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Traditional Chinese medicine for transformation of gastric precancerous lesions to gastric cancer: A critical review

Zhong YL *et al*. TCM for GPL and GC

Yi-Lin Zhong, Peng-Qian Wang, Dan-Li Hao, Feng Sui, Feng-Bin Zhang, Li Bing

Abstract

Gastric cancer (GC) is a common gastrointestinal tumor. Gastric precancerous lesions (GPL) are the last pathological stage before normal gastric mucosa transforms into GC. However, preventing the transformation from GPL to GC remains a challenge. Traditional Chinese medicine (TCM) has been used to treat gastric disease for millennia. A series of TCM formulas and active compounds have shown therapeutic effects in both GC and GPL. This article reviews recent progress on the herbal drugs and pharmacological mechanisms of TCM in preventing the transformation from GPL to GC, especially focusing on anti-inflammatory, anti-angiogenesis, proliferation, and apoptosis. This review may provide a meaningful reference for the prevention of the transformation from GPL to GC using TCM.

Key Words: Gastric cancer; Gastric precancerous lesions; Traditional Chinese medicine; Formulas; Pharmacological mechanism; Inflammation-cancer transformation

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Core Tip: Precancerous lesions are precursors of gastric cancer (GC). The molecular mechanism of the transformation of precancerous lesions into GC remains unclear. This article reviews the mechanism of traditional Chinese medicine in the treatment of precancerous lesions and GC, and describes the relationship between the molecular

mechanisms of Chinese medicine in treating these two pathological stages, providing a research idea for blocking GC progression through the gastric precancerous lesion stage.

INTRODUCTION

Gastric cancer (GC) is the fifth most commonly diagnosed cancer and the fourth leading cause of cancer-related death worldwide[1]. The direct cause of high mortality in GC is that early GC may occur without any specific symptoms and cannot be treated promptly[2]. Therefore, it is particularly important to prevent GC in early stage[3]. In the 19th century, Virchow proposed "the origin of cancer as a site of chronic inflammation"[4]. Mostly, gastric carcinogenesis is a chronic pathological process, from chronic superficial gastritis, atrophic gastritis, intestinal metaplasia (IM), gastric epithelial dysplasia (GED), to GC, which was demonstrated as the typical process of "inflammation-cancer transformation"[5]. IM and GED are the main pathological stages of gastric precancerous lesions (GPL)[6]. GPL is the last stage before the occurrence of GC. Once this stage is attained, the probability of GC increases by at least 10-fold[7,8]. Therefore, intervention of at the GPL stage and reversal of malignant transformation are of great importance for the prevention of GC. Currently, there is no recommended treatment for GPL in western medicine[9]. The only therapeutic treatment, endoscopic mucosal dissection, is applicable to cases of severe dysplasia and early GC[10]. *Helicobacter pylori* (*H. pylori*) eradication and supplementation with vitamins and minerals exert a positive effect on the treatment of GC; however, the current research is not sufficient to support their therapeutic effects on GPL[11].

Inflammation, angiogenesis, and proliferation are the three most important histological features of the transformation from GPL to GC[12-14]. Chronic inflammation is the core driver of GC[15,16]. Inflammation promotes angiogenesis, and its progression depends on the speed of angiogenesis[17,18]. Simultaneously, inflammatory cells are almost inseparable from tumor cells, and the proliferation of tumor cells is directly related to the promotion of inflammation[19]. Moreover, the microenvironment created

by tumors can promote further proliferation of inflammatory cells[20]. Angiogenesis can also promote the proliferation of tumor cells[21]. Furthermore, the establishment of a large number of new blood vessels also means that the tumor is about to transition from the dormant to the malignant stage[22]. An important feature is that when the diameter of the tumor tissue is larger than 1-2 mm, it relies heavily on neovascularization to deliver nutrients and clear metabolic wastes in tumor cells[23]. Clinically, tumor angiogenesis is believed to be directly proportional to tumor malignancy[24]. Seeking drugs that regulate the proliferation, inflammation, and angiogenesis of GPL and GC may be a promising avenue for improving clinical efficacy and further drug discovery.

GPL is generally defined as “stomach distension” and “stomach pain”, according to traditional Chinese medicine (TCM) theory, with symptoms including fatigue and weakness, dizziness and wasting, grayish-yellow face, and a pale and dark tongue. TCM has been used for millennia to treat GPL. A series classical formula (fangjis) was documented in Treatise on Febrile Diseases, and Prescriptions of the Pharmacy Bureausuch, and showed curative effects for GPL. For example, the sijunzi decoction, which can be dated back to 1151 AD, was effective in treating both precancerous lesions[25,26] and GC[27,28]. Currently, a variety of traditional Chinese patent medicines, such as the Weiqi decoction[29], WeiFuChun (WFC)[30], and Weipixiao (WPX)[31] have been developed for GPL. Many clinical studies have also suggested that TCM can hinder the transformation process of inflammation and cancer, treat precancerous lesions and early GC, and improve the progression of advanced GC (Table 1). For instance, WFC is a Chinese herbal compound approved by the National Medical Products Administration to treat GPL. Clinical trials have shown that WFC can significantly improve the pathological conditions of patients with GPL compared to vitamin C, especially in the case of atrophy or IM[16]. Moreover, with the advantages of TCM in precancerous lesions and GC, TCM has received increasing attention, and a growing number of clinical studies have been registered at ClinicalTrials.gov, such as the Jianpi Yangzheng Xiaozheng decoction (NCT03823248) and Yiqi Wenyang Jiedu decoction (NCT05229809).

Many experimental studies have investigated the efficacy and mechanisms of TCM. For example, WFC can increase the secretion of pepsin by inhibiting the MAPK signaling pathway, thereby regulating the weight of rats with GPL and improving histopathological changes in the gastric mucosa[32]. Another study showed that Ginsenoside Rb1 (GRb1), which is contained in WFC, can prevent the occurrence and progression of GPLs by reducing the protein expression and nuclear translocation of β-catenin, interfering with the interaction of β-catenin/TCF4, and inhibiting the transcriptional activity of downstream genes, including c-myc, Cyclin D1 and Birc5[33]. Therefore, it is important to study the effect of TCM on GPL to improve the clinical efficacy and transformation of drug research and development (R&D). In this study, we summarize the mechanisms and targets of TCM in the treatment of GPL and GC, with a particular focus on their action in the processes of inflammation, angiogenesis, cell proliferation, and apoptosis.

MECHANISM OF TCM IN THE TREATMENT OF GPL

The GPL stage is a critical stage in the development of GC. The intervention goal of GPL is to reverse malignant transformation and block the progression to GC. However, the molecular mechanisms underlying GPL have not yet been fully elucidated. Many TCMs have been shown to be effective in the treatment of GPL, focusing on the regulation of proliferation and apoptosis, anti-inflammation, and inhibition of angiogenesis (Tables 2 and 3, Figure 1).

Regulating proliferation and apoptosis related to GPL

In GPL and GC, the imbalance between proliferation and apoptosis of gastric epithelial cells may be the direct cause of malignant progression[34]. The PI3K/Akt/mTOR signaling pathway can regulate growth in normal cells and in cancers, and the activation of the Akt pathway through PI3K is directly related to tumorigenesis[35]. Pathological changes in the PI3K/Akt/mTOR pathway usually include downregulation of the tumor suppressor gene PTEN, abnormal activation of PI3K, and

overexpression/hyperactivation of Akt[36]. Erianin, which is one of the most important natural compounds in Dendrobium, can be directly extracted from Dendrobium. Moreover, dendrobium species are widely used to treat various digestive diseases. Wang *et al*[37] confirmed that Erianin can significantly reduce Harvey rat sarcoma viral oncogene homolog (HRAS), thereby inhibiting the downstream PI3K/Akt signal pathway; hence, it plays a role in the treatment of precancerous lesions. Green tea polyphenols have been recognized for their anti-GC effects. Epigalocatein gallate is the main component of green tea polyphenols. Similarly, Zhu *et al*[38] found that epigallocatechin gallate inhibits the downstream PI3K/Akt/mTOR signaling pathway by promoting PTEN expression. This process achieves a balance between cell proliferation and apoptosis. The Wnt/β-catenin signaling pathway is a conserved pathway that plays an important role in maintaining intracellular homeostasis[39]. Inappropriate activation of the Wnt/β-catenin signaling pathway often occurs in GPL gastric epithelial cells, which may be one of the reasons for the transition from GPL to GC[40,41]. Weipixiao is a TCM compound that is found in Radix Astragali, Radix Pseudostellariae, Rhizoma Atractylodis Macrocephalae, Radix Salviae Miltiorrhiz, Herba Hedyotis Diffusae, and other TCMs. It is widely used for the management of GPL in clinical practice. Zeng *et al*[33] found that Weipixiao can inhibit cell proliferation and induce apoptosis by inhibiting abnormal activation of the Wnt/β-catenin signaling pathway, while GRb1 can inhibit β-catenin protein expression. Downstream targets, such as c-myc, Cyclin D1, Lgr5, MMP-7, and Birc5, in this pathway are inhibited. Autophagy is an intracellular catabolic process[42]. Current research shows that promoting autophagy in the early stages of tumorigenesis has a positive significance in cancer treatment[43]. The Chinese medicine monomer, Astragaloside IV (As-IV), regulates autophagy by mediating the Ambra1/Beclin1 complex[44].

Regulating inflammation signaling pathways of GPL

Inflammation is the key to the progression of GPL to GC. Currently, it is generally believed that the noncanonical nuclear factor-kappaB (NF-κB) and STAT3 signaling

pathways are the two major signaling pathways that connect inflammation and cancer, and they link inflammation and cancer through synergistic action[45,46]. As one of the most important signaling pathways in the inflammatory response[47], the NF-κB signaling pathway can lead to the transcriptional activation of many pro-inflammatory mediators, including tumour necrosis factor alpha (TNF-α), interleukin-8 (IL-8), and IL-6[48]. Because it also regulates cell proliferation, angiogenesis, metabolism, inflammation, and cell migration and is in the key position of these mechanism-related pathways, it is not difficult to explain why this pathway has become the most important bridge connecting GPL and GC[49]. Calycosin may play an anti-inflammatory role by regulating the integrin β1/NF-κB/DARPP-32 pathway and downregulating STAT3 expression[50]. The upregulated expression of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1α (HIF-1α) in cells under hypoxic conditions lead to an inflammatory reaction[51]; therefore, WQD can play an anti-inflammatory role by inhibiting the HIF-1 signaling pathway[29].

In addition, TCM monomers and compounds can regulate various inflammatory factors. TCM monomers and compounds can also regulate a variety of inflammatory factors, including IL-6, TNF-α, IL-1, IL-8, COX-2, and IL-2. Among these, TNF-α, IL-6, and IL-8 can be regulated by more than three types of Chinese herbs. For example, TNF-α can be regulated by Tomentosin[52], artemisinin (ART)[53], rosmarinic acid (RA)[54], scutellarin (SC)[55].

Inhibition of angiogenesis signaling pathways and targets of GPL

HIF-1α binds to the target gene VEGF, and then leads to the transcription of Pro angiogenic protein, which is an important reason for the formation of new blood vessels, or neovasculogenesis[56,57]. Therefore, stabilizing the HIF-1α/VEGF pathway is of great significance for improving angiogenesis under hypoxic conditions. A study showed that early angiogenesis in GPL tissue is accompanied by HIF-1α and VEGF-A activation[58]. Both atractylenolide III (ATIII)[58] and WPX[59] can inhibit the HIF-

1α/VEGF signaling pathway, and WPX can also inhibit the downstream targets of the pathway, such as ERK1/Cyclin D1. It then plays a role in angiogenesis inhibition.

OTHER MECHANISMS OF ACTION IN THE TREATMENT OF GPL

Regulate GPL related metabolism

Metabolic disorder is a hallmark of GC, the most significant of which are disorders of glucose metabolism[60]. In contrast to normal cells, GC cells preferentially choose glycolysis as the main way to obtain energy, even under conditions of sufficient oxygen[61]. The rapid proliferation of GC cells depends largely on glycolysis[62]. Studies have found that glycolysis also occurs in GPL; therefore, glycolysis is likely to be one of the key points in the transition from GPL to GC[63]. Ginsenoside Rg3 (GRg3) blocks glycolysis by inhibiting the PI3K/AKT pathway and downregulating downstream miRNA-21[63], whereas WPX inhibits the PI3K/AKT/mTOR pathway by upregulating upstream miRNA-34a, and then blocks glycolysis[64]. Interestingly, both WPX and As-IV can regulate LDHA, MCT4, HIF-1α, and CD147 targets inhibits glycolysis[65].

Reverse GPL related epithelial-mesenchymal transition

Epithelial-mesenchymal transformation (EMT) refers to the transformation of epithelial cells into mesenchymal cells under specific conditions. EMT is a physiological process that occurs during tissue self-repair[66]. When it is out of control, it may lead to fibrosis, angiogenesis, loss of normal organ function, and cancer, making it one of the key characteristics of GC[67]. Gallic acid (GA) is found in many TCMs. As early as 1552 AD, the Compendium of Materia Medica recorded the method for obtaining GA and its medicinal properties. Liao *et al*[68] found that GA can inhibit the EMT process by downregulating the Wnt/β-catenin signaling pathway, thereby inhibiting the malignant proliferation of MC cells and finally achieving the goal of treating GPL. The Manpixiao Decoction is a compound used in Chinese medicine. Li *et al*[69] confirmed that this compound could inhibit the progression of PLGC by reducing the occurrence

of systemic inflammatory reactions in the local gastric mucosa and inhibiting the EGFR-PI3K-AKT related EMT pathway.

MECHANISM OF TCM IN THE TREATMENT OF GC

A variety of TCM formulas and active compounds have been demonstrated to be effective in the treatment of GC, mainly involving the regulation of proliferation, apoptosis, and inflammation (Tables 2 and 3, Figure 1).

Regulating proliferation and apoptosis related to GC

The imbalance between cell proliferation and apoptosis destroys tissue homeostasis and promotes tumor occurrence[70]. Therefore, regulating the proliferation and apoptosis of GC cells is an important therapeutic strategy for preventing GC progression[71]. In GC, the PI3K/AKT/mTOR pathway is often activated, and this pathway plays a role in promoting cancer progression[72]. Multiple targets of this pathway have been shown to be mutated or otherwise dysregulated during tumorigenesis[73]. Naringin and pectinarigenin (PEC) can inhibit the PI3K/Akt signaling pathway, and PEC can also inhibit downstream mTOR[74,75]. Weifufang promoted the upregulation of PTEN and inhibited the PI3K/Akt signaling pathway[76]. Aloin (ALO) inhibits the Akt/mTOR signaling pathway mediated by NOX2-ROS[77]. They can both play a role in inhibiting cell formation. Recent studies have shown that the STAT signaling pathway has a strong carcinogenic potential, which can promote proliferation and has an extremely significant anti-apoptotic effect[78,79]. Therefore, dysregulation of the STAT3 signaling pathway is common in GC[80]. Ponicidin can induce apoptosis in MKN28 cells, which may be related to the inhibition of the VEGFR2-mediated JAK2-STAT3 signaling pathway[81]. The study showed that micheliolide inhibited the growth of GC *in vitro* and *in vivo*, and this effect was related to downregulation expression of IL-6 and thus inhibition of the STAT3 pathway[82]. ALO can inhibit cell proliferation by inhibiting the NOX2-ROS mediated Stat3 signal pathway[77].

Anti-Inflammation related signaling pathways and targets of GC

The occurrence of GC is mostly the result of inflammation, and blocking the inflammatory signaling pathway is essential for the treatment of GC[83]. During GC, continuous activation of NF-κB leads to chronic inflammation and further tumorigenesis. ART and its derivatives can be used to treat GC caused by *H. pylori* infection by downregulating inflammatory factors and inhibiting the NF-κB signaling pathway *in vivo*. The STAT3 signaling pathway plays an important role in the development of inflammation-related GC, and its activation can induce tumors to promote inflammation[84,85]. RA can downregulate the anti-inflammatory factor IL-10 and upregulate pro-inflammatory cytokines such as TNF-α and IL-1β Expression of. Inhibition of IL-6/STAT3 pathway[54].

Inhibition of angiogenesis signaling pathways and targets of GC

Without angiogenesis, it is difficult to achieve large-scale proliferation and invasion of GC cells[86]. Angiogenesis in GC is regulated by a variety of angiogenic or anti-angiogenic factors[87]. For example, VEGF is the most representative promoter of angiogenesis. Currently, it is considered one of the most promising targets for the treatment of GC[88]. Therefore, Weining granules inhibit angiogenesis by downregulating VEGF expression[89]. As an upstream regulator of VEGF, HIF-1α also plays a role in regulating other pro angiogenic factors and anti-angiogenic factors[90,91]. Therefore, the inhibition of HIF-1α and VEGF expression may be the direct reason for GRg3's excellent inhibition of angiogenesis[92].

OTHER MECHANISMS OF ACTION IN THE TREATMENT OF GC

Regulate GC related metabolism

Cancer is usually considered a metabolic disease because cancer cells proliferate rapidly by reprogramming their energy metabolism. Glycolysis is the main mechanism by which GC cells obtain energy[93,94]. Current research has shown that many TCMs can inhibit abnormal metabolic processes. Licochalcone A (Lic A) is an important active

compound extracted from licorice that has anti-inflammatory, antibacterial, antioxidant, antitumor, and other activities. Wu *et al* found that Lic A inhibits glycolysis by blocking the Akt/HK2 pathway. In nature, baicalein mainly exists in Scutellaria baicalensis Georgi and has anti-inflammatory, antibacterial, and other effects. Chen *et al*[95] found that baicalein can inhibit glycolysis by regulating the PTEN/Akt/HIF-1α signaling pathway.

Reverse GC related EMT

In the malignant progression of GC, tumor cells use the process of EMT to change their cell morphology to improve their invasiveness, metastatic ability, and drug resistance[96,97]. Therefore, the inhibition of EMT is a key factor in the treatment of GC. Wang *et al*[98] found that Poria acid can inhibit the EMT process by significantly increasing the expression of E-cadherin and inhibiting the expression of N-cadherin and Vimentin, thereby inhibiting the invasion and metastasis of GC cells. Babaodan (BBD) is a TCM compound that has been used in clinical treatment since the Ming Dynasty, (more than 400 years ago). Modern research has found that Babaodan has significant anti-tumor, anti-inflammatory, immune regulatory effects, as well as other effects. Liu *et al*[99] found that BBD can inhibit the TGF-β/Smad signaling pathway, thereby inhibiting TGF-β-induced EMT.

Improved GC related immune regulation

Compared with other therapies, immunotherapy has the characteristics of lasting remission, improving the quality of life of patients, and prolonging survival[100], which brings new hope to most patients with GC[101]. Modern experimental studies have found that many TCMs regulate immunity and eliminate immune disorders[102]. Oleanolic acid is widely found in many TCMs, such as hawthorns and black plums. Lu *et al*[103] found that OA destroyed IL-1 in GC cells β/NF-κB/TET3 axis, leading to DNA hypomethylation and downregulation of PD-L1. This suggests that OA can be used as an epigenetic modulator in GC immunotherapy. In addition, sophoridine, a monomer

of TCM, regulates immune function and can act on macrophages and $CD8^+$ T cells, thus reshaping the immune microenvironment of GC[104].

Suppress GC related intrusion and migration

The invasion and migration of cancer cells play an important role in tumor metastasis, and distant metastasis of GC is a direct cause of high mortality[105,106]. A variety of Chinese herbal monomers and compounds have been used, including crocin[107], betulinic acid[108], ALO[77], 18 β-glycyrrhetinic acid[109], baicalein[110], and YangZheng Sanjie decoction[111].

Kill Helicobacter pylori

As early as 1994, *H. pylori* was identified as a carcinogen in GC[112]. Currently, it is the first type of carcinogen to be identified in GC. Reducing *H. pylori* infections is an important means of preventing and treating GC[113]. The TCM monomers piperine[114], ART[53] and SC[55] have been proven to have corresponding therapeutic potentials.

CONCLUSION

As early as 40 years ago, GC was recognized as the end result of further development of GPL[115]. Recently, knowledge of the molecular basis of GC and GPL has been accumulating rapidly[116]. However, the molecular mechanism of the transformation from GPL to GC remains unclear[117]. In this study, we reviewed the progress of TCM in treating GPL and GC, while aiming to investigate the potential therapeutic treatment of TCM on the transformation from GPL to GC.

In this review (Tables 1-3, Figure 1), we found that multiple mechanisms of TCM can be identified in the treatment of both GPL and GC. The abnormal activation of the PI3K/ATK, NF-κB, IL-6/STAT3, and HIF-1α/VEGF signaling pathways in both GPL and GC indicated that some pathological changes in GC occurred as early as in the GPL stage. Therefore, in the treatment of GC, secondary prevention should be moved to the GPL stage[118]. According to these studies, active components of TCM, such as

Epigallocatechin Gallate, GRg3, AT-III and AS-IV, showed multiple therapeutic effects on both GPL and GC *via* different targets and signaling pathways. This suggests that these active ingredients may have the therapeutic potential to block the transition from GPL to GC through these targets and signaling pathways. For example, GRg3 has a significant anti-angiogenic effect in both the GPL and GC processes. In the GPL stage, GRg3 can inhibit angiogenesis by downregulating GLUT1 and GLUT4[119], and suppressing the PI3K/Akt/mTOR pathway and downstream HIF-1α[63]. In GC, GRg3 can also reduce HIF-1α, thereby reducing tumor angiogenesis[120]. This has revealed that in the process of progression from GPL to GC, the pro angiogenic effect of HIF-1α may be a theme throughout the two pathological stages. GLUT1, GLUT4, and other proteins may be potential targets for the progression of GPL to GC. In a broader perspective, the existence of the same TCM compound with obvious therapeutic effect both on GPL and GC indicate that "dual effects" in treating GC and its precancerous lesions: when TCM is used to treat GPL, it also eliminates the possibility of GC as a malignant progression.

Many cancers, including GCs, are preceded by precancers. Treating precancers to prevent GC is essential for reducing GC-associated morbidity and mortality. Effective cancer prevention is the best way to stop cancer, and TCM have been shown to be effective in preventing cancer[121]. GRb1, Notoginsenoside R1, AS-IV, GRg3, AT-III, Calycosin, and other active ingredients have shown a variety of therapeutic effects in the treatment of precancerous lesions, including anti-proliferation and apoptosis induction, anti-angiogenesis, inhibition of glycolysis, and anti-inflammatory activities, including PI3K/Akt, Wnt/β-catenin, NF-κB, and STAT3 signaling. Clinically, Chinese herbal medicines containing these active ingredients are often used to treat precancerous lesions, such as ginseng, Panax notoginseng, Atractylodes, Astragalus membranaceus, and Pseudostellariae radix. These TCMs are usually combined to form a TCM compound for the clinical treatment of precancerous lesions, such as WPX, Sancao Tiaowei decoction, and Guiqi Baizhu prescriptions. Interestingly, the mechanisms of action of these active ingredients and TCM prescriptions in the treatment of precancerous lesions are not the same, which suggests that the curative

effects of TCM are not caused by single chemical entities but result from their multi-ingredient prescription[122]. Chinese medicine differs from Western medicine in that many compounds in Chinese medicine act on multiple targets simultaneously, producing significant therapeutic effects[123]. For example, WPX can regulate proliferation and apoptosis by regulating the Wnt/β-catenin and Wnt/GSK3β pathways, playing an anti-angiogenic role by inhibiting the angiogenic factors HIF-1α, VEGF, and ERK1/CylinD1 pathway, and inhibiting glycolysis by regulating the miRNA-34a/PI3K/AkT/mTOR pathway. Interestingly, the Chinese herbal monomers contained in this formula, such as GRb1, AS-IV, AT-III, and Calycosin, can also regulate proliferation, apoptosis, angiogenesis, and glycolysis, and the targets of these monomers from WPX are not exactly same as those of WPX. In this comparison, TCM compounds change the mechanism of action of a single compound through the combination of a variety of TCMs and lead the creation of a new mechanism of action. This feature is precisely an advantage of TCM in treating GPL, as these medicines block its progression to GC, and fill the gap of Western medicine in treating GPL.

Clinical trials are one of the most reliable sources of evidence that guide medical practice. Current western medicine therapy for GPL generally includes the eradication of *H. pylori*, vitamin supplements, and other treatments[10]. However, for patients with advanced GPL, such as the IM stage, whether eradication of *H. pylori* have therapeutic effects remain controversial[124]. Compared with Western medicine, TCM has a curative effect at all stages of GPL. Currently, clinical trials have confirmed that TCM can block the progression of GPL to GC[125,126]. Taking WFC as an example, compared with vitacoenzyme (Vit), the total effective rates of the WFC and Vit groups in alleviating the degree of atrophy were 80.00% and 23.33%, respectively. The total effective rates of relieving IM in the WFC and Vit groups were 73.33% and 26.67%, respectively[16]. Notably, primary outcome measures, such as overall survival and 5-year survival rates, were employed in majority of these trials. These “head-to-head” trials demonstrated the efficacy of TCM in preventing the transformation of GPL to GC. Nevertheless, compared to the various mechanisms of TCM against GPL and GC reported by

experiments, the development of relevant clinical trials is still insufficient. In the future, more attention should be paid to the development of clinical trials of GPL and GC with TCM.

Figure Legends

Figure 1 A diagram of pathway targets of traditional Chinese medicine formulas and compounds for gastric precancerous lesions and gastric cancer. Targets involved in angiogenesis, inflammation, and proliferation and apoptosis were labelled grey, pink, and blue, respectively. Border of targets regulated in gastric precancerous lesions and gastric cancer stage were painted into green and yellow, respectively. The traditional Chinese medicine formulas and compounds regulating each target were labeled as "c" and "f", respectively. Red and green background of "c" and "f" represent up- and down-regulation of the target, respectively. The details of number of these formulas and compounds were shown in Tables 2 and 3. HRAS: Harvey rat sarcoma viral oncogene homolog; HIF-1α: Hypoxia-inducible factor 1α; VEGF: Vascular endothelial growth factor; NF-KB: Noncanonical nuclear factor-kappaB; TNF-α: Tumour necrosis factor alpha; IL: Interleukin.

Table 1 Clinical trials of traditional Chinese medicine in treating gastric cancer and precancerous lesions

Pathological stages	Ref.	Clinical drugs	Clinical sample size	Intervention	Control	Treatment duration	Outcome measures
GPL	Deng *et al*[124], 2012	Weining Granules	120	Weining Granules	Weifuchun tablets	6 mo	Overall response; gastroscopically-determined response; pathologically-confirmed response; eradication of Hp; microvessel density in the gastric mucosa; VEGF; IL-2; IL-6; T lymphocyte subsets; immunoglobulins; symptom scores; QOL; adverse reactions
	Bian *et al*[16], 2021	Weifuchun (WFC)	120	WFC tablets	Vitacoenzyme tablets	6 mo	Histopathology of gastric tissues; intestinal microbiota; sensitivity and specifcity of

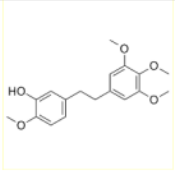
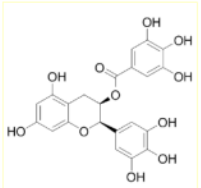
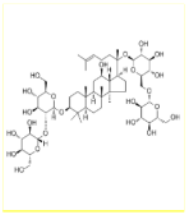
							diferent intestinal microbiota
	Li *et al*[125], 2006	Weiansan (WAS)	76	Weiansan	Weifuchun tablets	24 wk	Inflammation of gastric mucosa; degree of glandular atrophy; IM and dysplasia; Hp infection
	NCT03823248	MoLuoDan and Sanchi powder	480	Moluodan combined with Sanchi powder	Folic acid tablets	24 wk	The disappearance rate of dysplasia; Histopathological score; endoscopic findings score; main symptom score; the patient-reported outcome scale integrals
GC	Pan *et al*[127], 2020	Jianpi Yangzheng Xiaozheng decoction	210	Chemotherapy combined with JPYZXZ decoction	Chemotherapy	24 wk	One-year survival rate; progression-free survival; overall survival; immune related hematology test; objective response rate; tumor makers; TCM

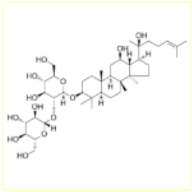
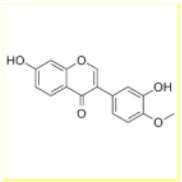
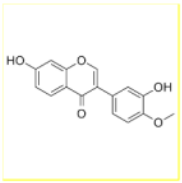
						syndrome points; fatigue scale; QOL scale
Xu *et al*[128], 2013	Wei Chang'An	399	Chemotherapy combined with Wei Chang'An decoction	Continuously	3 mo or more	Survival trends; survival time
Shu *et al* [129], 2019	Yiqi Huayu Jiedu decoction	489	Chemotherapy combined with YHJD	Chemotherapy	6 mo or more	Disease-free survival rate; 5-year survival rate; QOL; TCM symptoms
NCT05229809	Yiqi Wenyang Jiedu prescription	212	Yiqi Wenyang Jiedu prescription	Simulation agent of Yiqi Wenyang Jiedu prescription	24 wk	Two-year disease-free survival rate; disease-free survival; overall survival; cumulative annual recurrence and metastasis rate for 1-3 years; cumulative annual survival rate for 1-3 years; Indexes related to fat

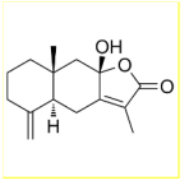
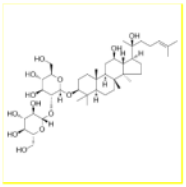
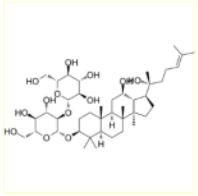
		distribution; visceral adiposity Index; tumor marker; peripheral blood inflammatory index; prognostic nutritional index; QOL of the patient; evaluation of the patient's symptoms; medication compliance; percentage of participants with adverse events

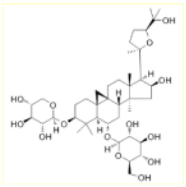
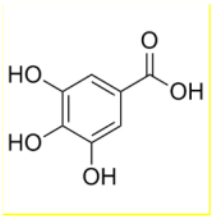
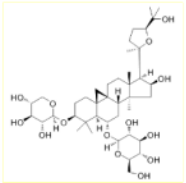
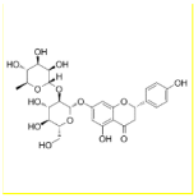
GPL: Gastric precancerous lesions; GC: Gastric cancer; WFC: Weifuchun; WAS: Weiansan; TCM: Traditional Chinese medicine; QOL: Quality of life; VEGF: Vascular endothelial growth factor.

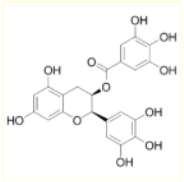
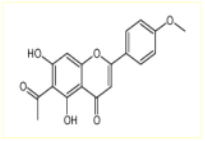
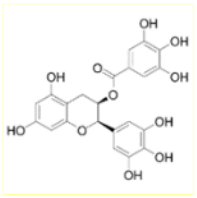
Table 2 ***In vitro*** **and** ***in vivo*** **protective effects of active components of Chinese herbal medicine on gastric precancerous lesions and gastric cancer**

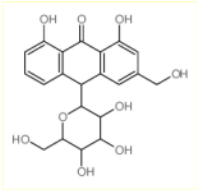
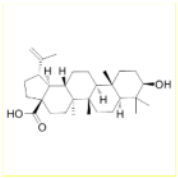
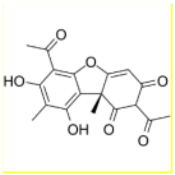
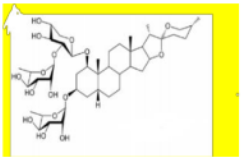
Pathological stages	Effect	No.	Ref.	Active component	Structure	Animal/cells	Pathways/targets
Gastric precancerous lesions (GPL)	Anti-proliferation inducing apoptosis	c1	Wang *et al*[37], 2021	Erianin		GES-1 cell	HRAS-PI3K-Akt↓; p-Gsk3β, MDM2, p21, CyclinD1↓
		c2	Zhu *et al*[38], 2021	Epigallocatechin gallate		Male Wistar rats, PLGC model	PI3K/Akt/mTOR↓ PTEN↑; PI3K, Akt, mTOR↓
		c3	Zeng *et al*[33], 2021	Ginsenoside Rb1		Sprague-Dawley rats, PLGC model	β-catenin/TCF4↓; c-myc, cyclin, Birc5↓

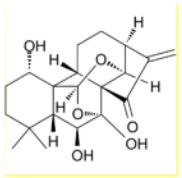
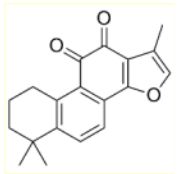
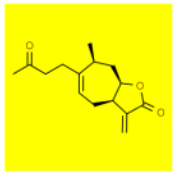
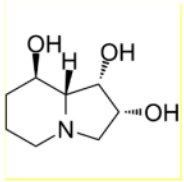
	c4	Lv *et al*[130], 2022	Ginsenoside Rg3		Male Sprague-Dawley rats, PLGC model GPL cell	TIGAR, G6PDH, NADP, GSH↓; ROS↑
Anti-inflammatory	c5	Liu *et al*[50], 2020	Calycosin		Male (SD) rats, PLGC model	Integrinβ1/NF-κB/DARPP-32; Integrinβ1, NF-κB, DARPP-32↑; STAT3↓
Anti-angiogenesis	c5	Liu *et al*[50], 2020	Calycosin		Male (SD) rats, PLGC model	Integrinβ1/NF-κB/DARPP-32; Integrinβ1, NF-κB, DARPP-32↑; STAT3↓

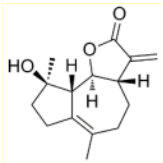
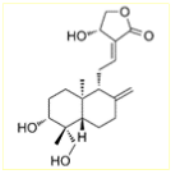
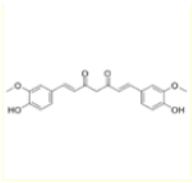
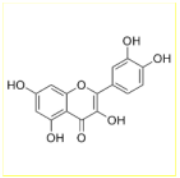
	c6	Gao *et al*[58], 2022	Atractylenolide III		female SD rats, Gastric Precancerous, Lesions Model	HIF-1α, VEGF-A, DLL4↓
	c4	Zeng *et al*[119], 2022	Ginsenoside Rg3		Male Sprague Dawley rats, PLGC model AGS cell, HGC-27 cell	GLUT1, GLUT4↓
Inhibit glycolysis	c4	Liu *et al*[63], 2020	Ginsenoside Rg3		Male Atp4a/ C57Bl/6 mice, PLGC model	PI3K/Akt/mTOR↓; PI3K/Akt/miRNA-21↓; PI3K, AKT, mTOR, HIF-1α, miRNA-21↓; caspase-3↑

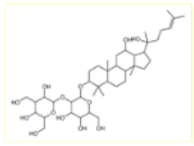
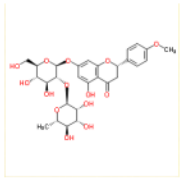
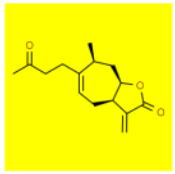
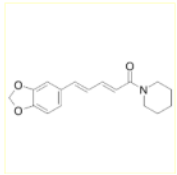
		c7	Zhang *et al*[65], 2018	Astragaloside IV		Male Sprague-Dawley rats, PLGC model	LDHA, MCT1, MCT4, HIF-1α, CD147, TIGAR↓; miRNA-34a, p53↑
	Improvement of EMT	C8	Liao *et al*[68], 2023	Gallic acid		GES-1 cell, MC cells	Wnt/β-catenin↓
	Induce autophagy	c7	Cai *et al*[44], 2018	Astragaloside IV		Sprague Dawley rats, PLGC model	Bcl-2/Bax, p53, Beclin1, p62, ATG5, ATG12↓; caspase3↑
GC	Anti-proliferation inducing apoptosis	c9	Xu *et al*[74], 2021	Naringin		SNU-1 cell, GES-1 cell	PI3K/Akt↓; PI3K, Akt, Bcl2↓; caspase 3, Bax↑

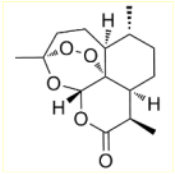
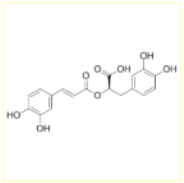
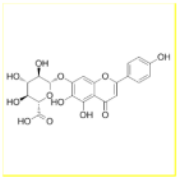
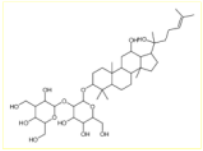
c10	Yang *et al*[131], 2016	Epigallocatechin-3-gallate		SGC-7901 cells, Nude mouse tumour xenograft model	Wnt/β-catenin↓; GSK3b, β-catenin↓
c11	Lee *et al*[75], 2018	Pectolinarigenin		AGS cell, MKN28 cell	PI3K/Akt/mTOR↓; PI3K, p-Akt, mTOR, p-p70S6K, p-4EBP1↓
c10	Fu *et al*[132], 2019	Epigallocatechin-3-gallate		SGC7901 cell	VEGF, HIF-1α↓

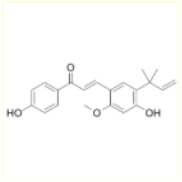
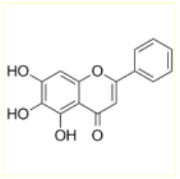
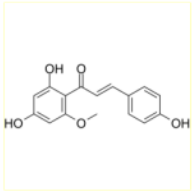
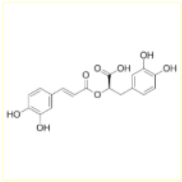
c12	Wang *et al*[77], 2020	Aloin		HGC-27 cell, BGC-823 cell	Akt/mTOR, Stat3, NF-κB↓; NOX2, ROS, Akt, mTOR, Stat3, IκBα, p65↓
c13	Chen *et al*[108], 2020	Betulinic acid		BGC-823 cells, MNK45 cells	NF-κB, VASP↓
c14	Geng *et al*[133], 2018	Usnic acid		BGC823 cell, SGC7901 cell	Bax, LC3-II↑; Bcl-2, p62↓
c15	Xu *et al*[134], 2020	T-17		SGC-7901, AGS cell, MGC-803 cell, BGC-823 cell, NCI-N87 cell,HUVEC	JNK, Bcl-2↑

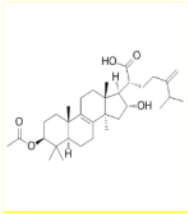
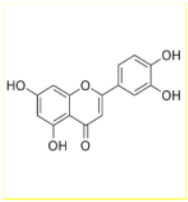
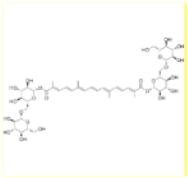
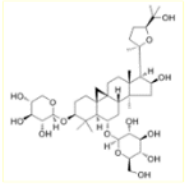
				cell	
c16	Liu *et al*[81], 2015	Ponicidin		MKN28 cell	JAK2/STAT3↓; Bcl-2, VEGF, VEGFR2, JAK2 STAT3↓; Bax, caspase-3↑
c17	Chen *et al*[135], 2012	Tanshinone IIA		MKN45 cell, SGC7901 cell	cyto-c, Bax, Caspase-9↑; Bcl-2↓
c18	Yang *et al*[52], 2020	Tomentosin		GCCs cell, AGS cell	IL-6, TNF-α, IL-1, IL-8, Bcl-2↓; Bax↑
c19	Sun *et al*[136], 2007	Swainsonine		SGC-7901 cell, BALB/c nu/nu mice, GC model	p53, Bcl-2↓; cmyc↑

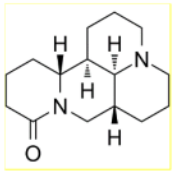
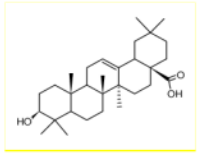
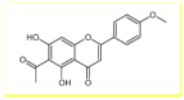
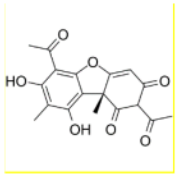
c20	Tang *et al*[82], 2019	Micheliolide		AGS cell, N87 cell	IL-6, STAT3, cyclinD1, Mcl-1, MMP-2↓
c21	Li *et al*[137], 2013	Andrographolide		BGC-823 cell	Bax, caspasase-3↑; Bcl-2↓
c22	Liu *et al*[138], 2016	Curcumin		SGC7901 cell, GES-1 cell	c-Myc/H19↓; c-Myc, H19↓; p53↑
c23	Lee *et al*[139], 2016	Quercetin		NOD/SCID mice, PLGC model SNU719 cell, MKN74 cells	p53, p21, Bax, Puma, caspase-3, caspase-9, PARP↑

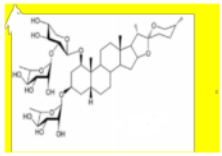
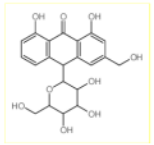
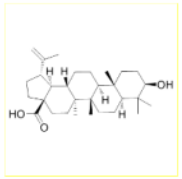
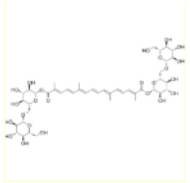
		c4	Aziz *et al*[120], 2016	Ginsenoside Rg3		SGC-7901 cell	caspases-3, caspase-8, caspase-9, PARP, SP1↑; HSF1, FUT4↓
		c24	Saralamma *et al*[140], 2015	Poncirin		AGS cells	Fasl, caspase-8, caspase-3, PARP↑
	Anti-inflammatory	c18	Yang *et al*[52], 2020	Tomentosin		GCCs cell, AGS cell	IL-6, TNF-α, IL-1, IL-8, Bcl-2↓; Bax↑
		c25	Tharmalingam *et al*[114], 2016	Piperine		AGS cell	β-catenin, IL-8↓

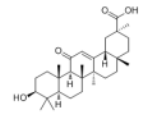
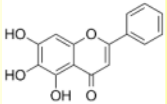
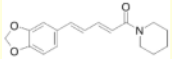
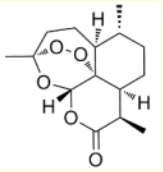
		c26	Su *et al*[53], 2019	Artemisinin		SGC-7901 cell, GES-1 cells, C57BL/6 J mice	NF-κB↓; IL-8, IL-6, TNF-α, IL-1β, COX-2, p-IκBα↓; IκBα↑
		c27	Han *et al*[54], 2015	Rosmarinic acid		MKN45 cell	IL-6/STAT3↓; IL-6, IL-1β, TNF-α, TNFsR-1, HIF-1α, miRNA-155-5p↓; IL-10↑
		c28	Sun and Meng[55], 2022	Scutellarin		AGS cell, albino Wistar rats, GC modelr	TNF-α, IL-1β, IL-2↓
	Anti-angiogenesis	c4	Li and Qu[89], 2019	Ginsenoside Rg3		BGC823 cell	HIF 1α, VEGF↓

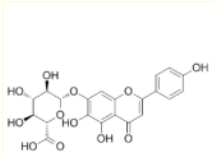
Inhibit glycolysis	C29	Wu *et al*[141], 2018	Licochalcone A		MKN45 cell, SGC7901cell, GES-1 cell	Akt/HK2↓; Akt, HK2↓
	C30	Chen *et al*[95], 2015	Baicalein		AGS cell	PTEN/Akt/HIF-1α↓; HK2, LDH-A, PDK1,Akt, HIF-1α↓; PTEN↑
	C31	Wang *et al*[142], 2021	Helichrysetin		MGC803 cell, HCT-8 cell	mTOR/p70S6K/c-Myc/PDHK1↓; mTOR/p70S6K, c-Myc, PDHK1↓
	C27	Han *et al*[54], 2015	Rosmarinic acid		MKN45 cell	IL-6/STAT3↓; IL-6, IL-1β, TNF-α, TNFsR-1, HIF-1α, miRNA-155-5p↓; IL-10↑

Improvement of EMT	C32	Wang *et al*[98], 2022	Poria acid		AGS cell, MKN-28 cell	E-cadherin↑; N-cadherin, Vimentin↓
	C33	Zang *et al*[143], 2017	Luteolin		NCI-N87 cell, MKN28 cell, Hs-746T cell	E-cadherin↑; N-cadherin, vimentin, Snail↓
	c34	Zhou *et al*[107], 2019	Crocin		AGS cell, HGC-27 cell, GES-1 cell	miR-320/KLF5/HIF-1α; KLF5/HIF-1α; KLF5, HIF-1α↓; miR-320↑
	c7	Zhu and Wen, 2020[144], 2020	Astragaloside IV		BGC-823 cell, MKN-74 cell, GES-1 cell	PI3K/Akt/NF-κB↓; TGF-β1↓

Regulate immune function	c35	Zhuang *et al*[104], 2020	Sophoridine		MFC cell, RAW264.7 cell	iNOS, IFN-β, IL-12α, Granzyme-B, TNF-α, Perforin↑; Arg-1, CD206, IL-10, PD-1, Tim-3, Lag-3, CCR2↓
	C36	Lu *et al*, 2020[103]	Oleanolic acid		MKN-45, Jurkat T cell	IL-1β/ NF-κB /TET3↓; PD-L1↓
Induce autophagy	c11	Lee *et al*, 2018[75]	Pectolinarigenin		AGS cell, MKN28 cell	PI3K/Akt/mTOR↓; PI3K, p-Akt, mTOR, mTOR, p-p70S6K, p-4EBP1↓
	c14	Geng *et al*[133], 2018	Usnic acid		BGC823 cell, SGC7901 cell	Bax, LC3-II↑; Bcl-2, p62↓

	c15	Xu *et al*[134], 2020	T-17		SGC-7901, AGS, MGC-803, BGC-823, NCI-N87, HUVEC cell	JNK, Bcl-2↑
Inhibits migration, and invasion	c12	Wang *et al*[77], 2020	Aloin		HGC-27 cell, BGC-823 cell	Akt/mTOR, Stat3, NF-κB↓; NOX2, ROS, Akt, mTOR, Stat3, IκBα, p65↓
	c13	Chen *et al* [108] , 2020	Betulinic acid		BGC-823 cells, MNK45 cells	NF-κB, VASP↓
	c34	Zhou *et al*[107], 2019	Crocin		AGS cell, HGC-27 cell, GES-1 cell	miR-320/KLF5/HIF-1α; KLF5/HIF-1α; KLF5, HIF-1α↓;

						miR-320↑
		c37	Cai *et al*[109], 2018	18β-glycyrrhetinic acid		SGC-7901 cell	ROS/PKC-α/ERK↓; ROS, PKC-α, ERK↓
		c30	Yan *et al*[110], 2015	Baicalein		SGC7901 Cell, MGC803 cell	MMP-2, mmp-9, p38↓
	Anti-helicobacter pylori	c25	Tharmalingam *et al*[114], 2016	Piperine		AGS cell lines	β-catenin, IL-8↓
		c26	Su *et al*[53], 2019	Artemisinin		SGC-7901 cell, GES-1 cells	NF-κB↓; IL-8, IL-6, TNF-α, IL-1β, COX-2, p-IκBα↓; IκBα↑

c28	Sun and Meng[55], 2022	Scutellarin		(AGS) cell, albino Wistar rats, GC model	TNF-α, IL-1β, IL-2↓

GPL: Gastric precancerous lesions; GC: Gastric cancer; EMT: Epithelial-mesenchymal transformation; NF-KB: Noncanonical nuclear factor-kappaB; TNF-α: Tumour necrosis factor alpha; IL: Interleukin; HIF-1α: Hypoxia-inducible factor 1α.

Table 3 ***In vitro*** **and** ***in vivo*** **protective effects of Chinese herbal compound on gastric precancerous lesions and gastric cancer**

Pathological stages	Effect	No.	Ref.	Formulas	Main component	Animal/cells	Pathways/targets
GPL	Anti-proliferation inducing apoptosis	fa	Zeng *et al*[31], 2016	Weipixiao (WPX)	Radix Astragali, Radix Pseudostellariae, Rhizoma Atractylodis Macrocephalae, Radix Salviae Miltiorrhiz, Herba Hedyotis Diffusae	Male Sprague Dawley (SD) rats, PLGC model	Wnt/β-catenin↓; Lgr5, MMP-7, Wnt1, β-catenin↓
		fa	Zeng *et al*[145], 2018	Weipixiao (WPX)	Astragalus Membranaceus,Pseudostellaria Heterophylla, Atractylodis Macrocephalae,Curcuma zedoaria, Salvia Miltiorrhiza and Hedyotis Diffusa Willd	Male Sprague-Dawley (SD) rats, PLGC model	Wnt/GSK3β; GSK3β↑; C-myc↓
		fb	Yin *et al*[29], 2019	Weiqi decoction (WQD)	Radix Angelicae Sinensis, Radix Astragali, Radix Codonopsis, Rhizoma Curcumae, Fructus Aurantii, Fructus Akebiae and	Male Wistar rats, CAG with Precancerous	PGE2, caspase 3↑; Ki67, HIF-1, COX-2, VEGF, VEGFR1↓

				Herba Taraxaci	Lesion Mode	
fc	Cai *et al*[146], 2022		Sancao Tiaowei Decoction	Pseudostellariae Radix, stirbaked Atractylodis Macrocephalae Rhizoma inbran, Poria, Agrimoniae Herba, Taraxaci Herba, Hedyotis Diffusa Willd, Salviae Miltiorrhizae Radix Etrhizoma, Curcumae Rhizoma and Glycyrrhizae Radix Et Rhizoma	SD male rats, PLGC model	Hh signaling↓; Shh, Gli-1, Smo, cyclinD1, CDKN2A/p16INK4a, NF-kBP65↓; Ptch↑
fd	Hao *et al*[147], 2022		Huazhuoji edu decoction	Artemisia capillaris Thunb, Scutellaria baicalensis Georgi, Oldenlandia diffusa Roxb, Isatis indigotica Fortune, Lobelia chinensis Lour, Pogostemon cablinBenth, Scutellaria barbata D. Don, Sophora flavescens Aiton, Coptis chinensis Franch,	Male Sprague-Dawley (SD) rats, PLGC model	lnc517368↓

				Gynostemma pentaphyllum Makino, and Eupatorium fortunei Turcz		
	fe	Xu *et al*[148], 2018	Xiao Tan He Wei Decoction	radix bupleuri, processed rhizomapinelliae, poriacocos, coptischinensis, oldenlandiadiffusa, dandelion,cassia twig, rhubarb, radix paeoniae alba, radix glycyrrhizae preparata	GES-1 cell, Wistar rats, PLGC rat animal models	Bax, caspase-3↑; Bcl-2, NF-kB↓
	ff	Shen *et al*[149], 2008	Jinguo Weikang Capsule (JWC)	tinospora root, trifoliate-orange Immature fruit, kaempfer dutchmanspipe root	SD rats, PLGC model	H-ras, EGFR, P53, c-myc↓
Anti-inflammatory	fb	Yin *et al*[29], 2019	Weiqi decoction (WQD)	Radix Angelicae Sinensis, Radix Astragali, Radix Codonopsis, Rhizoma Curcumae, Fructus Aurantii, Fructus Akebiae, and	Male Wistar rats, CAG with Precancerous	PGE2, caspase 3↑; Ki67, HIF-1, COX-2, VEGF,VEGFR1↓

				Herba Taraxaci	Lesion Mode	
	fg	Deng *et al*[125], 2012	Weining granule	Radix Astragali Mongolici, Herba Hedyotdis, Rhizoma Curcumae Phaeocau, Fructus Lycii	Male Wistar rats, PLGC model	VEGF, IL-6, IgG↓; $CD4^+$, $CD4^+/CD8^+$, IL-2↑
Anti-angiogenesis	fb	Yin *et al*[29], 2019	Weiqi decoction (WQD)	Radix Angelicae Sinensis, Radix Astragali, Radix Codonopsis, Rhizoma Curcumae, Fructus Aurantii, Fructus Akebiae, and Herba Taraxaci	Male Wistar rats, CAG with Precancerous Lesion Mode	PGE2, caspase 3↑; Ki67, HIF-1, COX-2, VEGF,VEGFR1↓
	fa	Zeng *et al*[59], 2018	Weipixiao (WPX)	Astragalus Membranaceus, Pseudostellaria Heterophylla, Atractylodis Macrocephalae, Curcuma zedoaria, Salvia Miltiorrhiza and Hedyotis Diffusa Willd.	Male Sprague-Dawley rats, PLGC model	ERK1/CylinD1; HIF-1α, VEGF, ERK1, CylinD1↓
	fh	Wang *et al*[150], 2020	Jinlongshe (JLS)	Rhizoma Pinelliae, Radix, Rhizome Arisaemat, Glycyrrhizaepreparata, corium stomachiumgalli, *etc*.	Male Sprague-Dawley (SD)	Apelin, CD34↓

					rats, PLGC model	
Protecting gastric mucosa	fi	Yi *et al*[151], 2022	Elian granules	Curcumae Rhizoma, Salviae Miltiorrhizae Radix et Rhizoma, Angelicae Sinensis, Diels, Coptidis Rhizoma, Hedyotis Diffusa, Codonopsis Radix, Atractylodis Macrocephalae Rhizoma, Glycyrrhizae Radix et Rhizoma, Pinelliae Rhizoma, Citri Reticulatae Pericarpium, Poria	male Sprague Dawley (SD) rats, PLGC model	MAPK; JNK, p38↑
	fj	Wang *et al*[32], 2020	WeiFuChun (WFC)	Radix Ginseng Rubra (red ginseng), Rabdosia amethystoides H. Hara, and fried Fructus Aurantii.	Male Sprague-Dawley rats, PLGC model	MAPK; VEGF, FOXO4, AKT, TP53, FAS, MAPK8, MAPK11, MAPK14↓
Inhibit glycolysis	fa	Cai *et al*[64], 2019	Weipixiao (WPX)	Astragalus, Radix Pseudostellariae, Atractylodes macrocephala, Salvia	Male Sprague-	miRNA-34a/PI3K/AKT/Mt

				miltiorrhiza Bge, Oldenlandia diffusa(Willd.)Roxb.	Dawley (SD) rats, PLGC model	or; LDHA, CD147, MCT4, PI3K, AKT, mTOR, HIF-1α, miRNA-34a↓
	fk	Liu *et al*[152], 2019	Weipiling (WPL)	Hedysarum multijugum Maxim, Pseudostellaria heterophylla Pax, Atractylodes macrocephala Koidz, Poria cocos Wolf, Panax notoginseng F.H. Chen, Curcuma zedoaria, Roscoe,Hedyotis diffusa Willd,Hericium erinaceus Pers	Male Atp4a-/-C57Bl/6 mice	mTOR/HIF-1α↓; CDX2, MUC2, ki-67, PTEN and p53, mTOR, HIF-1a, AMPK↓; TSC1, TSC2↑
Improvement of EMT	fl	Li *et al*[69], 2022	Manpixiao decoction	heterophylla falsestarwort root, root of red rooted salvia, drug solomonseal, common perilla stem, largehead atractylodes rhizome, corydalis ambigua, japanese apricot fruit, citron, rose, villous amomum fruit, spreading hedyotis	Wistar male rats, PLGC model	EGFR-PI3K-AKT↓; EGFR, β-catenin,N-cadherin protein↓

					herb, liquorice		
GC	Anti-proliferation inducing apoptosis	fm	He *et al*[76], 2020	Weifufang	Astragalus, Codonopsis pilosula, Atractylodes macrocephala, Poria cocos, Nutgrass Galingale Rhizome, Radix Curcumae, Sappan Wood, Rhizoma Curcumae, Zaoxiu Paris Root Rhizoma Paridis, Barbed Skullcap Herb, Ligustrum lucidum, South Dodder Seed, Oldenlandia, Liquorice Root,Chicken's Gizzard-membrane, fry malt, and fry Rice-grain Sprout	BALB/c-nu nude mice, BGC-823 cell, Nude mice with xenografts	PTEN↑
		fn	Fang *et al*[153], 2021	Huosu Yangwei (HSYW)	Huoxiang, Zisugeng, Baizhu, Zhike, Doukou, Foshou, Wumei, Shengjiang, Dazao, Gancao,	Male Balb/c mice, PLGC model	DNAJB4, CALD1, AKR1C1, CST1, CASP1, PREX1, SOCS3, PRDM1

					24 Huangqi, Dihuang, Mudanpi, Tianhuafen, Danggui, Chuanxiong, Ezhu, Gouqizi, Huanglian, Dangsheng, and Pugongying		
		fo	Yuan *et al*[154], 2020	Jianpi Yangzheng Xiaozheng (JPYZXZ) decoction	Radix astragali, Radix codonopsis pilosulae, Rhizoma Sparganiiand Rhizoma Curcumae	HGC-27 cells ,THP-1 cell, MFC cell	PI3Kγ, NF-κB, AKT, p-C/EBPβ, IL-10↓; IL-1β, TNF-α, IL-12p↑
		fg	Deng *et al*[92], 2019	Weining granule	Radix Astragali Mongolici and Herba Hedyotdis Rhizoma Curcumae Phaeocaulis,Fructus Lycii	male Wistar rats, PLGC model	Bcl-2, VEGF↓; caspase-3, PTEN↑
	Anti-inflammatory	fp	Li *et al*[155], 2021	Guiqi Baizhu prescription	Astragali radix, Atractylodis macrocephalae, Angelicae,Paeoniae radix alba, Pericarpium citri reticulatae,	MKN-45 cell, SGC-7901 cell, BGC-823 cell, GES-	HER2, PD-L1↑

				Rhubarb, Glycyrrhizae	1cell	
Anti-angiogenesis	fg	Deng *et al*[92], 2019	Weining granule	Radix Astragali Mongolici and Herba Hedyotdis Rhizoma Curcumae Phaeocaulis, Fructus Lycii	Male Wistar rats, PLGC model	Bcl-2, VEGF↓; caspase-3, PTEN↑
Improvement of EMT	fq	Liu *et al*[99], 2020	Babao Dan	natural bezoar, snake gall, antelope horn, pearl, musk, and Panax notoginseng	AGS cell, MGC803 cell	TGF-b/Smad↓; TGF-b1, p-Smad2/3↓
	fo	Yuan *et al*[154], 2020	Jianpi Yangzheng Xiaozheng (JPYZXZ) decoction	Radix astragali, Radix codonopsis pilosulae, Rhizoma Sparganiiand Rhizoma Curcumae	HGC-27 cells, THP-1 cell, MFC cell	PI3Kγ, NF-κB, AKT, p-C/EBPβ, IL-10↓; IL-1β, TNF-α, IL-12p↑
Inhibits migration, and invasion	fr	Chen *et al*[111], 2018	Yangzheng Sanjie Decoction (YZSJD)	Astragali Radix, Scutellariae Barbatae Herba, Arisaematis Rhizoma Preparatum, Citri Sarcodactylis	MKN-45 cell	EGFR, miR7↑

	Fructus, Cremastrae Pseudobulbus and Curcumae Longae Rhizoma

GPL: Gastric precancerous lesions; GC: Gastric cancer; EMT: Epithelial-mesenchymal transformation; NF-KB: Noncanonical nuclear factor-kappaB.

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