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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

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**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](#_ENREF_1" \o "Sung, 2021 #7)]. The direct cause of high mortality in GC is that early GC may occur without any specific symptoms and cannot be treated promptly[[2](#_ENREF_2" \o "Zhang, 2014 #98)]. Therefore, it is particularly importantto prevent GC in early stage[[3](#_ENREF_3" \o "Shin, 2015 #8)]. In the 19th century, Virchow proposed “the origin of cancer as a site of chronic inflammation”[[4](#_ENREF_4" \o "Coussens, 2002 #99)]. 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](#_ENREF_5)]. IM and GED are the main pathological stages of gastric precancerous lesions (GPL)[[6](#_ENREF_6" \o "You, 1999 #19)]. 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](#_ENREF_7),[8](#_ENREF_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](#_ENREF_9" \o "Zhao, 2016 #12)]. The only therapeutic treatment, endoscopic mucosal dissection, is applicable to cases of severe dysplasia and early GC[[10](#_ENREF_10" \o "Pimentel-Nunes, 2019 #151)]. *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](#_ENREF_11" \o "Dawsey, 2014 #14)].

Inflammation, angiogenesis, and proliferation are the three most important histological features of the transformation from GPL to GC[[12-14](#_ENREF_12" \o "Balkwill, 2001 #130)]. Chronic inflammation is the core driver of GC[[15](#_ENREF_15),[16](#_ENREF_16)]. Inflammation promotes angiogenesis, and its progression depends on the speed of angiogenesis[[17](#_ENREF_17),[18](#_ENREF_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](#_ENREF_19" \o "Schetter, 2010 #91)]. Moreover, the microenvironment created by tumors can promote further proliferation of inflammatory cells[[20](#_ENREF_20" \o "Mantovani, 2008 #103)]. Angiogenesis can also promote the proliferation of tumor cells[[21](#_ENREF_21" \o "Folkman, 2002 #104)]. 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](#_ENREF_22" \o "Carmeliet, 2011 #105)]. 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](#_ENREF_23" \o "Cao, 2009 #92)]. Clinically, tumor angiogenesis is believed to be directly proportional to tumor malignancy[[24](#_ENREF_24" \o "Jiang, 2020 #93)]. 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](#_ENREF_25),[26](#_ENREF_26)] and GC[[27](#_ENREF_27),[28](#_ENREF_28)]. Currently, a variety of traditional Chinese patent medicines, such as the Weiqi decoction[[29](#_ENREF_29)], WeiFuChun (WFC)[[30](#_ENREF_30)], and Weipixiao (WPX)[[31](#_ENREF_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](#_ENREF_16" \o "Bian, 2021 #140)]. 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](https://clinicaltrials.gov/ct2/show/NCT03823248?term=MoLuoDan&cond=gastric+precancerous+lesions&draw=2&rank=1)) and Yiqi Wenyang Jiedu decoction ([NCT05229809](https://clinicaltrials.gov/ct2/show/NCT05229809?term=Yiqi+Wenyang&cond=gastric+carcinoma&draw=2&rank=1)).

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](#_ENREF_32" \o "Wang, 2020 #13)]. 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](#_ENREF_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](#_ENREF_34" \o "Brenes, 1993 #21)]. 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](#_ENREF_35" \o "Zhang, 2017 #41)]. 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](#_ENREF_36" \o "Bonizzi, 2019 #23)]. 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](#_ENREF_37" \o "Wang, 2021 #18)] 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](#_ENREF_38" \o "Zhu, 2021 #95)] 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](#_ENREF_39" \o "Silva-García, 2019 #48)]. 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](#_ENREF_40),[41](#_ENREF_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](#_ENREF_42" \o "Chen, 2016 #119)]. Current research shows that promoting autophagy in the early stages of tumorigenesis has a positive significance in cancer treatment[[43](#_ENREF_43" \o "Zhao, 2020 #121)]. The Chinese medicine monomer, Astragaloside IV (As-IV), regulates autophagy by mediating the Ambra1/Beclin1 complex[[44](#_ENREF_44" \o "Cai, 2018 #28)].

***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](#_ENREF_45),[46](#_ENREF_46)]. As one of the most important signaling pathways in the inflammatory response[[47](#_ENREF_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](#_ENREF_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](#_ENREF_49)]. Calycosin may play an anti-inflammatory role by regulating the integrin β1/NF-κB/DARPP-32 pathway and downregulating STAT3 expression[[50](#_ENREF_50" \o "Liu, 2020 #40)]. 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](#_ENREF_51)]; therefore, WQD can play an anti-inflammatory role by inhibiting the HIF-1 signaling pathway[[29](#_ENREF_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](#_ENREF_52)], artemisinin (ART)[[53](#_ENREF_53)], rosmarinic acid (RA)[[54](#_ENREF_54)], scutellarin (SC)[[55](#_ENREF_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](#_ENREF_56),[57](#_ENREF_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](#_ENREF_58" \o "Gao, 2022 #14)]. Both atractylenolide III (ATIII)[[58](#_ENREF_58)] and WPX[[59](#_ENREF_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](#_ENREF_60" \o "Kroemer, 2008 #145)]. In contrast to normal cells, GC cells preferentially choose glycolysis as the main way to obtain energy, even under conditions of sufficient oxygen[[61](#_ENREF_61" \o "Flaveny, 2015 #144)]. The rapid proliferation of GC cells depends largely on glycolysis[[62](#_ENREF_62" \o "Hirayama, 2009 #118)]. 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](#_ENREF_63" \o "Liu, 2020 #80)]. Ginsenoside Rg3 (GRg3) blocks glycolysis by inhibiting the PI3K/AKT pathway and downregulating downstream miRNA-21[[63](#_ENREF_63)], whereas WPX inhibits the PI3K/AKT/mTOR pathway by upregulating upstream miRNA-34a, and then blocks glycolysis[[64](#_ENREF_64)]. Interestingly, both WPX and As-IV can regulate LDHA, MCT4, HIF-1α, and CD147 targets inhibits glycolysis[[65](#_ENREF_65" \o "Zhang, 2018 #29)].

***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](#_ENREF_66" \o "Dongre, 2019 #149)]. 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](#_ENREF_67" \o "Roussos, 2010 #150)]. 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](#_ENREF_68" \o "Liao, 2022 #148)] 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](#_ENREF_69" \o "Li, 2022 #147)] 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](#_ENREF_70" \o "Galluzzi, 2018 #115)]. Therefore, regulating the proliferation and apoptosis of GC cells is an important therapeutic strategy for preventing GC progression[[71](#_ENREF_71" \o "Tao, 2019 #116)]. In GC, the PI3K/AKT/mTOR pathway is often activated, and this pathway plays a role in promoting cancer progression[[72](#_ENREF_72" \o "Ohtsu, 2013 #22)]. Multiple targets of this pathway have been shown to be mutated or otherwise dysregulated during tumorigenesis[[73](#_ENREF_73" \o "Will, 2014 #42)]. Naringin and pectinarigenin (PEC) can inhibit the PI3K/Akt signaling pathway, and PEC can also inhibit downstream mTOR[74,[75](#_ENREF_75)]. Weifufang promoted the upregulation of PTEN and inhibited the PI3K/Akt signaling pathway[[76](#_ENREF_76" \o "He, 2020 #56)]. Aloin (ALO) inhibits the Akt/mTOR signaling pathway mediated by NOX2-ROS[[77](#_ENREF_77" \o "Wang, 2020 #67)]. 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](#_ENREF_78),[79](#_ENREF_79)]. Therefore, dysregulation of the STAT3 signaling pathway is common in GC[[80](#_ENREF_80" \o "Piao, 2020 #70)]. Ponicidin can induce apoptosis in MKN28 cells, which may be related to the inhibition of the VEGFR2-mediated JAK2-STAT3 signaling pathway[[81](#_ENREF_81" \o "Liu, 2015 #44)]. 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](#_ENREF_82" \o "Tang, 2019 #41)]. ALO can inhibit cell proliferation by inhibiting the NOX2-ROS mediated Stat3 signal pathway[[77](#_ENREF_77" \o "Wang, 2020 #67)].

***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](#_ENREF_83" \o "Crone, 2012 #74)]. 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](#_ENREF_84),[85](#_ENREF_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](#_ENREF_54" \o "Han, 2015 #73)].

***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](#_ENREF_86" \o "Tang, 2016 #81)]. Angiogenesis in GC is regulated by a variety of angiogenic or anti-angiogenic factors[[87](#_ENREF_87" \o "Xu, 2017 #82)]. 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](#_ENREF_88" \o "Yang, 2014 #83)]. Therefore, Weining granules inhibit angiogenesis by downregulating VEGF expression[[89](#_ENREF_89" \o "Li, 2019 #64)]. As an upstream regulator of VEGF, HIF-1α also plays a role in regulating other pro angiogenic factors and anti-angiogenic factors[[90](#_ENREF_90),[91](#_ENREF_91)]. Therefore, the inhibition of HIF-1α and VEGF expression may be the direct reason for GRg3’s excellent inhibition of angiogenesis[[92](#_ENREF_92" \o "Deng, 2019 #33)].

**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](#_ENREF_93),[94](#_ENREF_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*[95] 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*[[9](#_ENREF_95" \o "Chen, 2015 #125)6] 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[[9](#_ENREF_96)7,[9](#_ENREF_97)8]. Therefore, the inhibition of EMT is a key factor in the treatment of GC. Wang *et al*[[9](#_ENREF_98" \o "Wang, 2022 #119)9] 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*[[1](#_ENREF_99" \o "Liu, 2020 #117)00] 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[[10](#_ENREF_100)1], which brings new hope to most patients with GC[[10](#_ENREF_101)2]. Modern experimental studies have found that many TCMs regulate immunity and eliminate immune disorders[[10](#_ENREF_102" \o "Zhang, 2020 #133)3]. Oleanolic acid is widely found in many TCMs, such as hawthorns and black plums. Lu *et al*[[10](#_ENREF_103" \o "Lu, 2020 #130)4] 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[[10](#_ENREF_104" \o "Zhuang, 2020 #56)5].

***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[[10](#_ENREF_105)6,[10](#_ENREF_106)7]. A variety of Chinese herbal monomers and compounds have been used, including crocin[[10](#_ENREF_107)8], betulinic acid[[10](#_ENREF_108)9], ALO[[77](#_ENREF_77)], 18 β-glycyrrhetinic acid[[1](#_ENREF_109)10], baicalein[[11](#_ENREF_110)1], and YangZheng Sanjie decoction[[11](#_ENREF_111)2].

***Kill Helicobacter pylori***

As early as 1994, *H. pylori* was identified as a carcinogen in GC[[11](#_ENREF_112" \o ", 1994 #124)3]. 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[[11](#_ENREF_113" \o "Stoffel, 2015 #125)4]. The TCM monomers piperine[[11](#_ENREF_114)5], ART[[53](#_ENREF_53)] and SC[[55](#_ENREF_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[[11](#_ENREF_115" \o "Correa, 1975 #128)6]. Recently, knowledge of the molecular basis of GC and GPL has been accumulating rapidly[[11](#_ENREF_116" \o "Koulis, 2019 #97)7]. However, the molecular mechanism of the transformation from GPL to GC remains unclear[[11](#_ENREF_117" \o "Yuasa, 2003 #101)8]. 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[[11](#_ENREF_118" \o "Malik, 2017 #102)9]. 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[[1](#_ENREF_119)20], and suppressing the PI3K/Akt/mTOR pathway and downstream HIF-1α[[63](#_ENREF_63)]. In GC, GRg3 can also reduce HIF-1α, thereby reducing tumor angiogenesis[[12](#_ENREF_120" \o "Aziz, 2016 #80)1]. 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[[12](#_ENREF_121" \o "Zhang, 2020 #43)2]. 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[[12](#_ENREF_122)3]. Chinese medicine differs from Western medicine in that many compounds in Chinese medicine act on multiple targets simultaneously, producing significant therapeutic effects[[12](#_ENREF_123" \o "Dong, 2015 #79)4]. 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](#_ENREF_10" \o "Pimentel-Nunes, 2019 #151)]. However, for patients with advanced GPL, such as the IM stage, whether eradication of *H. pylori* have therapeutic effects remain controversial[[12](#_ENREF_124" \o "Wang, 2011 #152)5]. 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[[12](#_ENREF_125)6,[12](#_ENREF_126)7]. 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](#_ENREF_16" \o "Bian, 2021 #140)]. 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.

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**Footnotes**

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**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-ΚB: 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*[[12](#_ENREF_125)5], 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](#_ENREF_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*[[12](#_ENREF_126)6], 2006 | Weiansan (WAS) | 76 | Weiansan | Weifuchun tablets | 24 wk | Inflammation of gastric mucosa; degree of glandular atrophy; IM and dysplasia; Hp infection |
| [NCT03823248](https://clinicaltrials.gov/ct2/show/NCT03823248?term=MoLuoDan&cond=gastric+precancerous+lesions&draw=2&rank=1) | 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*[[12](#_ENREF_127)8], 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*[[12](#_ENREF_128)9], 2013 | Wei Chang’An | 399 | Chemotherapy combined with Wei Chang’An decoction | Continuously | 3 mo or more | Survival trends; survival time |
| Shu *et al*[[1](#_ENREF_129)30], 2019 | Yiqi Huayu Jiedu decoction | 489 | Chemotherapy combined with YHJD | Chemotherapy | 6 mo or more | Disease-free survival rate; 5-yr survival rate; QOL; TCM symptoms |
| [NCT05229809](https://clinicaltrials.gov/ct2/show/NCT05229809?term=Yiqi+Wenyang&cond=gastric+carcinoma&draw=2&rank=1) | 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 yr; cumulative annual survival rate for 1-3 yr; 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** | **Animal/cells** | **Pathways/targets** |
| Gastric precancerous lesions (GPL) | Anti-proliferation inducing apoptosis | c1 | Wang *et al*[[37](#_ENREF_37)], 2021 | Erianin | GES-1 cell | HRAS-PI3K-Akt↓; p-Gsk3β, MDM2, p21, CyclinD1↓ |
| c2 | Zhu *et al*[[38](#_ENREF_38)], 2021 | Epigallocatechin gallate | Male Wistar rats, PLGC model | PI3K/Akt/mTOR↓; PTEN↑; PI3K, Akt, mTOR↓ |
| c3 | Zeng *et al*[[33](#_ENREF_33)], 2021 | Ginsenoside Rb1 | Sprague-Dawley rats, PLGC model | β-catenin/TCF4↓; c-myc, cyclin, Birc5↓ |
| c4 | Lv *et al*[[13](#_ENREF_130)1], 2022 | Ginsenoside Rg3 | Male Sprague-Dawley rats, PLGC model GPL cell | TIGAR, G6PDH, NADP, GSH↓; ROS↑ |
| Anti-inflammatory | c5 | Liu *et al*[[50](#_ENREF_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](#_ENREF_50)], 2020 | Calycosin | Male (SD) rats, PLGC model | Integrinβ1/NF-κB/DARPP-32; Integrinβ1, NF-κB, DARPP-32↑; STAT3↓ |
| c6 | Gao *et al*[[58](#_ENREF_58)], 2022 | Atractylenolide III | Female SD rats, Gastric Precancerous, Lesions Model | HIF-1α, VEGF-A, DLL4↓ |
| c4 | Zeng *et al*[[1](#_ENREF_119)20], 2022 | Ginsenoside Rg3 | Male Sprague Dawley rats, PLGC modelAGS cell, HGC-27 cell | GLUT1, GLUT4↓ |
| Inhibit glycolysis  | c4 | Liu *et al*[[63](#_ENREF_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](#_ENREF_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](#_ENREF_68)], 2023 | Gallic acid | GES-1 cell, MC cells | Wnt/β-catenin↓ |
|  | Induce autophagy | c7 | Cai *et al*[[44](#_ENREF_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](#_ENREF_74)], 2021 | Naringin |  SNU‑1 cell, GES‑1 cell | PI3K/Akt↓; PI3K, Akt, Bcl-2↓; caspase 3, Bax↑ |
| c10 | Yang *et al*[[13](#_ENREF_131)2], 2016 | Epigallocatechin-3-gallate | SGC-7901 cells, Nude mouse tumour xenograft model | Wnt/β-catenin↓; GSK3b, β-catenin↓ |
| c11 | Lee *et al*[[75](#_ENREF_75)], 2018 | Pectolinarigenin | AGS cell, MKN28 cell  | PI3K/Akt/mTOR↓; PI3K, p-Akt, mTOR, p-p70S6K, p-4EBP1↓ |
| c10 | Fu *et al*[[13](#_ENREF_132)3], 2019 | Epigallocatechin-3-gallate | SGC7901 cell | VEGF, HIF-1α↓ |
| c12 | Wang *et al*[[77](#_ENREF_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*[[10](#_ENREF_108)9], 2020 | Betulinic acid | BGC-823 cells, MNK45 cells | NF-κB, VASP↓ |
| c14 | Geng *et al*[[13](#_ENREF_133)4], 2018 | Usnic acid | BGC823 cell, SGC7901 cell | Bax, LC3-II↑; Bcl-2, p62↓ |
| c15 | Xu *et al*[[13](#_ENREF_134)5], 2020 | T-17 | SGC-7901, AGS cell, MGC-803 cell, BGC-823 cell, NCI-N87 cell,HUVEC cell | JNK, Bcl-2↑ |
| c16 | Liu *et al*[[81](#_ENREF_81)], 2015 | Ponicidin | MKN28 cell | JAK2/STAT3↓; Bcl-2, VEGF, VEGFR2, JAK2 STAT3↓; Bax, caspase-3↑ |
| c17 | Chen *et al*[[13](#_ENREF_135)6], 2012 | Tanshinone IIA | MKN45 cell, SGC7901 cell  | cyto-c, Bax, Caspase-9↑; Bcl-2↓ |
| c18 | Yang *et al*[[52](#_ENREF_52)], 2020 | Tomentosin | GCCs cell, AGS cell  | IL-6, TNF-α, IL-1, IL-8, Bcl-2↓; Bax↑ |
| c19 | Sun *et al*[[13](#_ENREF_136)7], 2007 | Swainsonine | SGC-7901 cell, BALB/c nu/nu mice, GC model | p53, Bcl-2↓; cmyc↑ |
| c20 | Tang *et al*[[82](#_ENREF_82)], 2019 | Micheliolide | AGS cell, N87 cell | IL-6, STAT3, cyclinD1, Mcl-1, MMP-2↓ |
| c21 | Li *et al*[[13](#_ENREF_137)8], 2013 | Andrographolide | BGC-823 cell | Bax, caspasase-3↑; Bcl-2↓ |
| c22 | Liu *et al*[[13](#_ENREF_138)9], 2016 | Curcumin | SGC7901 cell, GES-1 cell | c-Myc/H19↓; c-Myc, H19↓; p53↑ |
| c23 | Lee *et al*[[1](#_ENREF_139)40], 2016 | Quercetin | NOD/SCID mice, PLGC model SNU719 cell, MKN74 cells | p53, p21, Bax, Puma, caspase-3, caspase-9, PARP↑ |
| c4 | Aziz *et al*[[12](#_ENREF_120)1], 2016 | Ginsenoside Rg3 |  SGC-7901 cell | caspases-3, caspase-8, caspase-9, PARP, SP1↑; HSF1, FUT4↓ |
| c24 | Saralamma *et al*[[14](#_ENREF_140)1], 2015 | Poncirin | AGS cells | Fasl, caspase-8, caspase-3, PARP↑ |
| Anti-inflammatory | c18 | Yang *et al*[[52](#_ENREF_52)], 2020 | Tomentosin | GCCs cell, AGS cell | IL-6, TNF-α, IL-1, IL-8, Bcl-2↓; Bax↑ |
| c25 | Tharmalingam *et al*[[11](#_ENREF_114)5], 2016 | Piperine | AGS cell | β-catenin, IL-8↓ |
| c26 | Su *et al*[[53](#_ENREF_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](#_ENREF_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](#_ENREF_55)], 2022 | Scutellarin | AGS cell, albino Wistar rats, GC modelr | TNF-α, IL-1β, IL-2↓ |
| Anti-angiogenesis | c4 | Li and Qu[[89](#_ENREF_89)], 2019 | Ginsenoside Rg3 | BGC823 cell | HIF 1α, VEGF↓ |
| Inhibit glycolysis | C29 | Wang *et al*[[14](#_ENREF_141)2], 2022 | Licochalcone A | MKN45 cell, SGC7901cell, GES-1 cell | Akt/HK2↓; Akt, HK2↓ |
| C30 | Chen *et al*[[9](#_ENREF_95)6], 2015 | Baicalein | AGS cell | PTEN/Akt/HIF-1α↓; HK2, LDH-A, PDK1, Akt, HIF-1α↓; PTEN↑ |
| C31 | Wang *et al*[[14](#_ENREF_142)2], 2022 | Helichrysetin | MGC803 cell, HCT-8 cell | mTOR/p70S6K/c-Myc/PDHK1↓; mTOR/p70S6K, c-Myc, PDHK1↓ |
| C27 | Han *et al*[[54](#_ENREF_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*[[9](#_ENREF_98)9], 2022 | Poria acid | AGS cell, MKN-28 cell  | E-cadherin↑; N-cadherin, Vimentin↓ |
| C33 | Zang *et al*[[14](#_ENREF_143)3], 2017 | Luteolin | NCI-N87 cell, MKN28 cell, Hs-746T cell | E-cadherin↑; N-cadherin, vimentin, Snail↓ |
| c34 | Zhou *et al*[[10](#_ENREF_107)8], 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[[14](#_ENREF_144)4], 2018 | Astragaloside IV | BGC-823 cell, MKN-74 cell, GES-1 cell | PI3K/Akt/NF-κB↓; TGF-β1↓ |
| Regulate immune function | c35 | Zhuang *et al*[[10](#_ENREF_104)5], 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*, 2021[[10](#_ENREF_103)4] | Oleanolic acid | MKN-45, Jurkat T cell | IL-1β/ NF-κB /TET3↓; PD-L1↓ |
| Induce autophagy | c11 | Lee *et al*, 2018[[75](#_ENREF_75)] | Pectolinarigenin | AGS cell, MKN28 cell  | PI3K/Akt/mTOR↓; PI3K, p-Akt, mTOR, mTOR, p-p70S6K, p-4EBP1↓ |
| c14 | Geng *et al*[[13](#_ENREF_133)4], 2018 | Usnic acid | BGC823 cell, SGC7901 cell  | Bax, LC3-II↑; Bcl-2, p62↓ |
| c15 | Xu *et al*[[13](#_ENREF_134)5], 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](#_ENREF_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*[[10](#_ENREF_108)9] , 2020 | Betulinic acid | BGC-823 cells, MNK45 cells | NF-κB, VASP↓ |
| c34 | Zhou *et al*[[10](#_ENREF_107)8], 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*[[1](#_ENREF_109)10], 2018 | 18β-glycyrrhetinic acid | SGC-7901 cell | ROS/PKC-α/ERK↓; ROS, PKC-α, ERK↓ |
| c30 | Yan *et al*[[11](#_ENREF_110)1], 2015 | Baicalein | SGC7901 Cell, MGC803 cell | MMP-2, mmp-9, p38↓ |
| Anti-*Helicobacter pylori* | c25 | Tharmalingam *et al*[[11](#_ENREF_114)5], 2016 | Piperine | AGS cell lines | β-catenin, IL-8↓ |
| c26 | Su *et al*[[53](#_ENREF_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](#_ENREF_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-κB: 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](#_ENREF_31)], 2016 | Weipixiao (WPX) | Radix Astragali, Radix Pseudostellariae, Rhizoma Atractylodis Macrocephalae, Radix Salviae Miltiorrhiz, Herba Hedyotis Diffusae | Male SD rats, PLGC model | Wnt/β-catenin↓; Lgr5, MMP-7, Wnt1, β-catenin↓ |
| fa | Zeng *et al*[[14](#_ENREF_145)5], 2018 | Weipixiao (WPX) | Astragalus Membranaceus, Pseudostellaria Heterophylla, Atractylodis Macrocephalae, Curcuma zedoaria, Salvia Miltiorrhiza and Hedyotis Diffusa Willd | Male SD rats, PLGC model | Wnt/GSK3β; GSK3β↑; C-myc↓ |
| fb | Yin *et al*[[29](#_ENREF_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↓ |
| fc | Cai *et al*[[14](#_ENREF_146)6], 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-κB P65↓; Ptch↑ |
| fd | Hao *et al*[[14](#_ENREF_147)7], 2022 | Huazhuojiedu 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, Gynostemma pentaphyllum Makino, and Eupatorium fortunei Turcz | Male SD rats, PLGC model | Lnc 517368↓ |
| fe | Xu *et al*[[14](#_ENREF_148)8], 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-κB↓ |
| 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](#_ENREF_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↓ |
| fg | Deng *et al*[[12](#_ENREF_125)5], 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](#_ENREF_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](#_ENREF_59)], 2018 | Weipixiao (WPX) | Astragalus Membranaceus, Pseudostellaria Heterophylla, Atractylodis Macrocephalae, Curcuma zedoaria, Salvia Miltiorrhiza and Hedyotis Diffusa Willd | Male SD rats, PLGC model | ERK1/CylinD1; HIF-1α, VEGF, ERK1, CylinD1↓ |
| fh | Wang *et al*[[15](#_ENREF_150)0], 2020 | Jinlongshe (JLS) | Rhizoma Pinelliae, Radix, Rhizome Arisaemat, Glycyrrhizaepreparata, corium stomachiumgalli, *etc*. | Male SD rats, PLGC model | Apelin, CD34↓ |
| Protecting gastric mucosa | fi | Yi *et al*[[15](#_ENREF_151)1], 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 SD rats, PLGC model | MAPK; JNK, p38↑ |
| fj | Wang *et al*[[32](#_ENREF_32)], 2020 | WeiFuChun (WFC) | Radix Ginseng Rubra (red ginseng), Rabdosia amethystoides H. Hara, and fried Fructus Aurantii | Male SD rats, PLGC model | MAPK; VEGF, FOXO4, AKT, TP53, FAS, MAPK8, MAPK11, MAPK14↓ |
| Inhibit glycolysis | fa | Cai *et al*[[64](#_ENREF_64)], 2019 | Weipixiao (WPX) | Astragalus, Radix Pseudostellariae, Atractylodes macrocephala, Salvia miltiorrhiza Bge, Oldenlandia diffusa(Willd.)Roxb | Male SD rats, PLGC model | miRNA-34a/PI3K/AKT/Mtor; LDHA, CD147, MCT4, PI3K, AKT, mTOR, HIF-1α, miRNA-34a↓ |
| fk | Liu *et al*[[15](#_ENREF_152)2], 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](#_ENREF_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 herb, liquorice | Wistar male rats, PLGC model | EGFR-PI3K-AKT↓; EGFR, β-catenin, N-cadherin protein↓ |
| GC | Anti-proliferation inducing apoptosis | fm | He *et al*[[76](#_ENREF_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*[[15](#_ENREF_153)3], 2021 | Huosu Yangwei (HSYW) | Huoxiang, Zisugeng, Baizhu, Zhike, Doukou, Foshou, Wumei, Shengjiang, Dazao, Gancao, Huangqi, Dihuang, Mudanpi, Tianhuafen, Danggui, Chuanxiong, Ezhu, Gouqizi, Huanglian, Dangsheng, and Pugongying | Male Balb/c mice, PLGC model | DNAJB4, CALD1, AKR1C1, CST1, CASP1, PREX1, SOCS3, PRDM1 |
| fo | Yuan *et al*[[15](#_ENREF_154)4], 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](#_ENREF_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*[[15](#_ENREF_155)5], 2021 | Guiqi Baizhu prescription | Astragali radix, Atractylodis macrocephalae, Angelicae,Paeoniae radix alba, Pericarpium citri reticulatae, Rhubarb, Glycyrrhizae | MKN-45 cell, SGC-7901 cell, BGC-823 cell, GES-1cell | HER2, PD-L1↑ |
| Anti-angiogenesis | fg | Deng *et al*[[9](#_ENREF_92)2], 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*[[1](#_ENREF_99)00], 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*[[15](#_ENREF_154)4], 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*[[11](#_ENREF_111)2], 2018 | Yangzheng Sanjie Decoction (YZSJD) | Astragali Radix, Scutellariae Barbatae, Herba, Arisaematis Rhizoma Preparatum, Citri Sarcodactylis, Fructus, Cremastrae Pseudobulbus and Curcumae Longae, Rhizoma | MKN-45 cell | EGFR, miR-7↑ |

SD: Sprague Dawley; GPL: Gastric precancerous lesions; GC: Gastric cancer; EMT: Epithelial-mesenchymal transformation; NF-κB: Noncanonical nuclear factor-kappa B.



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