]. Then, using these organ models, the key pathological processes of CAG, such as chronic inflammation and oxidative damage, can be simulated, followed by interventions with TCM-containing serum samples or specific monomers. Furthermore, high-throughput technologies such as single-cell transcriptomics can be employed to analyze the dynamic remodeling of the transcriptional network after TCM intervention at the cell subpopulation level, without bias [54,133]. The potential core targets or pathways identified via this approach can then undergo genetic editing or pharmacological validation in organoid models, thereby closing the mechanistic loop spanning from correlative discovery to causal confirmation. By integrating organoids with multi-omics technologies, this approach will allow for the visualization and analysis of the dynamic TCM-based multi-target regulation of the CAG pathological network in a highly biologically relevant system, advancing research in this field toward greater precision and depth.

To optimize the delivery process of TCM monomers in CAG, future research should shift from extensive screening to a focused strategy centered on high-potential candidates and cutting-edge validation tools, thereby accelerating the translation of preclinical findings into clinical practice.

Abbreviations

ACSL4, Acyl-CoA Synthetase Long-Chain Family Member 4; AGE, Advanced Glycation End Products; Akt, Protein Kinase B; APOB, Apolipoprotein B; AS-IV, Astragaloside IV; BA, Baicalin; BBR, Berberine; CAG, Chronic Atrophic Gastritis; Caspase-1, Cysteinyl Aspartate Specific Proteinase-1; CXCL10, C-X-C Motif Chemokine Ligand 10; CYP3A4, Cytochrome P450 3A4; E-cadherin, Epithelial Cadherin; EGCG, Epigallocatechin Gallate; EGFR, Epidermal Growth Factor Receptor; ERK, Extracellular Signal-Regulated Kinase; EVO, Evodiamine; GC, Gastric Cancer; GES-1, Gastric Epithelial Cell Line-1; Gli1, Glioma-Associated Oncogene Homolog 1; GPX4, Glutathione Peroxidase 4; G-Rg1, Ginsenoside Rg1; GSDMD, Gasdermin D; HDIs, Herb-Drug Interactions; HIF-1α, Hypoxia-Inducible Factor 1-Alpha; Hp, *Helicobacter pylori*; HRAS, Harvey Rat Sarcoma Viral Oncogene Homolog; IFN-γ, Interferon-Gamma; IL-6, Interleukin-6; IL-17, Interleukin-17; IM, Intestinal Metaplasia; IRF8, Interferon Regulatory Factor 8; JAK1, Janus Kinase 1; JAK2, Janus Kinase 2; JAT, Jatrorrhizine; KAE, Kaempferol; KLF5, Krüppel-Like Factor 5; LDHA, Lactate Dehydrogenase A; LUT, Luteolin; MAPK, Mitogen-Activated Protein Kinase; MCT1, Monocarboxylate Transporter 1; MCT4, Monocarboxylate Transporter 4; MDM2, Mouse Double Minute 2 Homolog; miRNA-34a, MicroRNA-34a; MNNG, N-methyl-N′-nitro-N-nitrosoguanidine; MTTP, Microsomal Triglyceride Transfer Protein; NAR, Naringenin; Nrf2, Nuclear factor erythroid 2-related factor 2; NF-κB, Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; NLRP3, NOD-Like Receptor Family Pyrin Domain Containing 3; NOX1, NADPH Oxidase 1; OA, Oleanolic Acid; p21, Cyclin-Dependent Kinase Inhibitor 1A; p53, Tumor Protein p53; PAL, Palmatine; PCD, Programmed Cell Death; PCNA, Proliferating Cell Nuclear Antigen; P-gp, P-Glycoprotein; PI3K, Phosphoinositide 3-Kinase; PK, Pharmacokinetics; PPIs, Proton Pump Inhibitors; PTEN, Phosphatase and Tensin Homolog; QUE, Quercetin; RAGE, Receptor for Advanced Glycation End Products; RCT, Randomized Controlled Trial; ROS, Reactive Oxygen Species; Shh, Sonic Hedgehog; STAT1, Signal Transducer and Activator of Transcription 1; STAT3, Signal Transducer and Activator of Transcription 3; STAT6, Signal Transducer and Activator of Transcription 6; TCM, Traditional Chinese Medicine; TGF-β1, Transforming Growth Factor Beta 1; TIGAR, TP53-Induced Glycolysis and Apoptosis Regulator; TNF-α, Tumor Necrosis Factor-Alpha; TP53, Tumor Protein p53 (Gene); UA, Ursolic Acid; Wnt2β, Wingless-Type MMTV Integration Site Family Member 2β; ZO-1, Zonula Occludens-1; 6-Gin, 6-Gingerol.

Author Contributions

Conceptualization: LC, PW and TL; investigation: TC, MZ, YL and CJ; literature search: TL; visualization: YJ; figure preparation: TL; writing—original draft: TL; writing—review and editing: TL; supervision: LC and PW. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Li K, Ma X, Li Z, Liu Y, Shen G, Luo Z, et al. A Natural Peptide from A Traditional Chinese Medicine Has the Potential to Treat Chronic Atrophic Gastritis by Activating Gastric Stem Cells. Advanced Science (Weinheim, Baden-Wurttemberg, Germany). 2024; 11: e2304326. https://doi.org/10.1002/advs.202304326

[2] Weck MN, Brenner H. Prevalence of chronic atrophic gastritis in different parts of the world. Cancer Epidemiology, Biomarkers & Prevention: a Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology. 2006; 15: 1083–1094. https://doi.org/10.1158/1055-9965.EPI-05-0931

[3] Dai YC, Tang ZP, Zhang YL. How to assess the severity of atrophic gastritis. World Journal of Gastroenterology. 2011; 17: 1690–1693. https://doi.org/10.3748/wjg.v17.i13.1690

[4] Massironi S, Zilli A, Elvevi A, Invernizzi P. The changing face of chronic autoimmune atrophic gastritis: an updated comprehensive perspective. Autoimmunity Reviews. 2019; 18: 215–222. https://doi.org/10.1016/j.autrev.2018.08.011

[5] Weck MN, Stegmaier C, Rothenbacher D, Brenner H. Epidemiology of chronic atrophic gastritis: population-based study among 9444 older adults from Germany. Alimentary Pharmacology & Therapeutics. 2007; 26: 879–887. https://doi.org/10.1111/j.1365-2036.2007.03430.x

[6] Annibale B, Esposito G, Lahner E. A current clinical overview of atrophic gastritis. Expert Review of Gastroenterology & Hepatology. 2020; 14: 93–102. https://doi.org/10.1080/17474124.2020.1718491

[7] Lahner E, Conti L, Annibale B, Corleto VD. Current Perspectives in Atrophic Gastritis. Current Gastroenterology Reports. 2020; 22: 38. https://doi.org/10.1007/s11894-020-00775-1

[8] Li Y, Xia R, Zhang B, Li C. Chronic Atrophic Gastritis: A Review. Journal of Environmental Pathology, Toxicology and Oncology: Official Organ of the International Society for Environmental Toxicology and Cancer. 2018; 37: 241–259. https://doi.org/10.1615/JEnvironPatholToxicolOncol.2018026839

[9] Neumann WL, Coss E, Rugge M, Genta RM. Autoimmune atrophic gastritis—pathogenesis, pathology and management. Nature Reviews. Gastroenterology & Hepatology. 2013; 10: 529–541. https://doi.org/10.1038/nrgastro.2013.101

[10] Shah SC, Piazuelo MB, Kuipers EJ, Li D. AGA Clinical Practice Update on the Diagnosis and Management of Atrophic Gastritis: Expert Review. Gastroenterology. 2021; 161: 1325–1332.e7. https://doi.org/10.1053/j.gastro.2021.06.078

[11] Uibo R. Contribution of epidemiological studies to gastritis immunology. International Reviews of Immunology. 2005; 24: 31–54. https://doi.org/10.1080/08830180590884495

[12] Namekata T, Miki K, Kimmey M, Fritsche T, Hughes D, Moore D, et al. Chronic atrophic gastritis and Helicobacter pylori infection among Japanese Americans in Seattle. American Journal of Epidemiology. 2000; 151: 820–830. https://doi.org/10.1093/oxfordjournals.aje.a010282

[13] Botezatu A, Bodrug N. Chronic atrophic gastritis: an update on diagnosis. Medicine and Pharmacy Reports. 2021; 94: 7–14. https://doi.org/10.15386/mpr-1887

[14] Du Y, Bai Y, Xie P, Fang J, Wang X, Hou X, et al. Chronic gastritis in China: a national multi-center survey. BMC Gastroenterology. 2014; 14: 21. https://doi.org/10.1186/1471-230X-14-21

[15] Adamu MA, Weck MN, Gao L, Brenner H. Incidence of chronic atrophic gastritis: systematic review and meta-analysis of follow-up studies. European Journal of Epidemiology. 2010; 25: 439–448. https://doi.org/10.1007/s10654-010-9482-0

[16] Sipponen P, Maaroos HI. Chronic gastritis. Scandinavian Journal of Gastroenterology. 2015; 50: 657–667. https://doi.org/10.3109/00365521.2015.1019918

[17] Alakoski A, Salmi TT, Hervonen K, Kautiainen H, Salo M, Kaukinen K, et al. Chronic gastritis in dermatitis herpetiformis: a controlled study. Clinical & Developmental Immunology. 2012; 2012: 640630. https://doi.org/10.1155/2012/640630

[18] Jia J, Zhao H, Li F, Zheng Q, Wang G, Li D, et al. Research on drug treatment and the novel signaling pathway of chronic atrophic gastritis. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2024; 176: 116912. https://doi.org/10.1016/j.biopha.2024.116912

[19] Pimanov SI, Makarenko EV. Chronic gastritis: last decade's achievements and problems. Klinicheskaia Meditsina. 2005; 83: 54–58.

[20] Kuwahara Y, Kono S, Eguchi H, Hamada H, Shinchi K, Imanishi K. Relationship between serologically diagnosed chronic atrophic gastritis, Helicobacter pylori, and environmental factors in Japanese men. Scandinavian Journal of Gastroenterology. 2000; 35: 476–481. https://doi.org/10.1080/003655200750023723

[21] El-Omar EM, Carrington M, Chow WH, McColl KEL, Bream JH, Young HA, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature. 2000; 404: 398–402. https://doi.org/10.1038/35006081

[22] Kuang W, Xu J, Xu F, Huang W, Majid M, Shi H, et al. Current study of pathogenetic mechanisms and therapeutics of chronic atrophic gastritis: a comprehensive review. Frontiers in Cell and Developmental Biology. 2024; 12: 1513426. https://doi.org/10.3389/fcell.2024.1513426

[23] Dzhulaĭ GS, Chernin VV, Iakovlev NA. Chronic gastritis: keys to understanding the internal picture of the disease. Eksperimental'naia i Klinicheskaia Gastroenterologiia = Experimental & Clinical Gastroenterology. 2002; 28–30, 191.

[24] Inoue M, Tajima K, Matsuura A, Suzuki T, Nakamura T, Ohashi K, et al. Severity of chronic atrophic gastritis and subsequent gastric cancer occurrence: a 10-year prospective cohort study in Japan. Cancer Letters. 2000; 161: 105–112. https://doi.org/10.1016/s0304-3835(00)00603-0

[25] Zhang N, Chen P, Liang X, Sun J, Liu Q, Guan S, et al. Luteolin targets the AGE-RAGE signaling to mitigate inflammation and ferroptosis in chronic atrophic gastritis. Aging. 2024; 16: 10918–10930. https://doi.org/10.18632/aging.205969

[26] Cai P, Song Q, Ye F, Chen R, Lin Z. Protective Role of Quercetin in Chronic Atrophic Gastritis: Modulation of Gastric Mucosal Integrity via the Transforming Growth Factor-beta1/Smads Signaling Pathway. Discovery Medicine. 2025; 37: 1062–1073. https://doi.org/10.24976/Discov.Med.202537197.94

[27] Ren L, Wang LB, Zhang M. Mechanism study of tanshinone IIA alleviating gastric mucosal injury in rats with chronic atrophic gastritis by inhibiting JAK2/STAT3 pathway. Tianjin Journal of Traditional Chinese Medicine. 2024; 41: 914–921. (In Chinese)
[28] Yang T, Wang R, Zhang J, Bao C, Zhang J, Li R, et al. Mechanism of berberine in treating Helicobacter pylori induced chronic atrophic gastritis through IRF8-IFN-γ signaling axis suppressing. Life Sciences. 2020; 248: 117456. https://doi.org/10.1016/j.lfs.2020.117456
[29] Duan LY, Zhu MY, Yu Y, Han H, Ding Y. Effect of baicalin on the expression of JAK1 and STAT3 in mice with chronic atrophic gastritis. Journal of Guangzhou University of Traditional Chinese Medicine. 2024; 41: 200–206. https://doi.org/10.13359/j.cnki.gzxbtcm.2024.01.030
[30] Sipponen P, Marshall BJ. Gastritis and gastric cancer. Western countries. Gastroenterology Clinics of North America. 2000; 29: 579–579–92, v–vi. https://doi.org/10.1016/s0889-8553(05)70131-x
[31] Zheng SY, Zhu L, Wu LY, Liu HR, Ma XP, Li Q, et al. Helicobacter pylori-positive chronic atrophic gastritis and cellular senescence. Helicobacter. 2023; 28: e12944. https://doi.org/10.1111/hel.12944
[32] Khazaaleh S, Alomari M, Rashid MU, Castaneda D, Castro FJ. Gastric intestinal metaplasia and gastric cancer prevention: Watchful waiting. Cleveland Clinic Journal of Medicine. 2024; 91: 33–39. https://doi.org/10.3949/ccjm.91a.23015
[33] Liu J, Chen Y, Zhang J, Zheng Y, An Y, Xia C, et al. Vitexin alleviates MNNG-induced chronic atrophic gastritis via inhibiting NLRP3 inflammasome. Journal of Ethnopharmacology. 2025; 340: 119272. https://doi.org/10.1016/j.jep.2024.119272
[34] Xia Q, Hu J, Jiao Z, Wang G, Sun J, Pang X, et al. Exploring the mechanisms of Yang Wei Shu granule for the treatment of chronic atrophic gastritis using UPLC-QTOF-MS/MS, network pharmacology, and cell experimentation. Journal of Ethnopharmacology. 2025; 341: 119326. https://doi.org/10.1016/j.jep.2025.119326
[35] Zhang X, Huang Z, Hu X, Tang Y, Zhong X, Li L, et al. Wendan Decoction ameliorates MNNG-induced chronic atrophic gastritis via the JAK2/STAT3 signaling pathway. Journal of Ethnopharmacology. 2026; 355: 120724. https://doi.org/10.1016/j.jep.2025.120724
[36] Wang L, Lian YJ, Dong JS, Liu MK, Liu HL, Cao ZM, et al. Traditional Chinese medicine for chronic atrophic gastritis: Efficacy, mechanisms and targets. World Journal of Gastroenterology. 2025; 31: 102053. https://doi.org/10.3748/wjg.v31.i9.102053
[37] Rui Q, Li C, Rui Y, Zhang C, Xia C, Wang Q, et al. Human umbilical mesenchymal stem cells ameliorate atrophic gastritis in aging mice by participating in mitochondrial autophagy through Ndufs8 signaling. Stem Cell Research & Therapy. 2024; 15: 491. https://doi.org/10.1186/s13287-024-04094-4
[38] Liu M, Dong J, Wang L, Li Y, Wu Q, Zheng Q, et al. Ursolic and oleanolic acids suppress MNNG induced malignant transformation of human gastric mucosal epithelium by regulating the PI3 K/AKT pathway. Scientific Reports. 2025; 15: 21623. https://doi.org/10.1038/s41598-025-03606-3
[39] Zhou Y, Wang Q, Tang W, Ma Z, Yang Z, Li X, et al. Palmatine ameliorates N-methyl-N'-nitrosoguanidine-induced chronic atrophic gastritis through the STAT1/CXCL10 axis. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology. 2024; 38: e70037. https://doi.org/10.1096/fj.202401624R
[40] Liu S, Shu L, Yang J, Liu Y, Zhang S, Wang N, et al. Rhein Exhibits Anti-Inflammatory Effects in Chronic Atrophic Gastritis via Nrf2 and MAPK Signaling. The Turkish Journal of Gastroenterology: the Official Journal of Turkish Society of Gastroenterology. 2023; 34: 525–532. https://doi.org/10.5152/tjg.2023.22251
[41] Yang T, Wang R, Liu H, Wang L, Li J, Wu S, et al. Berberine regulates macrophage polarization through IL-4-STAT6 signaling pathway in Helicobacter pylori-induced chronic atrophic gastritis. Life Sciences. 2021; 266: 118903. https://doi.org/10.1016/j.lfs.2020.118903
[42] Tong Y, Liu L, Wang R, Yang T, Wen J, Wei S, et al. Berberine Attenuates Chronic Atrophic Gastritis Induced by MNNG and Its Potential Mechanism. Frontiers in Pharmacology. 2021; 12: 644638. https://doi.org/10.3389/fphar.2021.644638
[43] Chen L, Wang X, Li J, Zhang L, Wu W, Wei S, et al. Elucidation of the mechanism of berberine against gastric mucosa injury in a rat model with chronic atrophic gastritis based on a combined strategy of multi-omics and molecular biology. Frontiers in Pharmacology. 2024; 15: 1499753. https://doi.org/10.3389/fphar.2024.1499753
[44] Bao Z, Hu SN, Yang LZ, Yu WJ, Yang JY. Discussion on the regulatory effect of astragaloside IV as a health food on chronic atrophic gastritis based on network pharmacology. Food and Fermentation Industries. 2024; 50: 284–291. https://doi.org/10.13995/j.cnki.11-1802/ts.036270 (In Chinese)
[45] Tu W, Hong Y, Huang M, Chen M, Gan H. Effect of kaempferol on hedgehog signaling pathway in rats with --chronic atrophic gastritis - Based on network pharmacological screening and experimental verification. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2022; 145: 112451. https://doi.org/10.1016/j.biopha.2021.112451
[46] Li D, Yu YQ, Gao HB, Liu DQ. Protective effect of atractylenolide I on gastric mucosa in rats with chronic atrophic gastritis. Journal of Hebei Traditional Chinese Medicine and Pharmacology. 2016; 31: 5–8. https://doi.org/10.16370/j.cnki.13-1214/r.2016.03.002 (In Chinese)
[47] Song J, Zhang X, Li D, He S, Zhang H, Bai Y, et al. Nobiletin alleviates MNNG-induced gastric injury *in vivo* and the damage of GES-1 cells in vitro through ALOX5 and PTGS2. Journal of Agricultural and Food Chemistry. 2025; 73: 22362–22374. https://doi.org/10.1021/acs.jafc.5c03216
[48] Mao WL, Liang RZ, Ji ZL, Fang XY. Therapeutic effect of paeoniflorin on chronic atrophic gastritis in rats by regulating IL-6/STAT3 signaling pathway. Xiandai Mianyi Xue. 2025; 45: 179–184+210. (In Chinese)
[49] Ouyang JG, Zha AS, Wang JX, Zou XH, Zhang XP. Effect and mechanism of hesperidin on chronic atrophic gastritis in rats based on Keap1/Nrf2/ARE signaling pathway. Journal of Chinese Medicinal Materials. 2024; 47: 3132–3136. https://doi.org/10.13863/j.issn1001-4454.2024.12.034 (In Chinese)
[50] Wei Y, Wu W, Duan M, Li T, Liu M, Li J. Formononetin Alleviates MNNG-Triggered Chronic Atrophic Gastritis: Its Potential Mechanisms. Combinatorial Chemistry & High Throughput Screening. 2026; 29: 717–730. https://doi.org/10.2174/0113862073409559250618212035
[51] Sha ZG, Lin S, Fan ZL, Yang ZC, Gong YT, Qin T, et al. Efficacy and potential mechanisms of jatrorrhizine on MNNG-induced chronic atrophic gastritis in rats based on serological metabolomics and molecular docking. Scientific Reports. 2025; 15: 21018. https://doi.org/10.1038/s41598-025-05502-2
[52] Zhou Z, Hu C, Cui B, You L, An R, Liang K, et al. Ginsenoside Rg1 Suppresses Pyroptosis via the NF-κB/NLRP3/GSDMD Pathway to Alleviate Chronic Atrophic Gastritis *In Vitro* and *In Vivo*. Journal of Agricultural and Food Chemistry. 2024. https://doi.org/10.1021/acs.jafc.4c01271 (online ahead of print)
[53] Yang T, Lu M, Jiang W, Jin D, Sun M, Mao H, et al. Galangin alleviates gastric mucosal injury in rats with chronic atrophic gastritis by reducing ferroptosis. Histology and Histopathology. 2025; 40: 1631–1638. https://doi.org/10.14670/HH-18-878

[54] Wang R, Zhao Y, Zhou L, Lin F, Wan M, Gan A, et al. Costunolide ameliorates MNNG-induced chronic atrophic gastritis through inhibiting oxidative stress and DNA damage via activation of Nrf2. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology. 2024; 130: 155581. https://doi.org/10.1016/j.phymed.2024.155581
[55] Yang JY, Kim JB, Lee P, Kim SH. Evodiamine inhibits Helicobacter pylori growth and Helicobacter pylori-induced inflammation. International Journal of Molecular Sciences. 2021; 22: 3385. https://doi.org/10.3390/ijms22073385
[56] Dang Y, Zhang Y, Xu L, Zhou X, Gu Y, Yu J, et al. PUMA-mediated epithelial cell apoptosis promotes Helicobacter pylori infection-mediated gastritis. Cell Death & Disease. 2020; 11: 139. https://doi.org/10.1038/s41419-020-2339-x
[57] Tan CY, Tao JY, Lin CZ. Mechanism study of Anwei Decoction inducing MC cell cycle arrest. Lishizhen Medicine and Materia Medica Research. 2026; 37: 21–26. (In Chinese)
[58] Hu W, Liang K, Zhu H, Zhao C, Hu H, Yin S. Ferroptosis and Its Role in Chronic Diseases. Cells. 2022; 11: 2040. https://doi.org/10.3390/cells11132040
[59] Xu C, Liu Z, Xiao J. Ferroptosis: A Double-Edged Sword in Gastrointestinal Disease. International Journal of Molecular Sciences. 2021; 22: 12403. https://doi.org/10.3390/ijms222212403
[60] Zhao Y, Zhao J, Ma H, Han Y, Xu W, Wang J, et al. High Hepcidin Levels Promote Abnormal Iron Metabolism and Ferroptosis in Chronic Atrophic Gastritis. Biomedicines. 2023; 11: 2338. https://doi.org/10.3390/biomedicines11092338
[61] Liao Q, Guo Z, Ding C, Zuo R, Liu G. Integrating network analysis and experimental validation to reveal the ferroptosis-associated mechanism of velvet antler in the treatment of chronic atrophic gastritis. Journal of Food and Drug Analysis. 2025; 33: 119–131. https://doi.org/10.38212/2224-6614.3546
[62] Meng KQ, Qi F, Song J, Shen SW, Zhu JX, Yang JJ. Cellular and animal experimental study of Compound Jinguo Weikang Powder in improving chronic atrophic gastritis by inducing ferroptosis via regulating SLC7A11/GPX4 axis. Journal of Chinese Medicinal Materials. 2025; 48: 957–964. https://doi.org/10.13863/j.issn1001-4454.2025.04.027
[63] Dou J, Liu X, Yang L, Huang D, Tan X. Ferroptosis interaction with inflammatory microenvironments: Mechanism, biology, and treatment. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2022; 155: 113711. https://doi.org/10.1016/j.biopha.2022.113711
[64] Liu Y, Miao R, Xia J, Zhou Y, Yao J, Shao S. Infection of Helicobacter pylori contributes to the progression of gastric cancer through ferroptosis. Cell Death Discovery. 2024; 10: 485. https://doi.org/10.1038/s41420-024-02253-3
[65] Wang CY, Wang MH, Xie C. Targeting ferroptosis in *Helicobacter pylori*-associated gastric cancer development: From molecular mechanisms to application prospects (Review). International Journal of Oncology. 2026; 68: 4. https://doi.org/10.3892/ijo.2025.5817
[66] Zhao Z, Gong S, Wang S, Ma C. Effect and mechanism of evodiamine against ethanol-induced gastric ulcer in mice by suppressing Rho/NF-κB pathway. International Immunopharmacology. 2015; 28: 588–595. https://doi.org/10.1016/j.intimp.2015.07.030
[67] Tsukanov VV, Smirnova OV, Kasparov EV, Sinyakov AA, Vasyutin AV, Tonkikh JL, et al. Dynamics of Oxidative Stress in *Helicobacter pylori*-Positive Patients with Atrophic Body Gastritis and Various Stages of Gastric Cancer. Diagnostics (Basel, Switzerland). 2022; 12: 1203. https://doi.org/10.3390/diagnostics12051203
[68] Zeng X, Yang M, Ye T, Feng J, Xu X, Yang H, et al. Mitochondrial GRIM-19 loss in parietal cells promotes spasmolytic polypeptide-expressing metaplasia through NLR family pyrin domain-containing 3 (NLRP3)-mediated IL-33 activation via a reactive oxygen species (ROS) -NRF2- Heme oxygenase-1(HO-1)-NF-κB axis. Free Radical Biology & Medicine. 2023; 202: 46–61. https://doi.org/10.1016/j.freeradbiomed.2023.03.024
[69] Sun LH, Yu Y. Lycopene treats Helicobacter pylori-associated chronic atrophic gastritis by up-regulating the expression of Nrf2-Ho-1/Nqo1 proteins. Chinese Journal of Microecology. 2023; 35: 993–1000. https://doi.org/10.13381/j.cnki.cjm.202309001
[70] Chen P, Ding ZJ, Jin YZ. Effect of allicin on chronic atrophic gastritis in rats by regulating JAK2/STAT3 signaling pathway. Journal of Traditional Chinese Medicine. 2023; 38: 1053–1060. https://doi.org/10.16368/j.issn.1674-8999.2023.05.174
[71] Tang L, Tang B, Lei Y, Yang M, Wang S, Hu S, et al. *Helicobacter pylori*-Induced Heparanase Promotes *H. pylori* Colonization and Gastritis. Frontiers in Immunology. 2021; 12: 675747. https://doi.org/10.3389/fimmu.2021.675747
[72] Fujimori S. Progress in elucidating the relationship between *Helicobacter pylori* infection and intestinal diseases. World Journal of Gastroenterology. 2021; 27: 8040–8046. https://doi.org/10.3748/wjg.v27.i47.8040
[73] Li H, Hu Y, Huang Y, Ding S, Zhu L, Li X, et al. The mutual interactions among Helicobacter pylori, chronic gastritis, and the gut microbiota: a population-based study in Jinjiang, Fujian. Frontiers in Microbiology. 2024; 15: 1365043. https://doi.org/10.3389/fmicb.2024.1365043
[74] Hsieh H, Yang HB, Sheu BS, Yang YJ. Atrophic gastritis in Helicobacter pylori-infected children. Helicobacter. 2022; 27: e12885. https://doi.org/10.1111/hel.12885
[75] Souissi S, Makni C, Belhadj Ammar L, Bousnina O, Kallel L. Correlation between the intensity of Helicobacter pylori colonization and severity of gastritis: Results of a prospective study. Helicobacter. 2022; 27: e12910. https://doi.org/10.1111/hel.12910
[76] Yu M, Ma J, Song XX, Shao QQ, Yu XC, Khan MN, et al. Gastric mucosal precancerous lesions in *Helicobacter pylori*-infected pediatric patients in central China: A single-center, retrospective investigation. World Journal of Gastroenterology. 2022; 28: 3682–3694. https://doi.org/10.3748/wjg.v28.i28.3682
[77] Wu XT, Yao F, Wu R, Ling L, Liu C, Yang JJ, et al. Clinical observation on treating chronic atrophic gastritis with Helicobacter pylori resistance by spleen-strengthening, heat-clearing, and dampness-eliminating method. Jiangxi Journal of Traditional Chinese Medicine. 2025; 56: 32–34+38. https://doi.org/10.20141/j.0411-9584.2025.05.10 (In Chinese)
[78] Xia T, Ding XP, Zhu M, Wang W. Relationship between expression of Runx3 gene and protein in gastric mucosa of patients with chronic atrophic gastritis and Helicobacter pylori infection. Chongqing Medicine. 2019; 48: 625–629.
[79] Xu YM. Clinical study on eradication of Hp in patients with chronic atrophic gastritis. Chinese Journal of Modern Drug Application. 2018; 12: 131–133. https://doi.org/10.14164/j.cnki.cn11-5581/r.2018.11.073 (In Chinese)
[80] Xie F, Yao S. Jatrorrhizine attenuates inflammatory response in Helicobacter pylori-induced gastritis by suppressing NLRP3 inflammasomes and NF-κB signaling pathway. Archives of Microbiology. 2025; 207: 177. https://doi.org/10.1007/s00203-025-04374-4
[81] Xiang W, Long JS, Xie YT, Wang YL. Rutaecarpine ameliorates Helicobacter pylori-induced chronic atrophic gastritis by regulating macrophage polarization. Journal of Guangzhou University of Traditional Chinese Medicine. 2025; 42: 2556–2563. https://doi.org/10.13359/j.cnki.gzxbtcm.2025.10.028
[82] Wei N, Zhou M, Lei S, Zhong Z, Shi R. A meta-analysis and systematic review on subtypes of gastric intestinal metaplasia and neoplasia risk. Cancer Cell International. 2021; 21: 173.

https://doi.org/10.1186/s12935-021-01869-0
[83] Jang B, Lee SH, Dovirak I, Kim H, Srivastava S, Teh M, et al. CEACAM5 and TROP2 define metaplastic and dysplastic transitions in human antral gastric precancerous lesions and tumors. Gastric Cancer: Official Journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association. 2024; 27: 263–274. https://doi.org/10.1007/s10120-023-01458-2
[84] Song L, Song M, Rabkin CS, Chung Y, Williams S, Torres J, et al. Identification of anti-Helicobacter pylori antibody signatures in gastric intestinal metaplasia. Journal of Gastroenterology. 2023; 58: 112–124. https://doi.org/10.1007/s00535-022-01933-0
[85] Jin D, Huang K, Xu M, Hua H, Ye F, Yan J, et al. Deoxycholic acid induces gastric intestinal metaplasia by activating STAT3 signaling and disturbing gastric bile acids metabolism and microbiota. Gut Microbes. 2022; 14: 2120744. https://doi.org/10.1080/19490976.2022.2120744
[86] Xu X, Yan C, Bian L, Li Z, Yu Y, Zhu X, et al. Genomic Analyses Reveal the Evolving Characteristics of Intestinal Metaplasia and Gastric Cancer. Cancer Research. 2025; 85: 3123–3138. https://doi.org/10.1158/0008-5472.CAN-24-4065
[87] Zhang C, Cai T, Zeng X, Cai D, Chen Y, Huang X, et al. Astragaloside IV reverses MNNG-induced precancerous lesions of gastric carcinoma in rats: Regulation on glycolysis through miRNA-34a/LDHA pathway. Phytotherapy Research: PTR. 2018; 32: 1364–1372. https://doi.org/10.1002/ptr.6070
[88] Zhu F, Xu Y, Pan J, Li M, Chen F, Xie G. Epigallocatechin Gallate Protects against MNNG-Induced Precancerous Lesions of Gastric Carcinoma in Rats via PI3K/Akt/mTOR Pathway. Evidence-based Complementary and Alternative Medicine: ECAM. 2021; 2021: 8846813. https://doi.org/10.1155/2021/8846813
[89] Xu J, Zhang C, Wang L, Wang M, Liang J, Yang Y, et al. Effect and Mechanism of 6-Gingerol against Precancerous Lesions of Gastric Cancer Based on Network Pharmacology and *In Vitro* Experiment. Combinatorial Chemistry & High Throughput Screening. 2025; 28: 2452–2462. https://doi.org/10.2174/0113862073303380240722112207
[90] Huang X, Zhang M, Gu L, Zhou Z, Shi S, Fan X, et al. Naringenin inhibits the microsomal triglyceridetransfer protein/apolipoprotein B axis to inhibit intestinal metaplasia progression. Phytotherapy Research: PTR. 2024; 38: 4541–4554. https://doi.org/10.1002/ptr.8279
[91] Wang Y, Chu F, Lin J, Li Y, Johnson N, Zhang J, et al. Erianin, the main active ingredient of Dendrobium chrysotoxum Lindl, inhibits precancerous lesions of gastric cancer (PLGC) through suppression of the HRAS-PI3K-AKT signaling pathway as revealed by network pharmacology and in vitro experimental verification. Journal of Ethnopharmacology. 2021; 279: 114399. https://doi.org/10.1016/j.jep.2021.114399
[92] Wei W, Wang R, Zhu B, Liu Y, Meng X, Du K, et al. Integrating network pharmacology, pharmacokinetics and experimental validation to reveal the potential mechanism of Physochlaina physaloides (L.) G. Don in chronic atrophic gastritis. Journal of Ethnopharmacology. 2026; 354: 120487. https://doi.org/10.1016/j.jep.2025.120487
[93] Qiang R, Li Y, Dai X, Lv W. NLRP3 inflammasome in digestive diseases: from mechanism to therapy. Frontiers in Immunology. 2022; 13: 978190. https://doi.org/10.3389/fimmu.2022.978190
[94] Zhu X, Liu S, Zhou J, Wang H, Fu R, Wu X, et al. Effect of Astragalus polysaccharides on chronic atrophic gastritis induced by N-methyl-N'-nitro-N-nitrosoguanidine in rats. Drug Research. 2013; 63: 597–602. https://doi.org/10.1055/s-0033-1341518
[95] Tang L, He D, Su B. Nrf2: A critical participant in regulation of apoptosis, ferroptosis, and autophagy in gastric cancer. Acta Histochemica. 2024; 126: 152203. https://doi.org/10.1016/j.acthis.2024.152203
[96] Vona R, Pallotta L, Cappelletti M, Severi C, Matarrese P. The Impact of Oxidative Stress in Human Pathology: Focus on Gastrointestinal Disorders. Antioxidants (Basel, Switzerland). 2021; 10: 201. https://doi.org/10.3390/antiox10020201
[97] Ding L, Dang S, Sun M, Zhou D, Sun Y, Li E, et al. Quercetin induces ferroptosis in gastric cancer cells by targeting SLC1A5 and regulating the p-Camk2/p-DRP1 and NRF2/GPX4 Axes. Free Radical Biology & Medicine. 2024; 213: 150–163. https://doi.org/10.1016/j.freeradbiomed.2024.01.002
[98] Liu Y, Huang T, Wang L, Wang Y, Liu Y, Bai J, et al. Traditional Chinese Medicine in the treatment of chronic atrophic gastritis, precancerous lesions and gastric cancer. Journal of Ethnopharmacology. 2025; 337: 118812. https://doi.org/10.1016/j.jep.2024.118812
[99] Chen L, Wei S, He Y, Wang X, He T, Zhang A, et al. Treatment of Chronic Gastritis with Traditional Chinese Medicine: Pharmacological Activities and Mechanisms. Pharmaceuticals (Basel, Switzerland). 2023; 16: 1308. https://doi.org/10.3390/ph16091308
[100] Li Y, Ren N, Li SH, Han XZ, Shang HT. Research progress on the mechanism of action of traditional Chinese medicine compounds and monomers in treating chronic atrophic gastritis. Acta Chinese Medicine and Pharmacology. 2025; 53: 118–122. https://doi.org/10.19664/j.cnki.1002-2392.250021 (In Chinese)
[101] Zhao Y, Li B, Wang G, Ge S, Lan X, Xu G, et al. *Dendrobium officinale* Polysaccharides Inhibit 1-Methyl-2-Nitro-1-Nitrosoguanidine Induced Precancerous Lesions of Gastric Cancer in Rats through Regulating Wnt/β-Catenin Pathway and Altering Serum Endogenous Metabolites. Molecules (Basel, Switzerland). 2019; 24: 2660. https://doi.org/10.3390/molecules24142660
[102] Lu Y, Li Z, Zhang S, Zhang T, Liu Y, Zhang L. Cellular mitophagy: Mechanism, roles in diseases and small molecule pharmacological regulation. Theranostics. 2023; 13: 736–766. https://doi.org/10.7150/thno.79876
[103] Yang TX. Exploring the mechanism of Huazhuo Jiedu Prescription in treating gastric precancerous lesions based on sirt3 regulating mitophagy. Hebei University of Chinese Medicine. 2023. https://doi.org/10.27982/d.cnki.ghbyz.2023.000005 (In Chinese)
[104] Liu Y, Cai C, Qin X. Regulation of gut microbiota of Astragali Radix in treating for chronic atrophic gastritis rats based on metabolomics coupled with 16S rRNA gene sequencing. Chemico-biological Interactions. 2022; 365: 110063. https://doi.org/10.1016/j.cbi.2022.110063
[105] Liu Y, Lian X, Qin X. Bile acid metabolism involved into the therapeutic action of Xiaojianzhong Tang via gut microbiota to treat chronic atrophic gastritis in rats. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology. 2023; 109: 154557. https://doi.org/10.1016/j.phymed.2022.154557
[106] Marchelak A, Gieleta M, Krasocka W, Magiera A. Berberis aristata DC. (Indian barberry): Current insight into botanical, phytochemical, and pharmacological aspects, pharmacokinetics, safety of use and modern therapeutic applications. Fitoterapia. 2025; 183: 106539. https://doi.org/10.1016/j.fitote.2025.106539
[107] Hocking A, Tommasi S, Sordillo P, Klebe S. The Safety and Exploration of the Pharmacokinetics of Intrapleural Liposomal Curcumin. International Journal of Nanomedicine. 2020; 15: 943–952. https://doi.org/10.2147/IJN.S237536
[108] Yao C, Dai S, Wang C, Fu K, Wu R, Zhao X, et al. Luteolin as a potential hepatoprotective drug: Molecular mechanisms and treatment strategies. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2023; 167: 115464.

https://doi.org/10.1016/j.biopha.2023.115464
[109] Yu B, Sun Z, Li X, Qv A, Sohail M, Li Y, et al. Research Progress of Novel Drug Delivery Systems of Chinese Medicine Monomers based on Natural Silk Fibroin: A Mini-Review. Current Drug Delivery. 2023; 20: 211–222. https://doi.org/10.2174/1567201819666220413111439
[110] Song B, Shuang L, Zhang S, Tong C, Chen Q, Li Y, et al. Research progress of nano drug delivery systems in the anti-tumor treatment of traditional Chinese medicine monomers. PeerJ. 2025; 13: e19332. https://doi.org/10.7717/peerj.19332
[111] Pang C, Zhang J, Gu Y, Zhang Q, Zhao Y. The biological roles of exosome-encapsulated traditional Chinese medicine monomers in neuronal disorders. Journal of Pharmaceutical Analysis. 2025; 15: 101131. https://doi.org/10.1016/j.jpha.2024.101131
[112] Thilakarathna SH, Rupasinghe HPV. Flavonoid bioavailability and attempts for bioavailability enhancement. Nutrients. 2013; 5: 3367–3387. https://doi.org/10.3390/nu5093367
[113] Jiangbo Z, Xuying W, Yuping Z, Xili M, Yiwen Z, Tianbao Z. Effect of astragaloside IV on the embryo-fetal development of Sprague-Dawley rats and New Zealand White rabbits. Journal of Applied Toxicology: JAT. 2009; 29: 381–385. https://doi.org/10.1002/jat.1422
[114] Gurley BJ. Clinically Relevant Herb-Drug Interactions: A 30-Year Historical Assessment. Journal of Dietary Supplements. 2025; 22: 78–104. https://doi.org/10.1080/19390211.2024.2327544
[115] Mohos V, Fliszár-Nyúl E, Ungvári O, Kuffa K, Needs PW, Kroon PA, et al. Inhibitory effects of quercetin and its main methyl, sulfate, and glucuronic acid conjugates on cytochrome P450 enzymes, and on OATP, BCRP and MRP2 transporters. Nutrients. 2020; 12: 2306. https://doi.org/10.3390/nu12082306
[116] Husain I, Idrisi M, Kotwal P, Khan IA, Khan SI. Ginger as a Modulator of Drug Metabolizing Enzymes and Transporters: Potential Implications for Herb-Drug Interactions. Journal of Dietary Supplements. 2026; 23: 240–256. https://doi.org/10.1080/19390211.2025.2606752
[117] Li W, Zhang T. Precancerous pathways to gastric cancer: a review of experimental animal models recapitulating the correa cascade. Frontiers in Cell and Developmental Biology. 2025; 13: 1620756. https://doi.org/10.3389/fcell.2025.1620756
[118] Tsukamoto T, Mizoshita T, Tatematsu M. Animal models of stomach carcinogenesis. Toxicologic Pathology. 2007; 35: 636–648. https://doi.org/10.1080/01926230701420632
[119] Kimura M, Fukuda T, Sato K. Effect of aging on the development of gastric cancer in rats induced by N-methyl-N'-nitro-N-nitrosoguanidine. Gan. 1979; 70: 521–525.
[120] Sharashidze LK, Beniashvili DS, Sherenesheva NI, Turkia NG. Induction of gastric cancer in monkeys by N-methyl-N-nitro-N-nitrosoguanidine (MNNG). Neoplasma. 1989; 36: 129–133.
[121] Werawatganon D. Simple animal model of Helicobacter pylori infection. World Journal of Gastroenterology. 2014; 20: 6420–6424. https://doi.org/10.3748/wjg.v20.i21.6420
[122] Zou TH, Gao QY, Liu SD, Li YQ, Meng XJ, Zhang GX, et al. Effectiveness and safety of Moluodan in the treatment of precancerous lesions of gastric cancer: A randomized clinical trial. Journal of Digestive Diseases. 2024; 25: 27–35. https://doi.org/10.1111/1751-2980.13251
[123] Jiang Q, Fan G, Wu K. Potential Action Mechanism of Erianin in Relieving MNNG-triggered Chronic Atrophic Gastritis. Cell Biochemistry and Biophysics. 2025; 83: 1035–1044. https://doi.org/10.1007/s12013-024-01536-x
[124] Yang L, Wang CQ. Clinical observation of berberine in treating chronic atrophic gastritis and its effect on expression of IL-6 and IL-17. Chinese Archives of Traditional Chinese Medicine. 2015; 33: 467–469. https://doi.org/10.13193/j.issn.1673-7717.2015.02.069 (In Chinese)
[125] Huang R, Su LL, Ji D, Yin FZ, Lu TL, Shao Y, et al. Panorama of organoid technology application in traditional Chinese medicine: opportunities and challenges from basic mechanisms to clinical practice. Journal of Nanjing University of Traditional Chinese Medicine. 2025; 41: 856–868. https://doi.org/10.14148/j.issn.1672-0482.2025.0856 (In Chinese)
[126] Huo C, Zhang X, Gu Y, Wang D, Zhang S, Liu T, et al. Organoids: Construction and Application in Gastric Cancer. Biomolecules. 2023; 13: 875. https://doi.org/10.3390/biom13050875
[127] Kan L, Yu Y, Wang Y, Shi L, Fan T, Chen H, et al. The application of organoids in investigating immune evasion in the microenvironment of gastric cancer and screening novel drug candidates. Molecular Cancer. 2025; 24: 125. https://doi.org/10.1186/s12943-025-02328-4
[128] Yin Y, Zeng S, Zhang H, Wang S, Ke F, Rui Q, et al. Patient-derived gastric cancer organoids model heterogeneity and stroma-mediated chemoresistance in poorly cohesive carcinoma. Frontiers in Molecular Biosciences. 2025; 12: 1631168. https://doi.org/10.3389/fmolb.2025.1631168
[129] Zu M, Hao X, Ning J, Zhou X, Gong Y, Lang Y, et al. Patient-derived organoid culture of gastric cancer for disease modeling and drug sensitivity testing. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2023; 163: 114751. https://doi.org/10.1016/j.biopha.2023.114751
[130] Xiao LH, Zhao WJ, Zhu GS, Yan YJ, Zhang XZ, Cao L, et al. Study on the functional material basis of Jinhong Tablets based on GES-1 cell model and mouse gastric organoid model. Journal of Nanjing University of Traditional Chinese Medicine. 2025; 41: 869–880. https://doi.org/10.14148/j.issn.1672-0482.2025.0869 (In Chinese)
[131] Seidlitz T, Koo BK, Stange DE. Gastric organoids-an in vitro model system for the study of gastric development and road to personalized medicine. Cell Death and Differentiation. 2021; 28: 68–83. https://doi.org/10.1038/s41418-020-00662-2
[132] Yu YY, Zhu YJ, Xiao ZZ, Chen YD, Chang XS, Liu YH, et al. The pivotal application of patient-derived organoid biobanks for personalized treatment of gastrointestinal cancers. Biomarker Research. 2022; 10: 73. https://doi.org/10.1186/s40364-022-00421-0
[133] Seidlitz T, Stange DE. Gastrointestinal cancer organoids-applications in basic and translational cancer research. Experimental & Molecular Medicine. 2021; 53: 1459–1470. https://doi.org/10.1038/s12276-021-00654-3