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Review paper

Natural products based on Correa's cascade for the treatment of gastric cancer trilogy: Current status and future perspective

Wenhao Liao [a, *, 1], Jing Wang [b, 1], Yuchen Li [c, **]

[a] Department of Nephrology, the Key Laboratory for the Prevention and Treatment of Chronic Kidney Disease of Chongqing, Chongqing Clinical Research Center of Kidney and Urology Diseases, Xinqiao Hospital, Army Medical University (Third Military Medical University), Chongqing, 400037, China
[b] Department of Obstetrics and Gynecology, Chongqing Bishan Hospital of Traditional Chinese Medicine, Chongqing, 402760, China
[c] Department of Laboratory Medicine, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, 610072, China

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ABSTRACT

Gastric carcinoma (GC) is a malignancy with multifactorial involvement, multicellular regulation, and multistage evolution. The classic Correa's cascade of intestinal GC specifies a trilogy of malignant transformation of the gastric mucosa, in which normal gastric mucosa gradually progresses from inactive or chronic active gastritis (Phase I) to gastric precancerous lesions (Phase II) and finally to GC (Phase III). Correa's cascade highlights the evolutionary pattern of GC and the importance of early intervention to prevent malignant transformation of the gastric mucosa. Intervening in early gastric mucosal lesions, i.e., Phase I and II, will be the key strategy to prevent and treat GC. Natural products (NPs) have been an important source for drug development due to abundant sources, tremendous safety, and multiple pharmacodynamic mechanisms. This review is the first to investigate and summarize the multi-step effects and regulatory mechanisms of NPs on the Correa's cascade in gastric carcinogenesis. In phase I, NPs modulate *Helicobacter pylori* urease activity, motility, adhesion, virulence factors, and drug resistance, thereby inhibiting *H. pylori*-induced gastric mucosal inflammation and oxidative stress, and facilitating ulcer healing. In Phase II, NPs modulate multiple pathways and mediators regulating gastric mucosal cell cycle, apoptosis, autophagy, and angiogenesis to reverse gastric precancerous lesions. In Phase III, NPs suppress cell proliferation, migration, invasion, angiogenesis, and cancer stem cells, induce apoptosis and autophagy, and enhance chemotherapeutic drug sensitivity for the treatment of GC. In contrast to existing work, we hope to uncover NPs with sequential therapeutic effects on multiple phases of GC development, providing new ideas for gastric cancer prevention, treatment, and drug development.

1. Introduction

The incidence and mortality of gastric carcinoma (GC) have declined in recent decades due to improved prevention and treatment, but the disease burden remains heavy [1]. Globally, GC remains the fifth most common cancer and the third leading cause of cancer death. In 2020, there was approximately 1.1 million new cases and approximately 770,000 new deaths from GC worldwide [2]. East Asia has the highest disease burden of GC, with the highest incidence and mortality rates in the world, accounting for more than 50% of both new cases and deaths worldwide [2]. Delays in detection, diagnosis and treatment contribute to the high mortality rate of GC, hence secondary prevention (early detection, diagnosis, and treatment of GC) is essential to reduce mortality and improve patients' quality of life [3]. Unfortunately, GC is insidious and early symptoms are mostly atypical, resulting in most patients being diagnosed with local infiltration and distant metastasis, which increases the difficulty and risk of treatment [2]. With the intensification of population aging, the prevention and control of GC will be more challenging in the future.

According to Lauren's criteria, adenocarcinoma is the main type of GC and classified into two main histologic types: intestinal and diffuse. The intestinal-type GC is characterized by a differentiating glandular structure and a complex multifactorial, multistep process [4]. *Helicobacter pylori* is the most clearly identified risk factor and has been classified as a class I carcinogen for GC [5]. Most cases of GC are thought to originate from *H. pylori* infection and the

* Corresponding author.
** Corresponding author.
E-mail addresses: liaowenhao@stu.cdutcm.edu.cn (W. Liao), lyc592@stu.cdutcm.edu.cn (Y. Li).
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[1] Both authors contributed equally to this work.

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H. pylori-driven Correa's cascade (normal gastric mucosa → superficial gastritis/non-atrophic gastritis → atrophic gastritis (AG) → intestinal metaplasia (IM) → dysplasia (DYS) → GC) [5].

Currently, systemic chemotherapy, radiotherapy, surgery, immunotherapy, and targeted therapy have all made great breakthroughs in the treatment of GC, but they have not yet fundamentally overcome GC, and the 5-year survival rate of GC worldwide is less than 35% [6]. No matter which treatment option is chosen, toxic side effects and the subsequent recurrence and metastasis are unavoidable problems. Current treatment direction and drug development are mainly focused on the GC stage, while Phase I and II of early intervention in Correa's cascade are ignored, thus missing the optimal treatment opportunity. Moreover, the development of GC is a multifactorial and multimechanistic process, and its pathogenesis and the interactions between different mechanisms have not been thoroughly investigated [5]. The molecular mechanisms of most existing drugs typically target one phase, one target protein, one signaling cascade or one disease mechanism, i.e., “one drug, one target”, which is not fully applicable to complex diseases involving multiple targets and developmental phases. Consequently, based on the current dilemma of GC prevention and treatment, there is an urgent need to find a new effective multi-target, multi-stage treatment for GC, i.e., “one drug, multiple targets".

Natural products (NPs) have traditionally been a source of medicines for the treatment of several major diseases, with the earliest written records dating back to 2600 BC. NPs, such as nicotine, codeine, atropine, and artemisinin, have gradually been discovered and play a crucial role in the treatment of some major diseases [7]. NPs, such as paclitaxel and its derivatives from yew (*Taxus*) species, and vincristine and vinblastine from periwinkle (*Catharanthus roseus* (L.) G. Don) also play an important role in anticancer therapy [7]. NPs have attracted increasing attention in GC therapy because of their highly safe, highly effective, multi-targeting, and multi-pathway regulatory properties, but relatively few researches has addressed GC prevention (pre-cancer or even early blockade). This review is the first stepwise study and summary of the multi-step effects of NPs on the Correa's cascade, with the intention of discovering more NPs to be used in the multi-step prevention and treatment of GC.

2. Correa's cascade: a trilogy of malignant transformation of the GC

In 1992, Professor Correa [8] proposed *H. pylori* as an initiator of cascade lesions in GC, especially in the intestinal-type gastric adenocarcinoma. Under chronic inflammatory stimulation, normal gastric mucosa undergoes three phases of development into GC (Fig. 1). Phase I: chronic active gastritis (CAG), which mainly manifests as chronic inflammation of the gastric mucosa with milder lesions limited to the superficial layer of the mucosa. Phase II: the

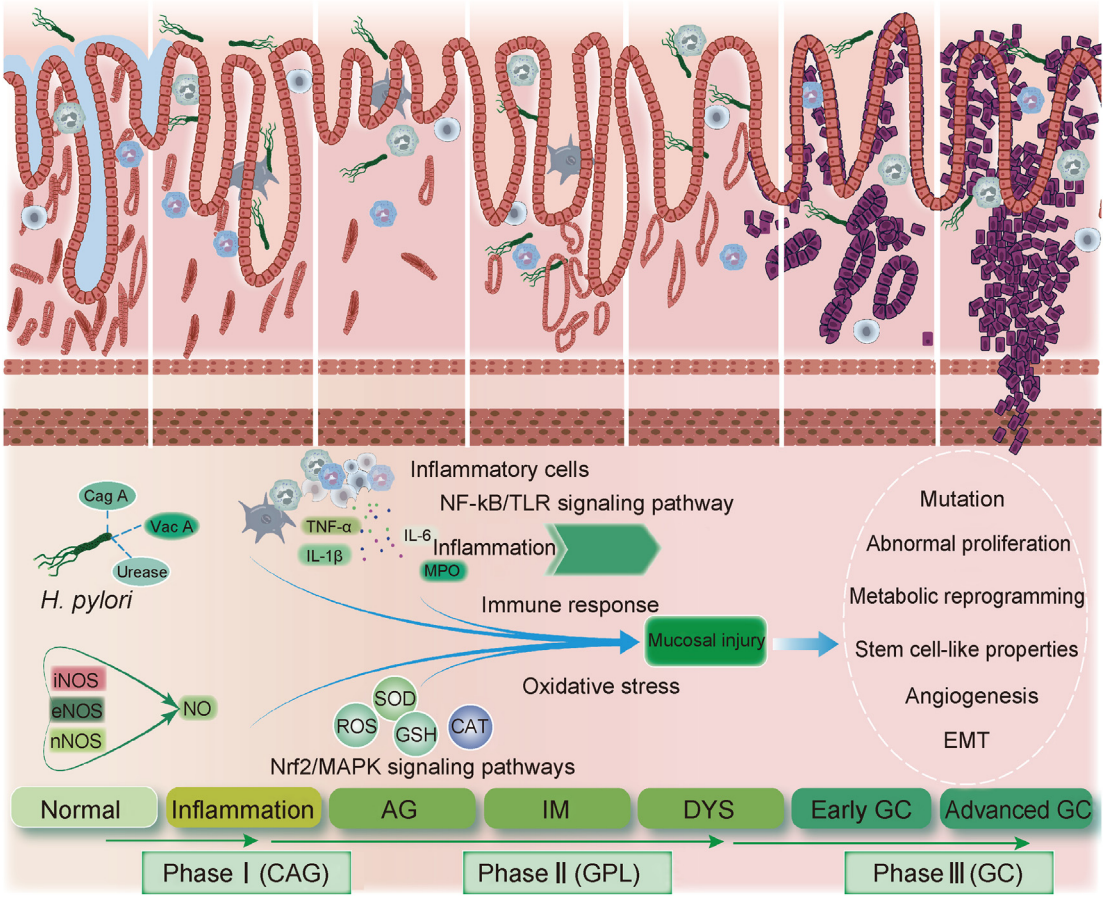

Fig. 1. The evolution of Correa's cascade in gastric carcinoma (GC). Inflammatory changes in the gastric mucosa are often the first step in carcinogenesis, which progresses to glandular destruction and atrophy, replaced by intestinal epithelial hyperplasia, and finally to GC, i.e. Correa's cascade, usually associated with *H. pylori* infection. AG: atrophic gastritis; Cag A: cytotoxin-associated gene A; CAG: chronic active gastritis; CAT: catalase; DYS: dysplasia; EMT: epithelial mesenchymal transition; GPL: gastric precancerous lesions; GSH: glutathione; *H. pylori: Helicobacter pylori*; IL: interleukin; IM: Intestinal metaplasia; MPO: myeloperoxidase; NO: nitric oxide; NOS: nitric oxide synthase; eNOS: endothelial NOS; NF-κB: nuclear factor kappa-B; nNOS: neural NOS; iNOS: inducible NOS; ROS: reactive oxygen species; SOD: superoxide dismutase; TLR: Toll-like receptor; TNF-α: tumor necrosis factor; Vac A: vacuolating cytotoxin A.

gastric precancerous lesions (GPL), which is a "critical turning point" in the transformation of gastritis to GC, referring to the development of IM and DYS of the gastric mucosa with the potential for malignant transformation, and often accompanied by chronic AG. GPL is generally considered to be an intermediate phase in the transition from benign to malignant lesions, and the risk of carcinogenesis increases with the severity of the lesion. Approximately 1.2% of patients with gastritis, 2% of patients with AG, 2.6% of patients with IM and 5.3% of patients with DYS will develop GC within twenty years [9]. Early intervention can effectively reverse the malignant transformation of the gastric mucosa and block the progression to GC. Phase III: GC, which is a serious threat to human health worldwide and lacks specific treatment options [8]. It can take months to years from *H. pylori* infection to precancerous and cancerous lesions [10]. Eradication of *H. pylori* reduces the risk of GC, especially in infected individuals without precancerous lesions at baseline [10].

The different phases of the Correa's cascade show distinct pathological features. In the gastritis phase, mononuclear cells and polymorphonuclear neutrophils accumulate in the lamina propria of the gastric mucosa [5]. In the AG phase, atrophy of the intrinsic glands of the gastric mucosa and fibrosis of the lamina propria can be observed. In severe cases, the epithelial cells of the gastric mucosa are gradually replaced by goblet and intestinal epithelial cells, accompanied by a gradual disappearance of microvilli, mucus secretion and changes in the "brush border", which evolve into IM. DYS is the phase of the Correa's cascade closest to GC and exhibits characteristic changes, such as abnormal cell differentiation, increased proportion of nuclei, and mucin gland dysfunction when tumor cells are still basal [5]. Gastric mucin is an important component of the mucin-bicarbonate barrier. With the progression of the Correa's cascade, the expression of gastric mucin gradually decreases, while non-gastric mucin gradually increases, resulting in the vulnerability of the gastric mucosa to various irritants [11].

3. Multi-step actions and mechanisms of NPs on the Correa's cascade

An increasing number of studies have shown that NPs have unique advantages due to their multi-components, multi-targets, and synergistic properties. NPs prevent and treat GC and block the Correa's cascade by regulating specific mechanisms or pathways. This review systematically describes the multi-step actions of NPs on the Correa's cascade and its regulatory mechanisms in GC in a phased manner, expecting to provide new ideas for the prevention and treatment of GC and new drug development.

This review followed the PRISMA guidelines [12] and searched databases including PubMed, EMBASE, Web of Science, Ovid, ScienceDirect, and Google Scholar from the original publication date to May 2023 to review the multi-step, multi-stage action of NPs that block the Correa's cascade to prevent and treat GC. 1,312 records were retrieved from the initial database search. After eliminating duplicate literature, 356 unique studies were evaluated based on title and abstract, of which 185 were excluded, resulting in 89 full-text evaluations (Fig. 2). NPs, such as atractylenolide, astragaloside, apigenin, berberine, curcumin, epigallocatechin-(−) gallate (EGCG), gallic acid (GA), kaempferol, palmatine, polysaccharides, and resveratrol, combined a multi-stage modulatory effect on Correa's cascade (Fig. 3). According to the process of GC development, we divided it into three stages to describe the inhibitory effects of NPs on the GC trilogy, namely inflammation, GPL, and GC.

3.1. Phase I: Inhibiting the inflammation of gastric mucosa

Inflammation runs through the Correa's cascade, and effective control of inflammation with NPs at an early stage can undoubtedly block the Correa's cascade at its source and reduce the risk of GC (Fig. 4 and Table 1) [13–49].

3.1.1. Anti-H. pylori

Inflammatory changes in the gastric mucosa are often the first step in carcinogenesis, which further progresses to glandular destruction, atrophy, IM and DYS, and finally develops into GC, which is usually associated with *H. pylori* infection [10]. *H. pylori* eradication regimen is effective in preventing the progression of pathologic changes in the gastric mucosa [50]. The best time to treat *H. pylori* infection, whether symptomatic or not, is before the patient progresses to AG and IM. This is because once AG and IM have progressed, even eradication treatment of *H. pylori* infection cannot completely reverse the pathological changes and eliminate the risk of GC [50].

H. pylori enters the gastric and causes infection through four main steps, namely survival in an acidic environment, movement towards the gastric epithelium, attachment to the gastric epithelium and tissue damage [51]. *H. pylori* can secrete large amounts of urease, which converts urea into bicarbonate and ammonia to neutralize gastric acid to raise the pH around the bacteria, thereby enhancing their ability to survive, colonize, and infect the stomach for long periods of time in the highly acidic environment, yet the host is unable to eliminate the infection [52]. In addition to its acid-neutralizing ability, urease induces angiogenesis, which is essential for GC growth and metastasis [52]. The helical shape and flagella of *H. pylori* help the bacteria to penetrate the mucus layer and move towards the gastric epithelium. *H. pylori* mediates tight bacterial adhesion to gastric epithelial cells and leads to persistent infection and host dysfunction through adhesins, including blood-antigen binding protein A/B (BabA/B), sialic acid-binding adhesin (SabA), adherence-associated proteins (AlpA/B), *H. pylori* outer membrane protein (HopZ), and lacdiNAc-binding adhesin (LabA) [51]. The virulence factors secreted by *H. pylori*, such as vacuolating cytotoxin A (VacA) and cytotoxin-associated gene A (CagA), can transfer bacterial products into gastric mucosal cells and activate many cellular signaling pathways, leading to apoptosis and tissue damage. Furthermore, Cag A acts as an oncogenic scaffolding protein, thereby allowing bacteria to adapt to the host environment and promote chronic inflammation, precancerous lesions and carcinogenesis in the gastric mucosa [53].

Eradication of *H. pylori* not only minimizes the risk of serious complications from infection, but also reduces the incidence of GC by blocking the Correa's cascade [54]. In clinical practice, very few antibiotics (e.g., amoxicillin, clarithromycin, metronidazole, tetracycline, and levofloxacin) are effective in eradicating *H. pylori* and are often used in combination with proton pump inhibitors and bismuth, i.e., triple or quadruple therapy, which attempts to kill all *H. pylori* in the gastric [55]. However, in recent years with the problems of antibiotic resistance, safety and recurrence, it makes eradication of *H. pylori* more and more challenging [55]. Recent studies have shown that NPs have significant inhibitory effects on *H. pylori* and may be a potential development pathway for the prevention and management of *H. pylori* infection and for blocking malignant transformation of the gastric mucosa [56].

3.1.1.1. Anti-urease activity. Urease is an important colonization and virulence factor of *H. pylori*, and its most critical catalytic feature is the presence of sulfhydryl groups and nickel $(Ni)^{2+}$ in the active site of the enzyme, which is essential for enzyme activity and converts urea to ammonia to neutralize gastric acid for bacterial survival conditions [57]. Mature and activated urease consists of urea A and urea B subunits and contains auxiliary subunits such as ureE, ureI, and ureH [58]. NixA is a high-affinity nickel transporter protein that

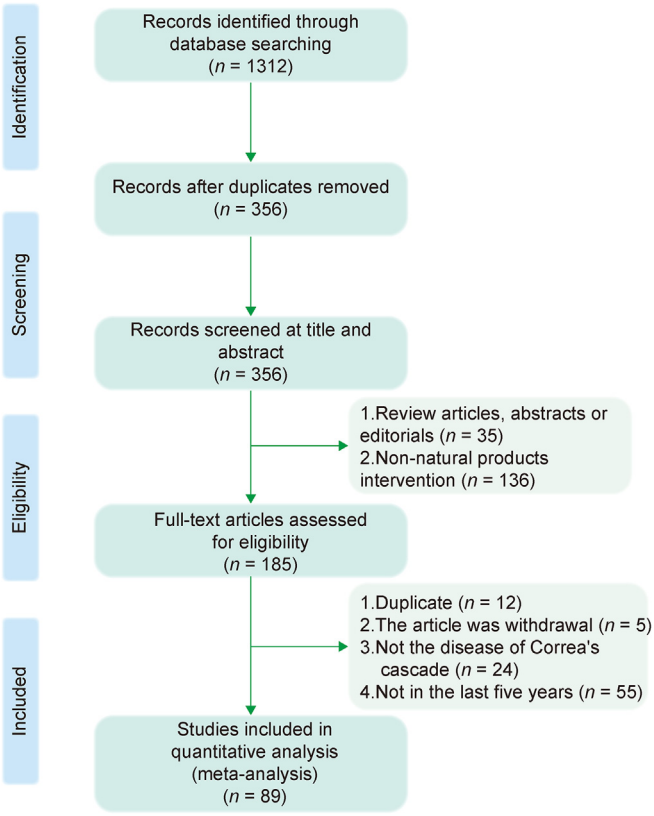

Fig. 2. Flow chart of the study selection.

penetrates the cytoplasmic membrane to insert Ni^{2+} into the active site of urease metalloenzymes and promote urease activity [57]. Conventional urease inhibitors suppress urease activity accompanied by high toxicity and instability, for which NPs offer a solution.

Rhizoma Coptidis (the rhizome of *Coptis chinensis* Franch.) is a natural medicinal plant commonly used in the treatment of *H. pylori* related gastrointestinal disorders. The main active components of the plant, such as berberine, coptisine, palmatine, epiberberine, and jatrorrhizine, possess a common core structure and are natural inhibitors of *H. pylori* and its urease [13]. Berberine, the most abundant alkaloid in Rhizoma Coptidis, exerts its pharmacological effects through a multi-step action on the Correa's cascade, showing great potential for clinical application in the prevention and treatment of GC [54]. Clinical trials have shown that berberine-containing quadruple therapy (adding berberine to standard triple therapy) is more effective in eradicating *H. pylori*, promoting ulcer healing and improving clinical symptoms [14,15]. The triple therapy of berberine, amoxicillin, and rabeprazole is not worse than the quadruple therapy containing bismuth and has a higher safety profile [16]. Berberine showed significant anti-*H. pylori* activity in an *in vitro* assay with a minimum inhibitory concentration (MIC) of 25 μg/mL [17]. Moreover, berberine was also a highly effective inhibitor of urease, which inhibited the production of gastric acid, thereby destroying the weak acidic local environment required for bacteria to survive and reproduce [13]. In addition, palmatine also possesses better anti-*H. pylori* activity and acid-neutralizing ability than berberine, showing excellent bactericidal activity both *in vitro* and *in vivo* [19,20]. Palmatine inactivated urease by interacting with the active site sulfhydryl group and inhibiting the active enzyme conformation through N–H·π interactions, which is potentially useful in the treatment of gastritis and peptic ulcer caused by *H. pylori* infection [21].

Kaempferol, a flavonoid naturally occurring in various plants such as *Polygonum tinctorium* Lour., *Spathodea campanulata* P. Beauv. and *Rubus ulmifolius*, has gradually been found to exert excellent anti-*H. pylori* activity [22]. ATP-binding cassette transporters are important for membrane genesis and functional maintenance. Kaempferol inhibited *H. pylori* by modulating ATP-binding cassette transporters to disrupt cell membranes [23]. In addition, the efficacy of kaempferol was closely related to its inhibition of genes involved in flagellar assembly and fatty acid metabolism. Structure-activity relationship analysis showed that each hydroxyl group of kaempferol contributed to its anti-*H. pylori* activity, which makes kaempferol's antibacterial ability not inferior to that of clindamycin or amoxicillin [23]. In the *H. pylori* genome, the hp1043 gene (also known as HsrA), acts as a transcriptional activator, interacts with DNA and binds to specific sequences located in the promoter and is involved in *H. pylori* pathogenesis [59]. In a study, apigenin and kaempferol were selected from more than 1,000 drugs for their excellent bactericidal activity and their ability to inhibit DNA binding activity of HsrA *in vitro*. They specifically bound to the C-terminal effector domain of HsrA, inhibiting the DNA-binding activity of HsrA and blocking the amino acid residues that form the helix-turn-helix DNA-binding motif of HsrA, thereby killing *H. pylori* [24]. This suggests that HsrA could be a novel and effective therapeutic target for *H. pylori*.

3.1.1.2. Anti-adhesive/motility activity. The motility and adhesion of *H. pylori* are important factors in its colonization and subsequent pathogenesis. Through the free movement of flagella (composed of flaA and flaB proteins), *H. pylori* can penetrate the gastric mucosa to reach the epithelial surface and adhere tightly to the epithelial cells through adhesion factors, and then secrete virulence factors to damage the adherent cells, thus driving the Correa's cascade and gastric mucosal malignancy [51]. Therefore, inhibition of its motility and adhesion can eradicate *H. pylori* and interfere with its infectious process. Kaempferol inhibited *H. pylori* by inhibiting flagellar assembly-associated proteins (flgH, flaA, and flaB) [23]. Besides, green tea has a long history of human consumption and may be a potential drug to reduce *H. pylori*-induced gastric epithelial damage and malignant progression. EGCG is the main component of green tea and has been found to have excellent anti-*H. pylori* efficacy [60]. EGCG can effectively inhibit the growth of *H. pylori* by binding to its histone-like DNA-binding proteins [25]. Moreover, EGCG inhibited urease activity and motility to deter *H. pylori* colonization [26,27]. In addition, EGCG blocks Toll-like receptor 4 (TLR-4) activation leading to extracellular signal-responsive kinase (ERK)1/2 and nuclear factor kappa-B (NF-κB) inactivation, alleviating *H. pylori*-induced apoptosis and DNA damage [28].

3.1.1.3. Inhibiting virulence factors. Virulence factors secreted by *H. pylori*, such as CagA and VacA, are essential for bacterial pathogenesis [53]. Curcumin, a natural compound from *Curcuma longa* L., has shown anti-*H. pylori* efficacy *in vitro* and *in vivo*, without toxicity or drug resistance [61]. *H. pylori* lacks the reductase (nicotinamide adenine dinucleotide phosphate hydrogen (NADPH)-dependent curcumin/dihydrocurcumin reductase) to effectively detoxify curcumin through metabolism, while other probiotics such as *Escherichia coli* escape the inhibitory effect of curcumin [29]. The oxidative metabolites of curcumin are key to its efficacy in inhibiting *H. pylori* [29,30]. Curcumin inhibited the vacuolating activity of *H. pylori* by binding to the p55 domain of VacA protein to reduce its virulence [30]. Curcumin attenuated the expression of *H. pylori* virulence genes CagE and CagF in a dose-dependent manner and inhibited the translocation and phosphorylation of CagA in gastric epithelial cells to reduce the virulence of *H. pylori*.

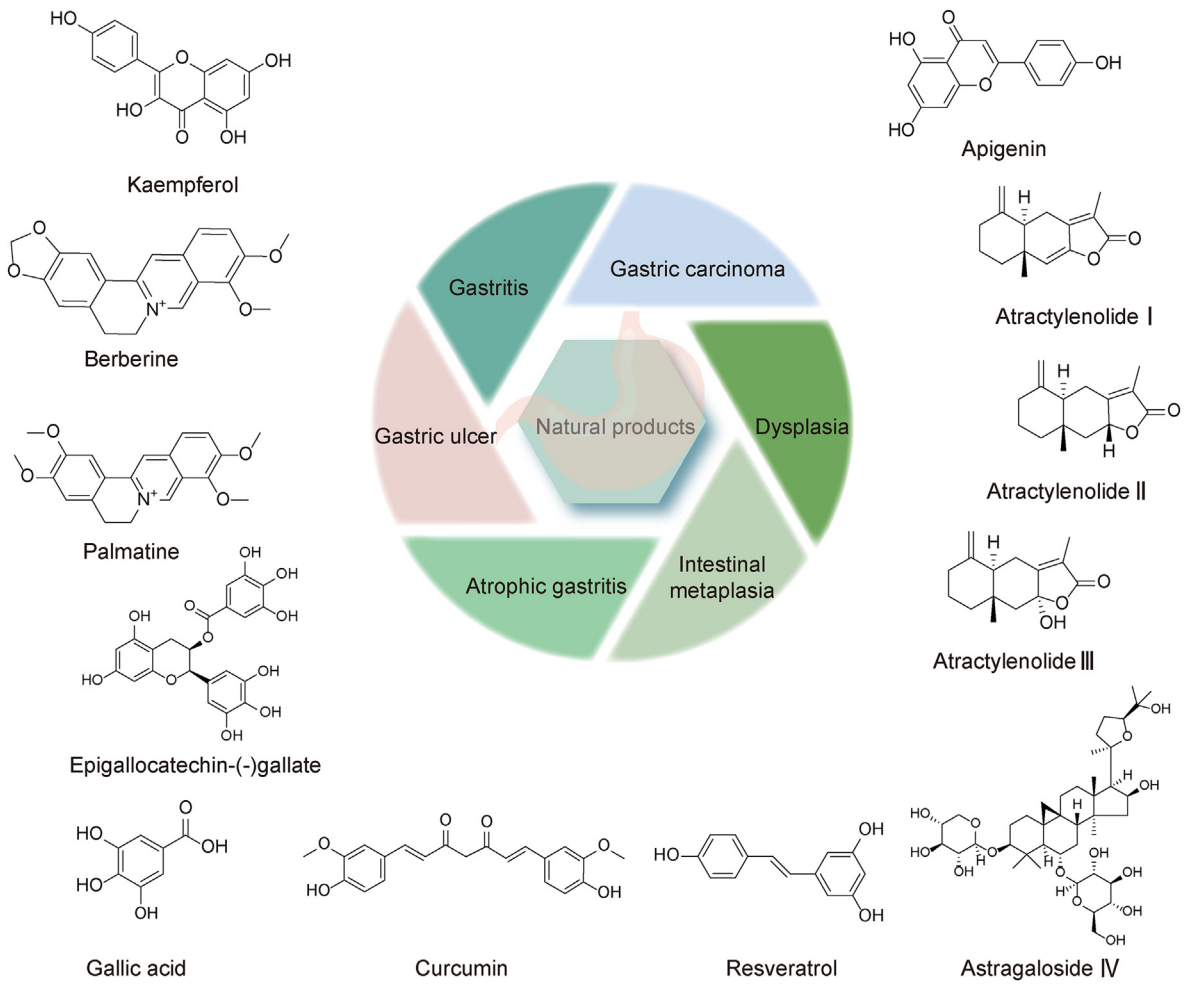

Fig. 3. Structural formulae and plant origin of natural products (NPs) targeting the Correa's cascade.

Furthermore, the inhibition of *H. pylori* virulence by curcumin was permanent, which undoubtedly shows that curcumin provides a long-term and excellent effect on *H. pylori*-induced gastric inflammation and carcinogenesis [29].

3.1.1.4. Suppressing inflammation and oxidative damage. The long-term colonizing presence of *H. pylori* in gastric induces a series of events, such as inflammatory responses and oxidative stress, that disrupt gastric epithelial cell plasticity and homeostasis [62]. Thus, NPs with antioxidant or anti-inflammatory effects can prevent *H. pylori*-associated gastritis and block the development process of the Correa's cascade.

Resveratrol, a polyphenol found in grapes, shows excellent anti-*H. pylori* ability. Resveratrol significantly alleviated *H. pylori*-induced gastric damage by regulating the translation, outer membrane proteins, transports, and ATP synthase of *H. pylori* and inhibiting the consequent inflammation and oxidative damage [31]. *H. pylori* induces reactive oxygen species (ROS) production and activates oxidant-mediated transcription factors, such as NF-κB, which in turn induces the expression of pro-inflammatory mediators interleukin (IL)-8 and inducible nitric oxide synthase (iNOS), and resveratrol inhibited these processes to reduce gastric inflammation [32]. Moreover, resveratrol activated the antioxidant key signaling pathway nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1), thereby alleviating *H. pylori*-induced oxidative stress and inflammation in the mucosa [32]. Apigenin, widely distributed in fruits and vegetables, such as *Apium graveolens* L., is a well-known low cytotoxic anti-inflammatory flavonoid. Apigenin inhibited NF-κB activation and expression of associated inflammatory factors (cyclooxygenase-2 (COX-2), intercellular adhesion molecule-1, ROS, IL-6, and IL-8) and suppressed *H. pylori*-induced widespread inflammation in gastric epithelial cells [33].

Recent evidence supports that *H. pylori*-induced gastritis is also associated with a T helper cell 17 (Th17) cellular immune response and that B-cell activating factor (BAFF) is a promoter of the Th17 response [63]. Berberine blocked the production of pro-Th17 cytokines (IL-6, transforming growth factor-β (TGF-β), and IL-1β) by inhibiting BAFF expression, thereby attenuating the Th17 cell response and reducing *H. pylori*-induced gastric mucosal inflammation [18].

3.1.2. Promoting the healing of gastric ulcers

Gastric ulcer is a multifactorial and complex chronic gastric disease, usually due to an imbalance between ulcerogenic and defensive factors. Ulcerogenic factors mainly include ethanol, drugs, gastric acid hypersecretion, pepsin, pro-inflammatory cytokines (e.g., IL-6, tumor necrosis factor (TNF)-α, and IL-1β), and oxidative stress (e.g., malondialdehyde (MDA), superoxide dismutase (SOD)); defense factors mainly include gastric mucus, gastric mucosa, epidermal growth factor (EGF) and epidermal growth factor receptor (EGFR), and prostaglandins (PGs). NPs possess both preventive and therapeutic effects on gastric ulcers due to their gastroprotective activity and gastric mucosal healing properties [34,35].

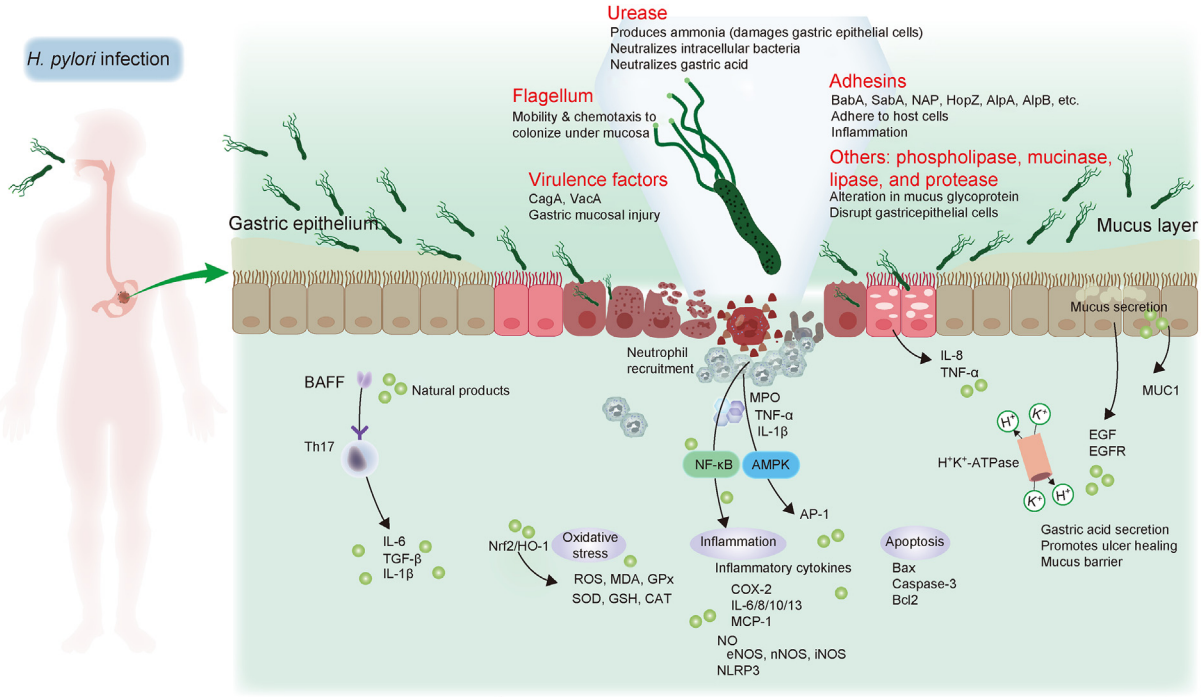

Fig. 4. The mechanism of natural products (NPs) action on gastric precancerous lesions (GPL) in phase I. NPs modulate the urease activity, motility, adhesion, virulence factors and drug resistance of *Helicobacter pylori* and inhibit *H. pylori* -induced gastric mucosal inflammation and oxidative stress. NPs also promote ulcer healing by restoring the gastric mucosal barrier and gastric acid secretion. AMPK: adenosine monophosphate-activated protein kinase; AP-1: activator protein 1; BabA: blood-antigen binding protein A; BAFF: B cell-activating factor; CagA: cytotoxin-associated gene A; CAT: catalase; COX-2: cyclooxygenase-2; EGF: epidermal growth factor; EGFR: epidermal growth factor receptor; GSH: glutathione; HopZ: *H. pylori* outer membrane protein; IL: interleukin; MCP-1: monocyte chemotactic protein 1; MDA: malondialdehyde; MPO: myeloperoxidase; NAP: neutrophil-activating protein; NF-κB: nuclear factor kappa-B; NLRP3: NLRF amily pyrin domain containing 3; NO: Nitric oxide; NOS: nitric oxide synthase; eNOS: endothelial NOS; nNOS: neural NOS; iNOS: inducible NOS; ROS: reactive oxygen species; SOD: superoxide dismutase; TGF-β: transforming growth factor-β; TH17: T help cell 17; TNF-α: tumor necrosis factor α; SabA: sialic acid-binding adhesin; VacA : vacuolating cytotoxin A.

3.1.2.1. Relieving inflammation of gastric mucosa. Excessive ethanol intake stimulates gastric mucosal epithelial cell apoptosis, inflammatory response and oxidative stress to induce gastric mucosal injury. NF-κB signaling pathway plays an important role in mediating between these events, where TLR and TNF receptor (TNFR) are the two major signaling pathways that activate NF-κB-related inflammatory responses. Moreover, TNF receptor-associated factor 2 (TRAF2) on the cell membrane amplifies NF-κB signaling pathway-mediated inflammation [35]. The inflammatory response and the mediators such as TNF-α, IL-1β and IL-6, are key pathogenic mechanisms of ethanol-induced gastric mucosal injury [35,39].

Myeloperoxidase (MPO) is a marker of neutrophil invasion and inflammatory response, which in turn activates the NF-κB signaling pathway and triggers the release of pro-inflammatory cytokines, leading to gastric mucosal damage [64]. Astragaloside IV (AS-IV) is a triterpene glycoside extracted from the dried root of *Astragalus*. AS-IV inhibited the TNF-α/NF-κB signaling pathway, accompanied by downregulation of TRAF2 and IL-1β and upregulation of anti-inflammatory IL-10, alleviating ethanol-induced inflammatory cell infiltration, edema, and hemorrhage in gastric tissues. Moreover, the effect of AS-IV in alleviating gastric mucosal inflammation was also closely related by its inhibition of MPO activity to suppress neutrophil infiltration [35]. In addition, Dendrobium officinale polysaccharides (DOP) significantly improved ethanol-induced gastric epithelial defects, inflammatory cell infiltration, redness, swelling, and ulceration by inhibiting mitogen-activated protein kinase (MAPK) signaling pathway and thus regulating inflammatory factor levels (such as IL-6 and EGFR) [39].

3.1.2.2. Inhibiting oxidative stress of gastric mucosa. Oxidative stress resulting from excessive production of ROS stimulated by risk factors such as ethanol is an important mechanism of gastric mucosal damage. Excessive intake of ethanol leads to migration of activated neutrophils to the site of injury, resulting in increased production of pro-oxidants, free radicals, and pro-inflammatory mediators thereby damaging the gastric [65]. Polysaccharides have been shown to alleviate oxidative damage to the gastric mucosa and ulcers [66]. DOP significantly attenuated ethanol-induced gastric ulcer and epithelial cell apoptosis *in vitro* and *in vivo* [40,41]. The underlying mechanisms were that DOP regulated adenosine monophosphate-activated protein kinase (AMPK)/mechanistic target of rapamycin kinase (mTOR) and Nrf2 signaling pathways, reduced oxidative damage and activated autophagy, thereby reversing ethanol-induced gastric mucosal damage [40–42].

Oxidative stress induces apoptosis in gastric mucosal epithelial cells and accelerates gastric injury. DOP significantly alleviated gastric mucosal epithelial cell apoptosis by inhibiting oxidative stress, which may be closely related to its inhibition of NF-κB signaling pathway regulating apoptosis-related protein expression (downregulation of Bax, caspase-3 and upregulation of Bcl2) [40,43]. Similarly, AS-IV prevents ethanol-induced gastric injury by blocking activation of mitochondrial oxidative stress and mitochondrial pathway of apoptosis by ethanol in the gastric mucosa [36]. *Hericium erinaceus* polysaccharide (HEP), derived from the medicinal and food plant *Hericium erinaceus*, has shown excellent gastric protection and ulcer healing effects by regulating gastric secretions, anti-inflammatory and antioxidant, and increasing the release of defense factors [44]. HEP reduced both the inflammatory response (inhibition of TNF-α, IL-6, and MPO) and oxidative damage (regulation of MDA, SOD, and glutathione peroxidase activity) at the ulcer and increased defense factors (nitric oxide (NO),

Table 1
Mechanisms of natural products (NPs) on Phase I of Correa's cascade.

NPs	Disease	Model	Dose	Targets/pathways/mechanisms	Refs.
Berberine	*H. pylori*	*H. pylori* strains	12.5 μM	↓*H. pylori* and urease	[13]
		Participants with *H. pylori* infection	100 mg	Berberine-containing quadruple regimen is noninferior to the efficacy of bismuth-containing quadruple regimen.	[14]
			300 mg	The 14-day berberine and amoxicillin-based quadruple therapy is not inferior to the efficacy of tetracycline and furazolidone based regimens.	[15]
				Triple therapy containing berberine, amoxicillin and rabeprazole is non-inferior to quadruple therapy containing bismuth.	[16]
		H. pylori strains	25 μg/mL	↓*H. pylori* and urease	[17]
	H. pylori-induced gastritis	*H. pylori*-infected mice; *H. pylori*-infected Th17 cells, macrophages, dendritic cells, or $CD4^+$ T cells	20 mg/kg; 5 μM	↓B cell-activating factor ↓IL-6, TGF-β, and IL-1β	[18]
Palmatine	Gastric ulcers	Acetic acid-induced gastric ulcer in rats	10 and 20 mg/kg	↑Prostaglandin E2 ↓Platelet-activating factor	[19]
	H. pylori	*H. pylori* strains	3.12, 6.25 μg/mL	↓*H. pylori*	[20]
		H. pylori strains	75–100 μg/mL	↓*H. pylori* and urease	[21]
Kaempferol	*H. pylori*	*H. pylori* strains	0.1, 1, and 10 mg/mL	↓HopZ, BabA, Cag A and urease	[22]
		H. pylori strains	0.025, 0.05, 0.075, and 0.1 mM	↓ATP-binding cassette transporters, flagellar assembly, fatty acid metabolism, and flagellum	[23]
		H. pylori strains	0.1, 0.5, 1, 2 mM	↓*H. pylori* and HsrA	[24]
Epigallocatechin-(−) gallate	*H. pylori*	Silico molecular docking-based virtual screening experiments	100 μM	↓*H. pylori*	[25]
		H. pylori strains; *H. pylori*-infected mice	8, 32, 64, and 128 μg/mL; 70 and 100 mg/head	↓Mucosal hemorrhage and erosion ↓The urease activity and motility of *H. pylori*	[26]
		H. pylori strains	50–100 μg/mL	↓*H. pylori*	[27]
	Gastric ulcers	Gastric mucosal cells infected by *H. pylori*	0.5, 5, and 50 μM	↓TLR-4 signaling ↓*H. pylori*-induced DNA damage and apoptotic cell death	[28]
Curcumin	*H. pylori*	*H. pylori* stimulated AGS gastric cancer cells; *H. pylori*-infected mice	2, 20, and 40 μM	↓*H. pylori* growth, translocation, and phosphorylation of Cag A	[29]
		H. pylori stimulated AGS cells	5 and 20 mM	↓The vacuolating activity and VacA	[30]
Resveratrol	*H. pylori*	*H. pylori* strains	64 μg/mL	↓Translation, ATP synthase and oxidative damage	[31]
	H. pylori-induced gastritis	*H. pylori*-infected mice	100 mg/kg	↓Oxidative stress and inflammation; ↓IL-8, iNOS, and NF-κB; ↑Nrf2/HO-1 pathway	[32]
Apigenin	*H. pylori*-induced gastritis	*H. pylori-infected* gastric adenocarcinoma MKN45 cells	9.3, 18.5, 37, and 74 μM	↓NF-κB activation and the inflammatory factor	[33]
Atractylenolide	Gastric ulcers	Ethanol-induced gastric ulcer in rats and in primary culture rat gastric mucosal cell	10 mg/kg; 100, 200, and 400 μM	↓Matrix metalloproteinase-2/9	[34]
Astragaloside IV	Gastric ulcers	Ethanol-induced gastric mucosal injury in rats	1, 2, and 4 mg/kg	↓Neutrophil infiltration ↓TNF-α/NF-κB signal pathway	[35]
			4 mg/kg	↓Oxidative stress, apoptosis, MDA, Bax/Bcl-2, caspase-3/9 ↑Glutathione	[36]
		Tween 80-induced gastric mucosal damage in rats	1, 10, and 50 mg/kg	↓MDA, TNF-α, Bax, and monocyte chemotactic protein 1 ↑HSP70 and mucus production	[37]
	Mucus barrier	STZ-induced diabetic rats	40 mg/kg	↓iNOS and COX-2 ↑MUC1	[38]
Dendrobium officinale polysaccharides	Gastric ulcers	Ethanol-induced gastric ulcer in rats and human gastric mucosal cells	0.12, 0.23, and 0.46 g/kg; 100, 200, and 400 ng/L	↑EGFR and TFF-1; ↓MAPK pathway	[39]
		Ethanol-induced gastric ulcer in rats and gastric epithelial cell line	100 mg/kg; 62.5, 125, 250 μg/mL	↓ROS and apoptosis ↓AMPK/mTOR signaling pathway	[40]
		Ethanol-induced gastric ulcer in rats	100 and 300 mg/kg	↓MAPK pathway and oxidative stress	[41]
		Ethanol-induced gastric ulcer in rats	–	↓Oxidative stress ↑Nrf2 and mucosal barrier	[42]
		Ethanol-induced gastric ulcer in rats and H_2O_2-induced cell apoptosis in HFE145 cells	124 and 248 mg/kg; 62.5, 125, 250, and 500 μg/mL	↓Oxidative stress ↓NF-κB	[43]
Hericium erinaceus polysaccharides	Gastric ulcers	Alcohol-induced gastric mucosal injury in rats and GES-1 cells	19.8 mg/kg; 100 μg/mL	↑Gastric-protecting activity	[44]
		Ethanol and pylorus ligation-induced gastric ulcer in rats	100, 200 and 400 mg/kg	↓Oxidative stress, TNF-α, IL-1β, and myeloperoxidase ↑NO, prostaglandin E_2, and EGF	[45]
			–		[46]

(*continued on next page*)

Table 1 (*continued*)

NPs	Disease	Model	Dose	Targets/pathways/mechanisms	Refs.
		Acetic acid-induced gastric ulcer in rats and H_2O_2-induced injury GES-1 cell model		↓Oxidative stress, TNF-α, IL-6, MDA, and myeloperoxidase ↑NO, PGE2, EGF, VEGF, and bFGF, and SOD	
		H_2O_2-induced oxidative damage in GES-1 cells	125, 250, and 500 μg/mL	↑Proliferation ↓Necrosis and ROS	[47]
		Ethanol-induced gastric ulcer in rats	125, 250, and 500 mg/kg	↑EGF, bFGF and PGE2 ↓MDA, IL-1β and TNF-α	[48]
Gallic acid	Gastric ulcers	Ethanol-induced gastric ulcer in rats	10, 30, and 50 mg/kg	↑Nrf2/HO-1 pathway ↓Apoptosis	[49]

↑, increase or promote; ↓, decrease or inhibit; -, no data available.
AMPK: adenosine monophosphate-activated protein kinase; BabA: blood-antigen binding protein A; IL: interleukin; TGF-β: transforming growth factor-β; bFGF: basic fibroblast growth factor; Cag A: cytotoxin-associated gene A; COX-2: cyclooxygenase-2; EGF: epidermal growth factor; EGFR: epidermal growth factor receptor; GES-1: gastric mucosal epithelial cells; HopZ: *H. pylori* outer membrane protein; HO-1: heme oxygenase-1; iNOS: inducible nitric oxide synthase; MAPK: mitogen-activated protein kinase; MDA: malondialdehyde; mTOR: mechanistic target of rapamycin kinase; NF-κB: nuclear factor kappa-B; Nrf2: nuclear factor erythroid 2-related factor 2; PGE2: prostaglandin E2; ROS: reactive oxygen species; SOD: superoxide dismutase; STZ: Streptozotocin; TFF-1: trefoil factor 1; TH17: T help cell 17; TNF-α: tumor necrosis factor alpha; VacA : vacuolating cytotoxin A; VEGF: vascular endothelial growth factor.

prostaglandin E_2, EGF, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor) to promote ulcer healing [45–48]. GA is a naturally occurring polyphenolic compound that exerts excellent gastric protection through anti-inflammatory, antioxidant, and NO-modulating properties [67]. GA alleviated ethanol-induced gastric ulcer by activating the Nrf2/HO-1 pathway that upregulated endogenous antioxidants (SOD, catalase, and glutathione) levels and alleviated oxidative stress-induced apoptosis by regulating Bax, Bcl-2, and caspase-3 [49].

3.1.2.3. Restoring the mucus barrier. The integrity of the gastric mucosal barrier is a critical factor in the protection and repair of gastric ulcers, including the cellular barrier and the mucus-bicarbonate barrier, which protects the gastric mucosal cells by resisting irritation from damaging factors [42]. DOP effectively strengthened the gastric mucosal barrier by stimulating mucus secretion and tight junction protein expression [42]. Similarly, AS-IV stimulated mucus production to restore gastric mucosal integrity [37]. Gastric mucosal hexosamine is the best indicator of mucin (MUC) production and is the first line of defense of gastric mucosa. AS-IV directly acted on gastric mucosal cells to promote their proliferation. It also prevented high glucose-stimulated gastric mucosal cell apoptosis by restoring the balance of iNOS, COX-2 and MUC1 proteins, which may help to alleviate diabetes-induced gastric mucosal damage [38].

3.2. Phase II: Reversing GPL

GPL is generally considered to be a critical stage in the transition from benign to malignant gastric lesions, and early intervention can effectively reverse gastric malignant transformation and reduce the risk of progression to GC [10]. NPs play a unique role in the reversal of the GPL (Fig. 5 and Table 2) [68–85].

3.2.1. Alleviating inflammation and oxidative stress

N-methyl-N′-nitro-N-nitrosoguanidine (MNNG), which combines mutagenic and carcinogenic effects, is a definitive modelling agent capable of causing AG, GPL, and even GC [86]. It was found that MNNG stimulates inflammation and oxidative stress in gastric mucosal cells, inducing malignant transformation of the gastric mucosa to GPL or even the development of GC [86]. DOP inhibited 8-hydroxydeoxyguanosine (8-OHdG) activity and increased nuclear expression of Nrf2, which in turn activated expression of downstream antioxidant genes and phase II detoxification enzymes (e.g. HO-1 and NADPH quinone oxidoreductase-1) to enhance antioxidant activity and alleviate precancerous lesions in gastric mucosal cells [80]. MNNG induces up-regulation of gastrin-17 secreted by the gastric sinus, a specific serological marker for the diagnosis of AG. Berberine significantly inhibited gastrin-17 expression and inflammation, and pathological changes in the gastric mucosa, including gastric gland arrangement, infiltration of lymphocytes and plasma cells, and loss of mural cells [68].

Inflammation proceeds through the Correa's cascade, with inflammatory cells and their secretion of key inflammatory factors involved in the development of the GPL [54]. Apigenin significantly reduced *H. pylori* colonization and its induced neutrophil and monocyte infiltration, and attenuated *H. pylori*-induced AG and GC progression [76]. Berberine inhibited the expression of pro-inflammatory cytokines, such as IL-8, IL-6, IL-1β, IL-17, NF-κB, TNF-α, COX-2, and monocyte chemotactic protein 1 (MCP-1) [68,69]. *H. pylori* induced increased expression of interferon regulatory factor 8 (IRF8) in gastric tissue, while interferon gamma (IFN-γ), a T helper cell 1 (Th1) cytokine, acted as a key regulator of IRF8 during *H. pylori*-induced inflammation, promoting the release of pro-inflammatory cytokines and enhancing *H. pylori*-induced inflammation and apoptosis [87]. Berberine blocked the IRF8-IFN-γ signaling axis and down-regulated the levels of inflammatory markers such as IFN-γ, IL-17, and chemokines (CXCL1/9) to alleviate chronic inflammation in the gastric mucosa. In addition, berberine induced $CD4^+$ T cells to Th1 differentiation to modify the adaptive immune response of gastric tissue to *H. pylori* [70]. *H. pylori* recruited macrophages (Mϕs) to the gastric mucosa, inducing gastric inflammation, lymphocyte activation, and immune response [88]. Berberine activated the IL-4/signal transducer and activator of transcription 6 (STAT6) signaling pathway to inhibit M1-polarized Mϕs (pro-inflammatory phenotype) and promote M2-polarized Mϕs (anti-inflammatory and tissue repair phenotype), reduced TNF-α, nitric oxide synthase 2, C–C motif chemokine receptor 7 and IRF-8 (M1-polarized Mϕs markers) and upregulated IL-4, STAT6, IL-10, and chitinase-like 3 (M2-polarized Mϕs markers) expression to alleviate inflammation [69].

The bacterially induced pro-inflammatory environment can initiate various inflammatory signaling cascades, such as EGFR, to promote malignant transformation of the gastric mucosa. *H. pylori* relies on the a disintegrin and metalloproteinase (ADAM) family proteases, such as ADAM10, to activate EGFR and induce inflammation [89]. Palmatine attenuated the mitochondrial membrane potential (MMP)-17-dependent inflammatory response in the gastric mucosa by blocking ADAM10/EGFR signaling, accompanied by a decrease in pro-inflammatory factors such as chemokine 16 (CXCL-16) and IL-8. Moreover, palmatine attenuated the inflammatory infiltration of $CD8^+$ T cells, attenuated gastric mucosal damage and enhanced host defense [71]. Aberrant expression of caudal-related homeobox 2 (CDX2) is an important trigger for IM

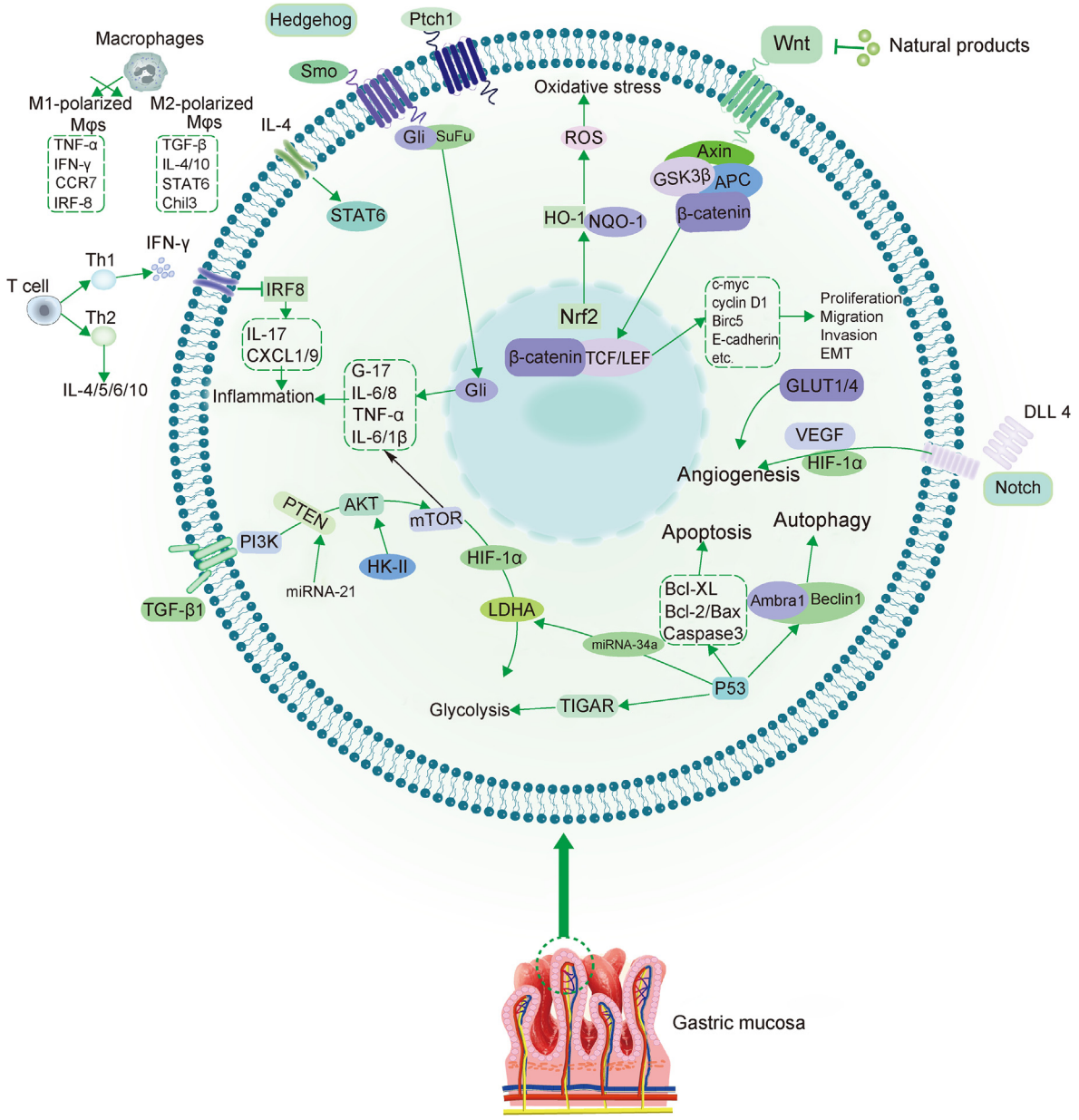

Fig. 5. The mechanism of natural products (NPs) action on gastric precancerous lesions (GPL) in phase II. NPs regulate multiple metabolic pathways and mediators that modulate gastric mucosal cell cycle, apoptosis, autophagy and angiogenesis to reverse GPL. CCR7: C-C motif chemokine receptor 7; Chil3: chitinase-like 3; EMT: epithelial mesenchymal transition; Gli: glioma-associated oncogene; GSK-3β: glycogen synthase kinase-3β; G-17: gastrin-17; HIF-1α: hypoxia-inducible factor 1α; HO-1: heme oxygenase-1; IFN-γ: interferon gamma; IRF8: interferon regulatory factor 8; LDHA: lactate dehydrogenase A; IL: interleukin; Mφs: macrophages; Smo: smoothened; Nrf2: nuclear factor erythroid 2-related factor 2; PTEN: phosphatase with tensin homology; Ptch: patched; PI3K: phosphatidylinositol 3-kinase; AKT: AKT serine/threonine kinase; mTOR: mechanistic target of rapamycin kinase; ROS: reactive oxygen species; STAT6: signal transducer and activator of transcription 6; SuFu: suppressor of fused homolog; Th1: T helper cell 1; TIGAR: TP53-induced glycolysis and apoptosis regulator; TNF-α: tumor necrosis factor alpha; TGF-β: transforming growth factor beta; TCF/LEF: T-cell factor/lymphoid enhancer-bi ding factor; VEGF: vascular endothelial growth factor.

[75]. Resveratrol activated the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway to promote forkhead box O4 phosphorylation and nuclear accumulation, and directly binded to the CDX2 promoter to inhibit CDX2 transcription, thereby alleviating bile acid-induced IM [75].

3.2.2. Regulating metabolism-related pathways

MNNG induces higher expression of Wnt/β-catenin signaling pathway, inhibits apoptosis and promotes malignant behaviors such as abnormal proliferation, epithelial mesenchymal transition (EMT), stem cell-like properties, invasion and migration of gastric mucosal epithelial cells [81–83]. DOP inhibited the Wnt/β-catenin pathway to suppress MNNG-induced GPL [81]. Besides, DOP altered endogenous metabolites (e.g., betaine), energy metabolism-related pathways and circadian rhythm signaling pathways to alleviate MNNG-induced gastric mucosal damage [81–83]. The Wnt/β-catenin signaling pathway regulates the EMT process, and GA may prevent the onset and development of GPL by inhibiting the Wnt/β-catenin signaling pathway and thus the EMT process [85]. Hedgehog signaling deficiency is an early change in gastric mucosal carcinogenesis and is one of the key mechanisms for the conversion of AG and IM to GC [90]. Kaempferol reduced IL-6 and IL-1β levels by modulating the hedgehog signaling pathway, thereby reversing AG [72].

Table 2
Mechanisms of natural products (NPs) on Phase II of Correa's cascade.

NPs	Disease	Model	Dose	Targets/pathways/mechanisms	Refs.
Berberine	GPL	MNNG-induced GPL in rats and GES-1 cell lines	14 and 28 mg/kg; 20 and 40 μM	↓TGF-β1/PI3K signal pathway ↓Gastrin-17 and inflammatory factors	[68]
		H. pylori-induced GPL in rats and GES-1 cell lines	14 and 28 mg/kg	↓IL-4-STAT6 signaling and M1-polarized Mϕs ↑M2-polarized Mϕs	[69]
		H. pylori-induced GPL in rats and GES-1 cell lines	14 and 28 mg/kg; 20 and 40 μM	↓IRF8-IFN-γ signaling	[70]
Palmatine	GPL	*H. pylori*-induced GPL in rats and GES-1 cell lines	10, 20, and 40 mg/kg; 20 and 40 μM	↓MMP-10 through ADAM17/EGFR signaling	[71]
Kaempferol	GPL	Ammonia solution and sodium deoxycholate solution-induced GPL in rats	0.24 g/kg	↓IL-6 and IL-1β by regulating hedgehog signaling pathway	[72]
Epigallocatechin-(−) gallate	GPL	MNNG-induced GPL in rats	50 mg/kg	↓PI3K/AKT/mTOR pathway ↑Cleaved caspase-3 and PTEN	[73]
Curcumin	GPL	Patients diagnosed with IM	1,000, 2,000, 4,000, 8,000, and 12,000 mg/day	Phase I clinical trial of curcumin in patients with IM	[74]
Resveratrol	GPL	GES-1, BGC823, SGC7901 and AGS cell lines	50, 100, and 200 μM	↑PI3K/AKT/p-FoxO4	[75]
Apigenin	GPL	*H. pylori*-induced GPL Mongolian gerbils	10, 30, and 60 mg/kg	↓Histological changes of neutrophil and monocyte infiltrations	[76]
Atractylenolide	GPL	MNNG-induced GPL in rats	1.2 and 2.4 mg/kg	↓Angiogenesis	[77]
Astragaloside IV	GPL	MNNG-induced GPL in rats	50 and 100 mg/kg	↓Glycolysis ↑The Ambra1/Beclin1 complex	[78] [79]
Dendrobium officinale Polysaccharides	GPL	MNNG-induced GPL in rats	2.4, 4.8, and 9.6 g/kg	↑Nrf2 and antioxidant enzymes HO-1 and NQO-1 ↓Wnt/β-catenin pathway	[80] [81]
		MNNG-induced human GES-1 cells damage model	400 and 800 μg/mL	↓Motility and migration ability of GES-1 cells and cell injury	[82]
		MNNG-induced GPL in rats	2.4, 4.8, and 9.6 g/kg	↑PER3 and AQP4 gene and modulating the Circadian Rhythm Signaling pathway	[83]
Hericium erinaceus polysaccharides	GPL	MNNG-induced GPL in GES-1 cell	100 and 500 μg/mL	↑Cell cycle arrest	[84]
Gallic acid	GPL	N-Nitroso-N-methylurea-induced GPL mice model and MNNG-induced GPL cell model	5 and 20 mg/kg; 60 and 90 μM	↓EMT and Wnt/β-catenin signaling pathway	[85]

↑, increase or promote; ↓, decrease or inhibit.
ADAM17: A disintegrin and metalloproteinase 17; AKT: AKT serine/threonine kinase; EGFR: epidermal growth factor receptor; EMT: epithelial mesenchymal transition; GES-1: gastric mucosal epithelial cells; GPL: gastric precancerous lesions; HO-1: heme oxygenase-1; IFN-γ: interferon gamma; IL: interleukin; IM: Intestinal metaplasia; IRF8: interferon regulatory factor 8; MMP-10: mitochondrial membrane potential 10; MNNG: N-methyl-N′-nitro-N-nitrosoguanidine; mTOR: mechanistic target of rapamycin kinase; Mφs: macrophages; PI3K: phosphatidylinositol 3-kinase; STAT6: signal transducer and activator of transcription 6; TGF-β1: transforming growth factor-β1.

Reprogrammed energy metabolism is a hallmark of cancer, and even in the presence of oxygen. Cancer cells preferentially obtain energy via glycolysis over mitochondrial oxidative phosphorylation [91]. PI3K/AKT/mTOR, a key pathway regulating glycolysis, upregulates hypoxia-inducible factor 1α (HIF-1α) and then increases lactate dehydrogenase A (LDHA) expression, thereby shifting metabolism to aerobic glycolysis and increasing glucose consumption providing an advantage to cancer cells during normoxia and hypoxia [91]. A hypoxia-like environment and dysfunctional organelle homeostasis were observed in precancerous gastric mucosa, which may contribute to the survival of cells in a glycolytic manner. AS-IV upregulated p53, which in turn regulated its downstream key genes TP53-induced glycolysis and apoptosis regulator and LDHA to dual-mediate the alleviation of glycolysis, and also inhibited the glycolytic process by restoring abnormalities in monocarboxylate transporter protein 1/4, CD147 and HIF-1α [78].

3.2.3. Inhibiting angiogenesis

Angiogenesis not only provides nutrients and oxygen for tumor growth, but also contributes to cancer progression by promoting cell migration, invasion, and formation of the tumor microenvironment, while early angiogenesis is also observed in GPL [92]. Progressive increase in microvasculature from IM to low-grade and high-grade DYS and early GC of the intestinal type [92]. Angiogenesis plays an important role in the initiation and progression of the Correa's cascade in GC. In the MNNG-induced GPL rat model, increased $CD34^{+}$ microvessel density and VEGF, HIF-1α expression indicated the presence of angiogenesis. Reduced lumen of gastric mucosal microvessels, thickened and rough basal lamina, irregular discontinuities and degenerative changes in the basement membrane were observed under transmission electron microscopy [77]. The delta-like ligands 4 (DLL4)/Notch signaling pathway also plays an important role in angiogenesis, with Notch1, Notch4, and DLL4 as key targets. Atractylenolide III attenuated precancerous lesions and their angiogenesis by downregulating DLL4, accompanied by downregulation of angiogenesis-related markers HIF-1α and VEGF [77].

3.2.4. Regulating cell cycle, apoptosis and autophagy

Gastric mucosal epithelial cell apoptosis is one of the major factors in gastric mucosal injury. p53 is an oncogene that binds to Bcl-2 family proteins and regulates the expression of apoptosis and autophagy [93]. Dysregulation of p53 and consequent inhibition of both apoptosis and activation of autophagy are important mechanisms and early events in MNNG-induced GPL. AS-IV upregulated p53 expression and activated the Ambra1/Beclin-1 complex in GPL to inhibit autophagy, while inhibiting Bcl-XL, and Bcl-2/Bax and upregulating caspase-3 to induce apoptosis, thereby alleviating gastric mucosal atrophy, IM and DYS [79]. The development of chronic AG can be attributed to the disruption of the dynamic balance between proliferation and apoptosis of gastric mucosal cells [94]. The PI3K/AKT/mTOR pathway is a classical signaling pathway for apoptosis regulation, and EGCG promoted apoptosis by downregulating the PI3K/AKT/mTOR

pathway and upregulating the expression of cleaved caspase-3 and phosphatase with tensin homology (PTEN) to reverse pathological lesions such as AG, IM and DYS [73]. TGF-β is a multifunctional cytokine that activates the PI3K/AKT/mTOR signaling pathway, regulates cell division, differentiation and apoptosis, and mediates the transformation and progression of AG to GC [95]. Berberine inhibited cell proliferation and induced apoptosis and autophagy by inhibiting the TGF-β1/PI3K/AKT signaling pathway and upregulating PTEN, light chain 3 (LC3)-II, and Beclin-1 to improve chronic AG [68].

MC cells, i.e., human gastric mucosal epithelial cells (GES-1) with MNNG intervention, are often used as a cellular model for GPL. DOP upregulated Bcl-2 and inhibited the expression of Bax and caspase-3, which inhibited GES-1 cell apoptosis and thus alleviated MNNG-induced gastric injury [82]. Hericius erinaceus polysaccharide (HEP) interfered with MC cell proliferation by inducing cellular G0/G1 phase arrest, indicating that the polysaccharide possesses excellent anti-AG activity [84].

3.3. Phase III: rescuing gastric carcinoma

GC is the final stage of the Correa's cascade trilogy and NPs have long been an important source of anti-cancer drugs, playing a major role in improving GC cell proliferation, migration, invasion, angiogenesis, and sensitivity to chemotherapeutic agents (Fig. 6 and Table 3) [96–128].

3.3.1. Regulating the cycle and proliferation of gastric carcinoma cells

IL, such as IL-8 and IL-6, is a cytokine of the CXC chemokine family, and its high expression in GC cells is associated with cell growth, differentiation as well as functional regulation [129]. The alkaloids in *Coptis chinensis* Franch., such as berberine and palmatine, showed excellent potential to inhibit GC cell viability and growth [96]. IL-6 activates the Janus kinase (JAK) 2/STAT3 signaling pathway to induce malignant behaviors such as proliferation, migration and invasion of GC cells. Berberine blocked the IL-6/JAK2/STAT3 signaling pathway to inhibit cell proliferation, migration and invasion, induce apoptosis and cell arrest *in vitro*, and inhibit xenograft tumor growth *in vivo* [97]. Atractylenolide II inhibited human GC cell proliferation and motility by regulating the AKT/ERK signaling pathway and induces apoptosis in a dose- and time-dependent manner [117]. HEP induced cell S-phase arrest and apoptosis to inhibit GC cell growth through a potential mechanism that regulates caspase-8/-3, p53-dependent mitochondrial function, and the PI3K/AKT pathway [126]. Circular RNAs (circRNAs) are important regulators of the malignant progression of GC. AS-IV inhibited GC cell proliferation and metastasis *in vitro* and *in vivo* by targeting the circRNA dihydrolipoamide S-succinyltransferase/microRNA-489-3p/eukaryotic translation initiation factor 4A1 pathway [120].

3.3.2. Promoting apoptosis and autophagy

Autophagy and apoptosis are two fundamental pathophysiological mechanisms of cell fate regulation, and induction of apoptosis and autophagy in cancer cells is a fundamental therapeutic tool for various tumors [130]. Curcumin induced both autophagy and apoptosis in GC cells by affecting PI3K and P53 signaling [104]. Curcumin decreased mitochondrial membrane potential and disrupted mitochondrial homeostasis, inducing GC cell apoptosis. Meanwhile, curcumin increased ROS production, and decreased oxidative phosphorylation activity and cellular glycolysis rate, resulting in the subsequent destruction of cellular bioenergy, DNA demethylation, and oxidative stress, thus inhibiting GC cell growth *in vitro* and *in vivo* [105–107]. Kaempferol significantly inhibited GC cell proliferation and induced apoptosis and G2/M phase cell cycle arrest through the PI3K/AKT and ERK-MAPK pathway, significantly inhibiting tumor growth *in vitro* and *in vivo* [100]. Endoplasmic reticulum, a key organelle involved in protein homeostasis, promotes cellular autophagy and apoptosis. Kaempferol is expected to apply endoplasmic reticulum stress-mediated autophagic cell death to fight against cancer cells by regulating the inositol-requiring enzyme 1(IRE1)/c-Jun N-terminal protein kinase-1(JNK1)/C/EBP homologous protein (CHOP) signaling pathway [131]. Kaempferol induced autophagic cell death through IRE1-JNK1-CHOP-mediated Bcl-2-Beclin-1 dissociation and histone deacetylase (HDAC)/G9a pathway-mediated epigenetic modifications in GC cells [101]. Apigenin induced apoptosis, and typical morphological changes such as incomplete nuclear membranes, condensation of chromatin, and fragmented nuclei were observed [115]. Moreover, under hypoxic conditions, apigenin activated autophagic cell death in GC cells by inhibiting HIF-1α and Ezh2, which would improve anticancer efficacy in hypoxic tumor microenvironment [116].

3.3.3. Inhibiting migration and invasion

Malignant tumor cells should overcome three major barriers to invade surrounding tissues, namely extracellular matrix (ECM) degradation, invasion and metastasis, and cell proliferation [132]. MMPs are capable of degrading essentially all ECM components, promoting tumor infiltration and metastasis, and four MMPs (MMP-1, -2, -7, and -9) are predominantly associated with GC [97,111]. GA inhibited NF-κB activity, downregulated PI3K/AKT/small GTPase signaling, and suppressed MMP-2/9 expression to inhibit GC cell metastasis and aggressive growth [127,128]. Resveratrol blocked Raf/MAPK signaling and inhibited IL-6 and MMP-2/9-induced GC cell invasion [111]. Berberine blocked GC cell migration and invasion through downregulation of MMP-9 in MKN-45 and HGC-27 cells [97]. The dissemination of GC cells into the circulation as circulating tumor cells and the formation of distal tumors, especially in the liver, are important causes of GC metastasis and progression. Curcumin significantly reduced the presence of circulating tumor cells and GC liver metastasis by inhibiting stromal cell-derived factor-1/ C-X-C motif chemokine receptor 4 (CXCR4) signaling [108].

EMT is a complex process in which epithelial cells lose cell polarity and adhesion, thus transforming into more motile and invasive mesenchymal cells. Aberrant activation of EMT confers cellular tumor initiation characteristics, motility, proliferative capacity, and drug resistance that are critical in the early stages of GC metastasis and malignant progression [133]. Signaling pathways such as TGF-β/Smad, PI3K/AKT, MAPK, and Wnt/β-catenin are the key signaling pathways that regulate EMT [133]. AS-IV reversed TGF-β1-induced EMT by inhibiting the PI3K/AKT/NF-κB pathway in GC cells [121]. Expression of programmed death ligand 1 (PD-L1) is associated with GC metastasis and differentiation. miR-195-5p binds to PD-L1 and promotes EMT and metastasis [134]. AS-IV inhibits EMT and angiogenesis in GC cells by increasing miR-195-5p expression and inducing miR-195-56p-mediated PD-L1 inhibition [122].

GC-derived mesenchymal stem cells (GC-MSCs) are an important component of the GC microenvironment, and they promote GC metastasis and EMT through abundant IL-6, IL-8, MCP-1, VEGF, and other factors [135]. Resveratrol targeted the EMT process induced by GC-MSCs and reversed GC metastasis by inhibiting Wnt/β-catenin signaling [112]. Similarly, by inhibiting the hedgehog pathway and thus the EMT process, resveratrol significantly inhibited GC invasion and metastasis [113]. Furthermore, the inhibition of EMT by resveratrol enhanced the chemosensitivity of GC cells, which may be a new option for the improvement of GC drug resistance [114].

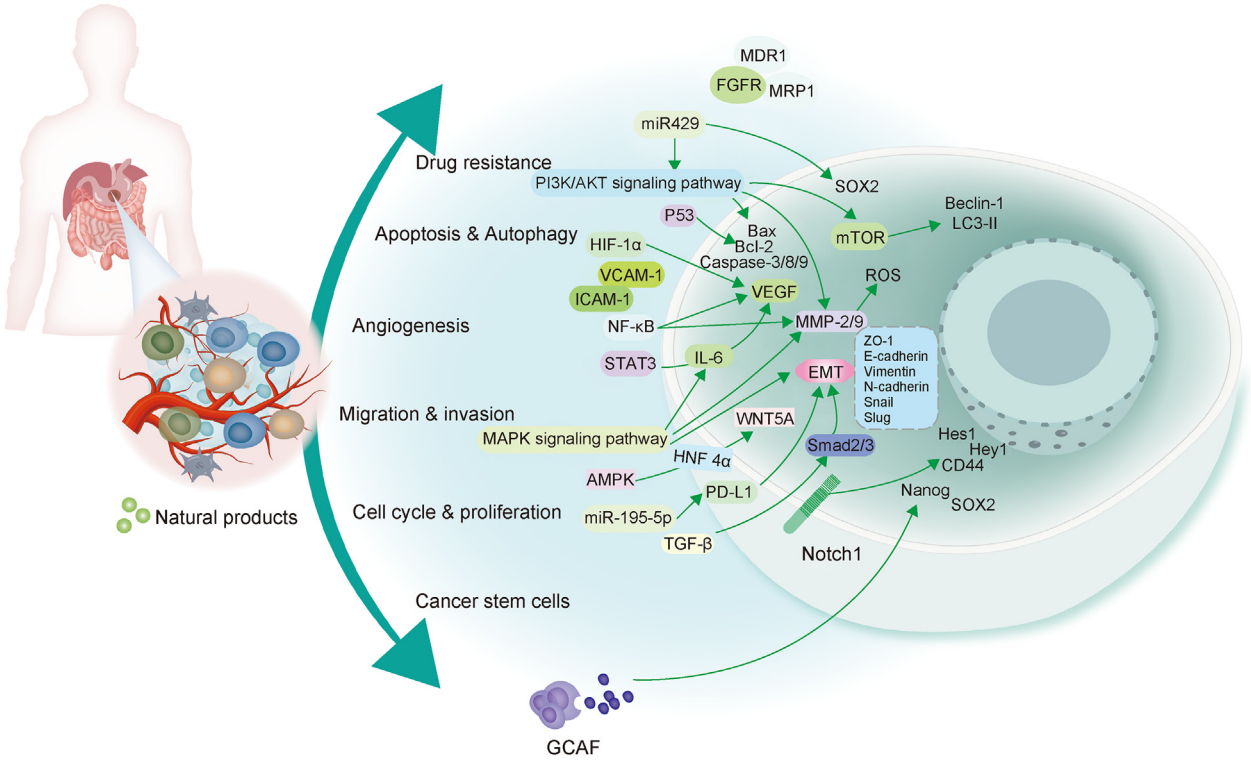

Fig. 6. The mechanism of natural products (NPs) action on gastric carcinoma (GC) in phase III. NPs inhibit cell proliferation, migration, invasion, angiogenesis, and cancer stem cells (CSCs), induce apoptosis and autophagy, and enhance chemotherapeutic drug sensitivity to treat GC. AMPK: AMP-activated protein kinase; EMT: epithelial mesenchymal transition; FGFR: fibroblast growth factor receptor; GCAF: gastric cancer-associated fibroblasts; HIF-1α: hypoxia-inducible factor 1α; HNF4α: hepatocyte nuclear factor 4 alpha; ICAM-1: intercellular adhesion molecule 1; IL: interleukin; LC3-II: microtubule-associated protein light chain 3 II; MAPK: mitogen-activated protein kinase; MDR1: multidrug resistance-1; MRP1: multidrug resistance-associated protein 1; MMP-2/9: mitochondrial membrane potential 2/9; mTOR: mechanistic target of rapamycin kinase; NF-κB: nuclear factor kappa-B; PD-L1: programmed death ligand 1; ROS: reactive oxygen species; SOX2: sex-determining region Y-box 2; STAT3: signal transducer and activator of transcription 3; TGF-β: transforming growth factor beta; VCAM-1: vascular cell adhesion molecule1; VEGF: vascular endothelial growth factor; WNT5A: wnt family member 5A; ZO-1: zonula occludens-1.

Tobacco smoke-induced EMT is also an important factor in cancer development and metastasis [102,109]. Tobacco smoke induced the activation of ERK5 and consequently the activation of EMT, accompanied by the downregulation of the epithelial markers E-cadherin, zonula occludens-1 (ZO-1), and cytokeratin 5 (CK5), and the upregulation of the mesenchymal markers Snail-1, vimentin, and N-cadherin. EGCG reversed the EMT induced by tobacco smoke and thereby inhibited the onset and malignant progression of GC [102]. Likewise, curcumin reversed tobacco smoke-induced EMT in mice by inhibiting the MAPK pathway [109].

3.3.4. *Inhibiting angiogenesis*

Angiogenesis is essential for tumor growth, and inhibiting GC angiogenesis is a promising anti-cancer approach [136]. VEGF has become a common target for antiangiogenic therapies, and EGCG inhibits the growth of GCs by reducing VEGF production and VEGF-induced angiogenesis [103,137]. IL-6 promotes tumor growth and metastasis through upregulation of VEGF expression and VEGF-mediated angiogenesis [137]. EGCG inhibited IL-6-induced VEGF expression and angiogenesis by suppressing STAT3 activity [103]. Berberine inhibited angiogenesis by inhibiting VEGF production and HIF-1α protein stability [98]. DOP induced apoptosis, inhibited angiogenesis and enhanced T cell immune response to inhibit tumor growth in mice, and its anti-GC activity was closely related to its molecular weight and O-acetyl group [124,125]. In addition, GC-MSCs play an important role in angiogenesis. Curcumin could inhibit GC-MSCs-mediated angiogenesis by regulating the NF-κB/VEGF signaling pathway, and is expected to be a new therapeutic target for GC [110].

3.3.5. *Improving drug resistance*

Chemotherapy is an important treatment for GC, but its effectiveness is limited by its toxicity and drug resistance. Berberine improved the sensitivity of GC cells to cisplatin through induction of apoptosis and inhibition of the PI3K/AKT/mTOR pathway, accompanied by reduced expression of drug transport proteins (multidrug resistance-1 and multidrug resistance-associated protein 1) [99]. Atractylenolide III enhanced the potency of doxorubicin-induced apoptosis of GC cells and tumor-suppression by inhibiting the expression of fibroblast growth factor receptors-1, -2, and -4 [118]. These data suggest that NPs may be able to improve the efficacy of conventional chemotherapeutic agents.

3.3.6. *Inhibiting gastric cancer stem cells (CSCs)*

CSCs, a distinct subpopulation of cells in cancer, usually <1%, that are highly self-renewing, multipotential, and tumorigenic, are the real “engine” of malignancy, invasion, metastasis, drug resistance, and cancer relapse [138]. Atractylenolide I attenuated the self-renewal ability of gastric CSCs by blocking the Notch pathway and reducing their sphere-forming ability and cell viability, accompanied by downregulating the expression of Hes1, Hey1, and CD44 [119]. Gastric cancer-associated fibroblasts (GCAF) are important components of the tumor microenvironment, producing and secreting high levels of factors that contribute to tumor survival and progression. It was found that GCAF significantly upregulated the expression of the stemness markers SOX2 and NANOG in GC cells, indicating that the promotion of the generation of CSCs and the support of their malignant phenotype are

Table 3
Mechanisms of natural products (NPs) on Phase III of Correa's cascade.

NPs	Disease	Model	Dose	Targets/pathways/mechanisms	Refs.
Berberine	GC	ACC-201 and NCI—N87 cells	0.999 and 2.023 μg/mL	↓The viability and growth	[96]
		MKN-45 and HGC-27 cells; MKN-45 xenograft mice	10, 20, and 40 μg/mL; 50, 100, and 150 mg/kg	↑Apoptosis, G0/G1 cell arrest ↓The proliferation, migration, and invasion	[97]
		Human umbilical vein endothelial and SC-M1 cells	7.5 μM	↓Angiogenesis and VEGF	[98]
		BGC-823 and SGC-7901 cells; mice	3, 10, and 30 μM; 10 mg/kg	↑Chemo-Sensitivity to Cisplatin and apoptosis	[99]
Palmatine	GC	ACC-201 and NCI—N87 cells	4.909 and 20.08 μg/mL	↓The viability and growth	[96]
Kaempferol	GC	MKN28, SGC7901 and GSE-1 cells; athymic mice	60 and 120 μM; 20 mg/kg	↑Apoptosis and G2/M phase cell cycle arrest	[100]
		AGS, SNU-216, NCI—N87, SNU-638, and MKN-74	25, 50, and 100 μM	↑Autophagic cell death	[101]
Epigallocatechin-(−) gallate	GC	Mice	50 or 100 mg/kg	↓EMT	[102]
		AGS cells; nude mice	5, 10, 25, and 50 μM	↓VEGF production and angiogenesis	[103]
Curcumin	GC	SGC-7901 and BGC-823 cells	10, 20, and 40 μM	↑Autophagy and apoptosis	[104]
		SGC-7901 and BGC-823 cells; nude mice	10 μg/mL; 25 mg/kg	↑Apoptosis and ROS	[105,107]
		MGC-803 cells	10, 20, 40, and 60 μM	↑Apoptosis and ROS	[106]
		Primary mouse gastric cancer cells transplanted into mice	10 mg/kg	↓Metastasis and stromal cell -derived factor-1/CXCR4 signaling	[108]
		Mice	50 mg/kg	↓EMT	[109]
		HGC-27 cells; nude mice	30 μM	↓NF-κB/VEGF signaling and angiogenesis	[110]
Resveratrol	GC	MKN-1, MKN-7, MKN-28, SGC7901, and HSC-39 cells; mice	10, 20, 30, 50, and 100 μM	↓Invasion	[111]
		Gastric-cancer-derived mesenchymal stem cells, HGC-27, and AGS cells	20 and 50 μM	↓Wnt/β-catenin signaling, EMT, and metastasis	[112]
		SGC-7901 cells	55 μM	↓Hedgehog signaling pathway, EMT, invasion, and metastasis	[113]
		SGC-7901 and MGC-803 cells; nude mice	50 and 100 mg/mL; 50 mg/kg	↓PTEN/AKT signaling pathway, EMT, and doxorubicin resistance	[114]
Apigenin	GC	SGC-7901 cells	20, 40, and 80 mM	↑Apoptosis.	[115]
		AGS, SNU-216, NCI—N87, SNU-638, MKN-7, and MKN-74 cells; Tumor xenograft mouse	50 μM; 200 or 300 mg/kg	↑Autophagy and cell death	[116]
Atractylenolide	GC	HGC-27 and AGS cells	50, 100, 200, and 400 μM	↓Proliferation, motility, and AKT/ERK signaling pathway ↑Apoptosis	[117]
		AGS and SGC-7901 cell lines	1, 5, 10, and 50 μM	↑LDH, apoptosis rate, and the ratio of BAX to Bcl-2	[118]
		MKN-45,MGC-803, HGC-27, and L-02 cells	25, 50, and 100 μM	↓Cancer stem cells and Notch pathway	[119]
Astragaloside IV	GC	HGC-27 and MKN-45 cells; Xenograft nude mice	10, 20, and 40 μg/mL; 40 mg/kg	↓circDLST/miR-489-3p/EIF4A1 axis	[120]
		BGC-823 and MKN-74 cells	10 and 20 μM	↓EMT and PI3K/AKT/NF-κB pathway	[121]
		SGC7901 and MGC803 cells	5, 10, 25, and 50 μg/mL	↓EMT and angiogenesis	[122]
		BGC-823 cells	10, 20, and 40 μM	↓Gastric cancer-associated fibroblast, SOX2 and NANOG	[123]
Dendrobium officinale Polysaccharides	GC	Tumor-bearing mice; Murine forestomach carcinoma cells	65.7, 131.4, and 262.8 mg/kg; 0.025, 0.05, 0.1, 0.2, 0.4, 0.8, 1.0 and 1.5 mg/mL	↑Apoptosis and T cell immune response ↓Angiogenesis	[124,125]
Hericium erinaceus polysaccharides	GC	SGC-7901 cells	20, 50, and 80 μg/mL	↑Cell cycle arrest and apoptosis	[126]
Gallic acid	GC	AGS cells	2, 2.5, 3, and 3.5 μM	↓Metastasis, NF-κB, and PI3K/AKT/small GTPase signals	[127]
		AGS cells; nude mice	3.5 μM; 0.25% and 0.5% solution		[128]

↑, increase or promote; ↓, decrease or inhibit.
CXCR4: C-X-C motif chemokine receptor 4; EMT: epithelial mesenchymal transition; ERK: extracellular signal-responsive kinase; GC: gastric carcinoma; LDH: lactate dehydrogenase; NF-κB: nuclear factor kappa-B; ROS: reactive oxygen species; SOX2: sex-determining region Y-box 2.

important oncogenic mechanisms of GCAF [139]. Astragaloside IV could lower the level of macrophage colony-stimulating factor and metalloproteinase 2 secreted by GCAF, thereby downregulating SOX2 and NANOG expression in GC cells to reduce cancer cell stemness, implying that astragaloside IV may act on GCAF to impair the ecological niche of gastric CSCs, thus fundamentally inhibiting GC progression [123].

4. Summary of the pharmacological mechanisms of NPs in the Correa's cascade

The pathogenesis of GC is a multifactorial involvement, multicellular regulation, and multistage evolutionary process, with *H. pylori* infection being the key initiating factor, inducing multiple cytokines, pathways, and gene dysregulation, which in turn drive

the progression of Correa's cascade: the gastric mucosa progresses through inflammation (Phase I), to GPL (Phase II), and finally to GC (Phase III). Therefore, blocking the Correa's cascade, especially Phases I and II, is a key therapeutic strategy for the prevention and treatment of GC. This review comprehensively investigates and summarizes the multistep effects of NPs such as atractylenolide, astragaloside, apigenin, berberine, curcumin, EGCG, GA, kaempferol, palmatine, polysaccharides, and resveratrol, on the Correa's cascade and their regulatory mechanisms in gastric carcinogenesis. In Phase I, NPs inhibit *H. pylori* infection, improve antibiotic resistance, reduce mucosal inflammation and oxidative stress, restore the mucosal barrier, and promote ulcer healing. In Phase II, NPs reverse AG, IM and DYS lesions by modulating metabolic pathways, ameliorating mucosal inflammation and oxidative stress, promoting apoptosis and autophagy, and inhibiting angiogenesis. In Phase III, NPs inhibit cell proliferation, migration, invasion, angiogenesis and CSCs, induce apoptosis and autophagy, and enhance chemotherapeutic drug sensitivity. NPs exert pharmacological effects through a multi-step action on the Correa's cascade reaction and exhibit multi-phenotypic modulation, which will have great potential for clinical application in the prevention and treatment of GC.

5. Critical considerations and prospects

5.1. Superiority of NPs-targeted Correa's cascade: Multi-step action and multi-phenotypic regulation

The Correa's cascade is a recognized process of GC development, namely the three phases of active gastritis, GPL and GC. Our current therapeutic tools are not yet able to completely cure GC, which is attributed to the fact that GC treatment, new drug development and basic research have focused on the GC stage, while neglecting early intervention in the Phase I and II of Correa's cascade, resulting in most GC cases developing to advanced stages at the time of initial diagnosis, thus missing the best time for treatment.

This review highlights the great potential of NPs in the prevention and treatment of GC. The advantage of NPs lies in their multi-step modulatory effect on the Correa's cascade, particularly in Phase I and II, which effectively prevents and blocks the malignant progression of the gastric mucosa to GC. In the GC phase, NPs possess multi-phenotypic regulation, targeting GC with multiple targets, multiple signaling cascades or multiple mechanisms, effectively inhibiting cancer cell proliferation, migration and angiogenesis, as well as inducing apoptosis and autophagy to prevent malignant progression of GC. In combination with conventional chemotherapeutic agents, NPs increase the sensitivity of chemotherapeutic agents and overcome multidrug resistance [118].

5.2. Bioavailability of NPs: Potential for future applications

Despite the numerous health benefits of NPs, their low bioavailability, lack of targeting, non-specific distribution, potential adverse effects, poor water solubility and stability have limited their efficacy and clinical application to some extent. Nanotechnology promises improved solutions to these NPs shortcomings, and the design and development of nano-delivery systems to encapsulate NPs will improve the prospects for NPs in GC therapy [140]. For example, EGCG, the major catechin in green tea, plays a key role in GC control due to its multi-step and multi-phenotypic modulation of Correa's cascade. EGCG is unstable, susceptible to oxidation under the influence of temperature and pH, and can be degraded by gastrointestinal fluids, reducing its effectiveness [141]. Nanoparticles slowed the release of EGCG in simulated gastric or intestinal fluids [142]. Compared to EGCG alone, nanoparticle-delivered EGCG acts directly in the interstitial space at the site of *H. pylori* infection, resulting in more potent *H. pylori* clearance and alleviation of *H. pylori*-associated gastric inflammation [143]. Targeted nanoparticle delivery of EGCG to GC tissues significantly inhibits cell proliferation and induces apoptosis *in vitro* and *in vivo* [144]. Thus, theoretically, nanoparticles could significantly improve the bioavailability and clinical properties of NPs, potentially improving the pharmacological response of patients and achieving better clinical outcomes. Currently, there are few trials of this combination and further studies are needed to determine whether nanotechnology can truly improve NPs efficacy in gastric diseases.

5.3. Nature plants: Multi-drug, multi-target

This review summarizes the multi-step and multi-phenotypic modulation of the Correa's cascade by NPs, i.e., “one drug, multiple targets”. However, the mechanisms of many diseases are complex, and a single component alone may not be able to truly target all pathogenic mechanisms. Nature itself may have solved this problem for us. Natural plants, including tradition Chinese medicine and Japan CPM, are the combination of compounds that work synergistically to provide excellent stomach protection. Berberine is the main active ingredient of *Coptis chinensis* Franch. (Huanglian in Chinese), which has excellent anti-*H. pylori* efficacy, but it was found that *Coptis chinensis* has anti-*H. pylori* activity superior to that of berberine. This suggests that the anti-*H. pylori* activity is not only dependent on the berberine but may be related to its other components in *Coptis chinensis* [145].

The combination of several natural plants, i.e., multi-drug and multi-target, has the potential to achieve even better gastric protection. Zuojin Pill (ZJP) is a classic Chinese herbal formula consisting of two botanicals, *Coptis chinensis* Franch. and *Tetradium ruticarpum* (A. Juss.) Hartley (Wuzhuyu in Chinese), which dates back to the Yuan Dynasty in China and has long been used to treat various acute and chronic gastric disorders [146,147]. In Phase I, ZJP significantly improved gastric mucosal inflammation, oxidative damage and ulceration by modulating inflammation and oxidative stress [146,147]. In Phase II, ZJP attenuated *H. pylori*/MNNG-induced chronic AG by modulating the COX-2/VEGF, high mobility group box-1 (HMGB1)/NF-κB, and TGF-β1/PI3K/AKT pathways [148,149]. In Phase III, ZJP inhibited cancer cell growth by activating ROS production and the mitochondria-dependent apoptosis pathway in SGC-7901 cells [150]. These examples demonstrate the outstanding potential of a multi-drug, multi-target strategy.

6. Conclusion

The development of GC is a multi-step chronic evolutionary process, and Correa's cascade is its general evolutionary pattern. Inflammation is controllable, while cancer is difficult to control. Therefore, the focus of GC prevention and control has been on early treatment of gastric mucosal lesions associated with Correa's cascade. This review is the first stepwise systematic description of the multi-step effects of NPs on the Correa's cascade and their regulatory mechanisms in GC occurrence, which is expected to provide new ideas for GC prevention and control and new drug development.

CRediT authorship contribution statement

Wenhao Liao: Writing – original draft, Software, Methodology, Conceptualization. **Jing Wang:** Supervision, Methodology, Conceptualization. **Yuchen Li:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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