



Review article

Progress in traditional Chinese medicine against chronic gastritis: From chronic non-atrophic gastritis to gastric precancerous lesions

Liangjun Yang^{a,1}, Xinying Liu^{a,1}, Jiajie Zhu^a, Xi Zhang^b, Ya Li^c, Jiabing Chen^a, Haiyan Liu^{a,*}

^a Tongde Hospital of Zhejiang Province, Hangzhou 310012, China

^b Guangzhou University of Chinese Medicine, Guangzhou 510405, China

^c Lin 'an Hospital of Traditional Chinese Medicine, Hangzhou 311300, China

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ABSTRACT

Chronic gastritis (CG) is a persistent inflammation of the gastric mucosa that can cause uncomfortable symptoms in patients. Traditional Chinese medicine (TCM) has been widely used to treat CG due to its precise efficacy, minimal side effects, and holistic approach. Clinical studies have confirmed the effectiveness of TCM in treating CG, although the mechanisms underlying this treatment have not yet been fully elucidated. In this review, we summarized the clinical research and mechanisms of TCM used to treat CG. Studies have shown that TCM mechanisms for CG treatment include *H. pylori* eradication, anti-inflammatory effects, immune modulation, regulation of gastric mucosal cell proliferation, apoptosis, and autophagy levels.

1. Introduction

Chronic gastritis (CG), a persistent inflammatory reaction of the gastric mucosa, is one of the most common diseases seen in endoscopy. According to the histopathology of gastric mucosa, it can be divided into chronic non-atrophic gastritis (CANG), chronic atrophic gastritis (CAG), and other special types. Intestinal metaplasia and dysplasia, which are commonly observed in atrophic gastritis, are known as gastric precancerous lesions, and are considered to be crucial steps in the progression from gastritis to gastric cancer [1]. It is estimated that millions of people worldwide may die prematurely each year from gastric cancer caused by CG [2]. Besides, CG usually manifests as epigastric pain, bloating, indigestion, nausea, vomiting, belching, loss of appetite, and other symptoms, which can significantly affect the quality of life of patients [3]. Therefore, intervention in patients with CG is essential not only to alleviate symptoms but also to decrease the incidence of gastric cancer and improve patient outcomes.

Traditional Chinese medicine (TCM) is an ancient system of traditional medicine developed in China that studies human physiology, pathology, disease diagnosis, and treatment. It has been widely applied in the treatment and prevention of diseases for at least 2,200 years and has played an important role in improving the physical health of people in China [4]. The treatment of diseases in TCM depends on identifying disease syndromes, which comprise a collection of interrelated clinical manifestations that adhere to TCM theories [5]. According to “*Expert consensus on TCM diagnosis and treatment of chronic gastritis*” authored by the Spleen and Stomach Diseases Branch of the China Association of Chinese Medicine, CNAG is typically marked by spleen-stomach weakness, spleen-stomach

* Corresponding author.

E-mail address: liuhaiyantd@tom.com (H. Liu).

¹ These authors contributed equally to this work.

List of abbreviations

CG	Chronic gastritis
CANG	Chronic non-atrophic gastritis
CAG	Chronic atrophic gastritis
TCM	Traditional Chinese medicine

damp-heat, and liver-stomach disharmony, whereas CAG is often characterized by spleen-stomach weakness, qi stagnation, and blood stasis based on TCM syndrome differentiation [6]. As for the treatment strategy using herbal prescriptions for CG, it should include herbs that invigorate the spleen and supplement qi, resolve turbidity, clear heat, remove toxin, and activate blood. Studies have confirmed that TCM can relieve the clinical symptoms of patients with CG and block the development of chronic atrophic gastritis to gastric cancer [7,8]. Additionally, many experimental studies have been carried out to reveal the mechanism of TCM in the treatment of CG, and have achieved promising results [9].

Although the guidelines for the treatment of CG with TCM were published in 2012 [10], the application of the guidelines was limited due to the lack of relevant evidence-based medicine support. In recent years, clinical research on the treatment of CG with TCM has gradually increased, with numbers of related experimental studies underway. Novel methods such as real-world clinical research [11], integrative pharmacology [12], and machine learning [13] are gaining popularity for their potential to enhance understanding of TCM's therapeutic mechanisms and clinical applications. In this article, we reviewed the clinical effects and summarized the underlying mechanisms of Chinese medicine in the treatment of CG in recent years, so as to promote the application of TCM.

Table 1
Chinese herbal formulations for CG.

Medicines	Ingredients	TCM Effects	Type of study
Banxia Xiexin decoction [16, 17]	<i>Rhizoma Pinelliae, Radix Scutellariae, Rhizome Coptidis, Rhizoma Zingibers, Radix Glycyrrhizae, Fructus Ziziphi Jujubae, Radix Ginseng.</i>	Clear heat and remove dampness	Meta-analysis
Huangqi Jianzhong Tang [18]	<i>Radix Astragali, Radix Paeoniae Alba, Ramulus Cinnamomi, Fructus Jujubae, Glycyrrhizae Radix Et Rhizoma Praeparata Cum Melle, Rhizoma Zingiberis Recens, Saccharum Granorum</i>	Invigorate the spleen-stomach and replenish qi	Meta-analysis
QiruiWeishu capsule [19]	<i>Panax notoginseng, Rheumofficinale, Alum, Ophicalcitum</i>	Remove stasis and dehumidification, guide hysteresis and clear heat	RCT
Shenling Baizhu Powder [20]	<i>Atractylodes macrocephala Koidz, Panax ginseng C.A.Mey, Smilax glabra Roxb, Coix lacryma-jobi var. ma-yuen (Rom.Caill.) Stapf, Lablab purpureus subsp. purpureus, Dioscorea oppositifolia L, Amomum villosum Lour, Nelumbo nucifera Gaertn, Platycodon grandifloras, Glycyrrhiza uralensis Fisch. ex DC</i>	Supplement Qi and strengthen the spleen	Meta-analysis
Sijunzi decoction [21]	<i>Radix Ginseng, Poria cocos, Rhizoma Atractylodis Macrocephalae, Radix Glycyrrhizae</i>	Replenish qi and invigorate the functions of the spleen	Meta-analysis
Hewei Decoction [22]	<i>Panax ginseng C. A. Mey, Poria Cocos (Schw.) Wolf, Atractylodes Macrocephala Koidz, Bulbus Lillii, Ophiopogon japonicus, Scrophularia ningpoensis Hensl, Dendrobii Caulis, Paeoniae Radix Alba, Angelicae Sinensis Radix, Anemone altaica Fisch, Alisma Orientale (Sam.) Juz, Chuanxiong Rhizoma, Corydalis Rhizoma, Radix Notoginseng, Radix Sanguisorbae, Endothelium Corneum Gigeriae Galli, Pollen Typhae, Linderiae Radix, and licorice.</i>	Invigorate the spleen, regulate Qi, promote blood circulation	RCT
Moluodan [23]	<i>Bulbus Lillii, Rhizoma Alismatis, Poria, Radix Notoginseng, Radix Sanguisorbae, Rhizoma Ligustici Chuanxiong, Rhizoma Acori Tatarinowii, Radix Ophiopogonis, Radix Linderiae, Herba Artemisiae, Scopariae, Radix Scrophulariae, Pollen Typhae, Radix Paeoniae Alba, Endothelium Corneum Gigeriae Galli, Herba Dendrobii, Radix Angelicae Sinensis, Rhizoma Corydalis, Rhizoma Atractylodis Macrocephalae</i>	Harmonize-stomach and lower adverse Qi, invigorate the spleen and eliminate distension, and activate blood circulation	RCT
Weierkang pills [24]	<i>Panax Ginseng C. A. Mey, Ganoderma, Hedysarum Multijugum Maxim, Vitamin A, Vitamin E, Vitamin C, Vitamin B1, Methyl Hesperidin</i>	Invigorate the spleen and supplement qi	RCT
Weining granules [25]	<i>Radix Astragali, Poria, Rhizoma Curcumae Longae, Fructus Lycii</i>	Promote Qi and invigorate the spleen, Tonify the kidney and remove blood stasis	RCT
Weisu Granules [26]	<i>Perilla frutescens (L.) Britton, Cyperi Rhizoma, Citrus Reticulata, Citri Fructus, Citri Sarcodactylis Fructus, Aurantii Fructus, Arecae Semen, and Endothelium Corneum Gigeriae Galli. Weifuchun, composed of three herbs including Panax ginseng, Isodon amethystoides, and Bran Fried hovenia dulcis</i>	Regulate qi and eliminate distension	RCT
Weifuchun tablets [26]	<i>Panax ginseng, Isodon amethystoides, Bran Fried hovenia dulcis</i>	Invigorate the spleen and qi, activate blood and detoxify	RCT

2. Clinical evidence of TCMs on CG

The introduction of evidence-based medicine into the field of TCM has led to a series of clinical studies on CG, which have had a profound impact on TCM research and clinical practice. Based on a multi-center, randomized, positive-controlled clinical trial, Chinese herbal compound prescriptions derived from TCM syndrome patterns in the treatment of erosive gastritis have been found to be effective in improving gastric mucosal erosion, reducing pathological scores of the gastric mucosa, and alleviating clinical symptoms [14]. Additionally, a meta-analysis suggests that TCM may be more effective than current conventional therapy in treating CG [15]. Here, we list the effective formulas used to treat CG in recent years (Table 1).

2.1. Banxia Xiexin decoction

Banxia Xiexin decoction is a classic formula recorded in *Shang Han Lun*, a book written by Zhang Zhongjing in the Han Dynasty. It consists of seven herbs, including *Rhizoma Pinelliae*, *Radix Scutellariae*, *Rhizome Coptidis*, *Rhizoma Zingibers*, *Radix Glycyrrhizae*, *Fructus Ziziphi Jujubae*, and *Radix Ginseng*, which together clear heat and remove dampness as described by TCM theory. Clinical studies have shown that Banxia Xiexin decoction is effective in treating chronic gastritis [16]. A meta-analysis of 26 randomized controlled trials (RCTs) showed that Banxia Xiexin decoction is more effective in inhibiting *H. pylori*, reducing *H. pylori*-related mucosal inflammation, and relieving symptoms such as stomach distending pain, and belching in treating CG [17]. Further studies have shown that *Rhizome Coptidis*, *Radix Scutellariae*, and *Rhizoma Pinelliae* were responsible for the inhibition of *H. pylori* infection [27].

2.2. Huangqi Jianzhong Tang

Huangqi Jianzhong Tang, consisting of *Radix Astragali*, *Radix Paeoniae Alba*, *Ramulus Cinnamomi*, *Fructus Jujubae*, *Glycyrrhizae Radix Et Rhizoma Praeparata Cum Melle*, *Rhizoma Zingiberis Recens*, and *Saccharum Granorum*, is usually used for the treatment of chronic gastrointestinal diseases by invigorating the spleen-stomach and replenishing qi. According to a meta-analysis including 9 RCTs and 979 participants in the treatment of CG, using Huangqi Jianzhong Tang alone or in combination with conventional western medicine was more effective in improving gastroscopy outcomes, *H. pylori* clearance rate, and TCM syndrome [18]. The results of the meta-analysis suggest that Huangqi Jianzhong Tang may be an effective treatment for atrophic gastritis.

2.3. Qirui weishu capsule

QiruiWeishu capsule is an herbal formula prescribed by Guang'anmen Hospital of China Academy of Chinese Medical Sciences for its effectiveness in treating CNAG with erosion dampness and heat stasis syndrome. It is composed of four herbs, including *Panax notoginseng*, *Rheumofficinale*, Alum, and Ophicalcicum, which synergistically act to remove stasis and dampness, guide hysteresis, and clear heat. A multicenter, double-blind, randomized controlled clinical trial was conducted to evaluate the effectiveness of QiruiWeishu capsule in the treatment of CNAG. The results showed that the capsule was effective in relieving stomach pain, reducing the inflammation of gastric mucosa, and improving the scores of TCM symptoms [19].

2.4. Shenling Baizhu powder

Shenling Baizhu Powder is a widely-used prescription for digestive tract diseases with spleen deficiency derived from the Song Dynasty. This formula contains *Atractylodes macrocephala Koidz*, *Panax ginseng C.A.Mey*, *Smilax glabra Roxb*, *Coix lacryma-jobi var. mayuen (Rom.Caill.) Stapf*, *Lablab purpureus subsp. purpureus*, *Dioscorea oppositifolia L*, *Amomum villosum Lour*, *Nelumbo nucifera Gaertn*, *Platycodon grandifloras*, and *Glycyrrhiza uralensis Fisch. ex DC*, which work together to supplement Qi and strengthen the spleen. According to a meta-analysis of fourteen studies involving 1,335 participants, Shenling Baizhu Powder was found to be more effective than Western medicine in reducing *H. pylori* seropositivity, recurrence rates, and symptoms such as epigastric stagnation, abdominal distension, and belching in patients with CG [20].

2.5. Sijunzi decoction

Sijunzi decoction is a classic Chinese herbal formula that has been used to treat gastrointestinal diseases with spleen qi deficiency syndrome. It is an empirical decoction composed of *Radix Ginseng*, *Poria cocos*, *Rhizoma Atractylodis Macrocephalae*, and *Radix Glycyrrhizae*, and is commonly used to replenish qi and invigorate the functions of the spleen. A meta-analysis of six RCTs has demonstrated that Sijunzi decoction can significantly improve the scores of histopathology of CAG and *H. pylori* clearance rate, and combining Sijunzi decoction with conventional Western medicines appears to provide benefits for CAG treatment [21].

2.6. Hewei decoction

Hewei Decoction is a herbal prescription used for treating atrophic gastritis by invigorating the spleen, regulating Qi, and promoting blood circulation. It is composed of 19 herbs, including *Panax ginseng C. A. Mey*, *Poria Cocos (Schw.) Wolf*, *Atractylodes Macrocephala Koidz*, *Bulbus Lillii*, *Ophiopogon japonicus*, *Scrophularia ningpoensis Hemsl*, *Dendrobii Caulis*, *Paeoniae Radix Alba*, *Angelicae Sinensis Radix*, *Anemone altaica Fisch*, *Alisma Orientale (Sam.) Juz*, *Chuanxiong Rhizoma*, *Corydalis Rhizoma*, *Radix Notoginseng*, *Radix*

Sanguisorbae, *Endothelium Corneum Gigeriae Galli*, *Pollen Typhae*, *Linderae Radix*, and *licorice*. A randomized control study conducted at a single center demonstrated that Hwei decoction can improve histological alterations in chronic atrophic gastritis, alleviate clinical symptoms, increase PGI and PGII levels, and decrease the PGR17 level [22]. Nevertheless, the study has some limitations, such as a small sample size, leading to a limited amount of statistical data, and potential bias in the results.

2.7. Moluodan

Moluodan, a traditional Chinese patent (approved No. Z13021324) commonly used in the treatment of CAG, is composed of *Bulbus Lili*, *Rhizoma Alismatis*, *Poria*, *Radix Notoginseng*, *Radix Sanguisorbae*, *Rhizoma Ligustici Chuanxiong*, *Rhizoma Acori Tatarinowii*, *Radix Ophiopogonis*, *Radix Linderae*, *Herba Artemisiae*, *Scopariae*, *Radix Scrophulariae*, *Pollen Typhae*, *Radix Paeoniae Alba*, *Endothelium Corneum Gigeriae Galli*, *Herba Dendrobii*, *Radix Angelicae Sinensis*, *Rhizoma Corydalis*, and *Rhizoma Atractylodis Macrocephalae*. It has been used to treat gastrointestinal disease by harmonizing-stomach and lowering adverse Qi, invigorating the spleen and eliminating distension, and activating blood circulation. Based on a multi-centered, double-blind, randomized controlled trial, after treatment with Moluodan, the dysplasia of gastric mucosa in patients with CAG was improved, and the patients with epigastric pain, epigastric choking, belching, and appetite were relieved [23].

2.8. Weierkang pills

Weierkang pills is a Chinese patent medicine that has been approved by the China Food and Drug Administration (approved No. Z22020104). This pill, composed of *Panax Ginseng C. A. Mey*, *Ganoderma*, *Hedysarum Multijugum Maxim*, Vitamin A, Vitamin E, Vitamin C, Vitamin B1, and Methyl Hesperidin, is used to treat various diseases by invigorating the spleen and supplementing qi. According to a randomized double-blind clinical trial investigating the efficacy and safety of Weierkang pills in the treatment of CAG, the results demonstrated that Weierkang could significantly improve the total effective rate of gastric atrophy/intestinal metaplasia, reduce the Kyoto total risk score and atrophy score, and improve symptoms such as epigastric pain. Furthermore, the expression of TFF3 in gastric mucosa was significantly decreased after Weierkang pills treatment, which may be related to the pathophysiology mechanism [24].

2.9. Weining granules

Weining granules, consisting of five Chinese herbs including *Radix Astragali*, *Poria*, *Rhizoma Curcumae Longae*, and *Fructus Lycii*, is a classic prescription for the treatment of CAG by promoting Qi and invigorating the spleen, tonifying the kidney and removing blood stasis. According to a study involving 60 patients with gastric precancerous lesions, the therapeutic effects of these granules following six months of treatment were effective in improving the gastric precancerous state, the main symptoms, and the quality of life. Its

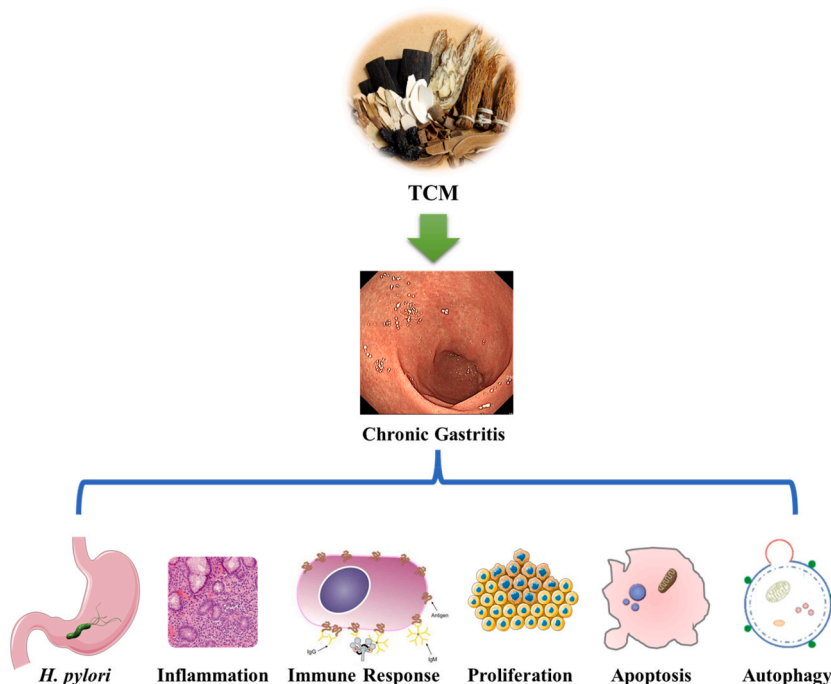


Fig. 1. The mechanism of action of TCM in the treatment of CG.

mechanism of action may involve inhibiting angiogenesis and enhancing immune function [25].

2.10. Weisu granule combined with weifuchun tablet

Weisu Granules, a proprietary Chinese medicine (approved No. Z10930002), is used for CG and consists of *Perilla frutescens* (L.) Britton, *Cyperus Rhizoma*, *Citrus Reticulata*, *Citri Fructus*, *Citri Sarcodactylis Fructus*, *Aurantii Fructus*, *Arecae Semen*, and *Endothelium Corneum Gigeriae Galli*. Weifuchun, composed of three herbs including *Panax ginseng*, *Isodon amethystoides*, and *Bran Fried hovenia dulcis*, is a classic Chinese patent medicine that has been approved by the China Food and Drug Administration for the treatment of chronic gastritis (approved No. Z20040003). A clinical study exploring the clinical efficacy of Weisu granules combined with Weifuchun tablets in the treatment of CAG, the result demonstrated that the TCM syndrome scores and gastric mucosal pathology scores of

Table 2

TCM formulas, Chinese herbs and extracts of herbs in the treatment of CG.

Herbs or Extracts	Property	Target or Indicator
Banxia Xiexin Decoction [17]	anti- <i>H. pylori</i>	/
Huangqi Jianzhong Tang [18,28]	anti- <i>H. pylori</i>	reduces the expression of <i>H. pylori</i> -related virulence factors, such as HpPrTc, OPIA, IceA1, and BabA2
Sijunzi decoction [21]	anti- <i>H. pylori</i>	/
Jinghua Weikang [29]	anti- <i>H. pylori</i>	reduce the adhesion and the expression of adhesins <i>NapA</i> , <i>SabA</i> , and <i>BabA</i>
Wei Bi Mei granule [30]	anti- <i>H. pylori</i>	/
HZJW [31]	anti- <i>H. pylori</i>	/
Burdock complex [32]	anti- <i>H. pylori</i>	inhibit the adhesion
Ethanol extract of <i>Pterocarpus santalinus</i>	anti- <i>H. pylori</i>	Reduce urease activity, lipid peroxidation, and lactate dehydrogenase
Sanguinarine	anti- <i>H. pylori</i>	suppress the activities of <i>H. pylori</i> urease and jack bean urease by targeting the thiols and Ni ²⁺ [33]
<i>Atractylodes lancea</i> volatile oils [34]	anti- <i>H. pylori</i>	inhibit the growth of <i>H. pylori</i> , reduce biofilm formation of <i>H. pylori</i> , decrease the translocation of Cag A
<i>Canarium album</i> Raeusch. fruit extracts [35]	anti- <i>H. pylori</i>	inhibit the growth of <i>H. pylori</i> , destroy the bacterial structure and down-regulate the expression of virulence factors
Lion's Mane mushroom and <i>Hericium erinaceus</i> [36]	anti- <i>H. pylori</i>	inhibit the growth of <i>H. pylori</i>
Zuojin pill [37,38]	anti-inflammation	decrease the levels of IL-6, MCP-1, PGE2, TNF- α , VEGF, COX-2, IL-4, and IL-17
Moluodan [39]	anti-inflammation	reduce the release of TNF- α and IL-6
Banxia Xiexin decoction [40]	anti-inflammation	reduce the levels of TNF- α , IL-2, and IL-8
Qinghuayin [41]	anti-inflammation	reduce the level of TNF- α , TLR4, MyD88, NF- κ B, and COX-2
<i>Atractylodes macrocephala</i> Koidz [42]	anti-inflammation	regulate the expression of IL-6 and IL-1 β
<i>Geranii Herba</i> [43]	anti-inflammation	inhibit the NF- κ B and MAPK signaling pathways
<i>Polygonum capitatum</i> [44]	anti-inflammation	affect the phosphorylation of I κ B α , NF- κ B p65, p38MAPK, and ERK1/2, and the nuclear transposition of NF- κ B p65 and p-p38MAPK
flavonoid glycosides of <i>Polygonum capitatum</i> [45]	anti-inflammation	regulate the levels of IFN-gamma and IL-4
quercetin [46]	anti-inflammation	reduce the expression of MMP-9, and suppress the TNFR-c-Src-ERK1/2 and c-Fos or NF- κ B pathways
Baicalin [47]	anti-inflammation	inhibit the levels of TNF- α , IL-8, and IL-1 β
Weifuchun [48]	Regulate the immune response	regulate immune cells like T cells and macrophages, related genes including TLR2 and CD14.
Sijunzi Decoction [49]	Regulate the immune response	Regulate TCR β
Huangqi Jianzhong Tang [50]	Regulate the immune response	Regulate glycine, serine and threonine metabolism
Poncirin [51]	Regulate the immune response	Inhibit the infiltration of immune cells including neutrophils
Qilianshupi decoction [52]	promote apoptosis and inhibit proliferation	Decrease the expression of survivin and p53
Jianpiyiqi formula [53]	inhibit proliferation	Reduce the expression of Wnt1, β -catenin, and cyclin D1 and increase the expression of GSK-3 β
Huazhuojiedu [54–70]	promote apoptosis and inhibit proliferation	Inhibit AKT1 and downregulate the lnc 517368
Erianin [56]	induce apoptosis	Inhibit the PI3K/Akt signaling pathway
A polysaccharide isolated from <i>Hericium erinaceus</i> (Rull ex F.) Pers [57]	induce apoptosis	regulate the expression of Bax, Bcl-2, and caspase-3
Quercetin [58]	promote apoptosis and inhibit proliferation	Reduce p38MAPK and BAX levels and increase BCL-2
Zuojin Pill [59]	Induce autophagy	increase the expression levels of PTEN, LC3-II, and Beclin-1
Berberine [60]	Induce autophagy	promote autophagy-related LC3-II and Beclin-1 and inhibit the PI3K/AKT signaling pathway
Weipingshu [61]	Induce autophagy	increase the number of autophagosomes
Anwei decoction [71]	Induce autophagy	increase the expression levels of ULK1, Atg13, beclin-1, and LC3
Huatan Xiaoyu formula [72]	Induce autophagy	promote autophagy-related LC3II/LCI and Beclin-1, reduce P62

the patients were significantly decreased after the combined use of the two drugs. Additionally, the study also found that the serum levels of G-17, PG I, and PG II in the experimental group were decreased [26].

3. Pharmacological mechanisms of TCM for the treatment of CG

Over the past few decades, a range of in vivo and in vitro experimental studies have contributed to a better understanding of the mechanisms behind TCM's effectiveness in treating CG. In this section, we provide a summary of the various mechanisms of action, including the eradication of *H. pylori*, anti-inflammatory effects, immune regulation, regulation of gastric mucosa cell proliferation, apoptosis, and autophagy levels (Fig. 1). Additionally, Table 2 provides an overview of some of the TCM formulas, Chinese herbs, and herbal extracts used in treating CG.

3.1. The eradication of *H. pylori*

As a special bacterium that colonizes the surface of gastric mucosal epithelial in the gastric antrum, *H. pylori* causes inflammation of the gastric mucosa by triggering a chronic immunoreaction. It is well known that *H. pylori* infection is associated with the gastric "inflammation-cancer" transition from CNAG, CAG, gastric intestinal metaplasia, gastric dysplasia, to gastric cancer [64]. Epidemiological surveys have found that *H. pylori* infects about 50% of the world's population, especially in China where the infection rate was 66.5% [65,66]. Thus, the prevention and treatment of *H. pylori* are of great significance in reducing the occurrence of malignant gastric diseases. Due to the long-term use and abuse of antibiotics, the resistance rate of *H. pylori* is increasing, resulting in a decline in the eradication rate [67,68]. It is essential to develop novel treatment and prevention strategies for the treatment of *H. pylori*. Recent research has demonstrated that some TCM preparations and herbal monomers possess inhibitory effects on *H. pylori*, primarily through the suppression of its growth and adhesion capabilities.

3.1.1. TCM preparations

It has been shown that some TCM compounds, such as Banxia Xiexin Decoction [17], Huangqi Jianzhong Tang [18,28], and Sijunzi decoction [21], are effective in inhibiting *H. pylori* according to clinical studies in the previous article. In addition, Jinghua Weikang capsule, a modern TCM (approved No. Z10970067) composed of *Chenopodium ambrosioides* and *Adina Pululifera*, is widely used in the treatment of CG and peptic ulcer. Studies have shown that Jinghua Weikang capsule and one of its individual herbs, *Chenopodium ambrosioides* L., exhibit significant bactericidal activity against antibiotic-resistant *H. pylori* strains [69,70]. Moreover, the formula has been found to reduce the adhesion of drug-resistant *H. pylori* to GES-1 cells, as well as the expression of adhesins *NapA*, *SabA*, and *BabA*, thus demonstrating a certain degree of bactericidal effect [29]. *Wei Bi Mei* granule, composed of three synthetic drugs (bismuth aluminate, heavy magnesium carbonate, sodium hydrogen carbonate) and five herbs (*licorice*, *cortex frangulae*, *fructus foeniculi*, *aloe*, and *Acorus gramineus*), has been confirmed to have better therapeutic effects in treating *H. pylori* infection than bismuth aluminate and colloidal bismuth subcitrate in vivo experiment [30]. HZJW is a Chinese herbal formula composed of 12 medicinal herbs, including *Macrocephalae Rhizoma*, *Scutellariae Barabtae Herba*, *Corydalis Rhizoma*, *Curcumae Radix*, *Cynanchi Paniculati Radix et Rhizoma*, *Alpiniae Officinarum Rhizoma*, *Coptidis Rhizoma*, *Perillae Fructus*, *Taraxact Herba*, *Typhae Pollen*, *Hedyotis diffusa Willd*, and *Herba Eupatorii*. It has been applied for treating patients with gastrointestinal disorders. An in vivo and in vitro study demonstrated that HZJW is effective and safe in the treatment of peptic ulcer and *H. pylori* infection, which contributes to the therapeutic effect in treating gastrointestinal diseases [31]. Burdock complex is a prescription originating from Taiwan Province of China and is composed of *Arctium lappa*, *Angelica sinensis*, *Lithospermum erythrorhizon*, and *Sesamum indicum* oil. In vitro and clinical studies have shown that it can reduce the infection of *H. pylori* by inhibiting its adhesion and ameliorate the inflammation and oxidative damage caused by *H. pylori* [32].

3.1.2. Chinese herbal extracts

Traditional Chinese herbal extracts, derived from native plants, are widely used in the treatment of clinical diseases and play a vital role in new drug discovery. Their molecular structures, predictable pharmacological action, and fewer drug interactions make them particularly attractive for the treatment of CG. Many studies have investigated the effect of Chinese herbal extracts on *H. pylori* infection and found them to be effective. *Pterocarpus santalinus* is a traditional medicinal plant that has a protective effect against gastric ulcers [73]. In vitro studies have demonstrated that an ethanol extract of *Pterocarpus santalinus* has potential anti-*H. pylori* activity by reducing urease activity, lipid peroxidation, and lactate dehydrogenase [74]. Sanguinarine is a natural alkaloid isolated from *Zanthoxylum nitidum*(Roxb.)DC, a Chinese herb utilized for the treatment of gastrointestinal diseases and *H. pylori* infection [75]. Research has proved that sanguinarine could remarkably suppress the activities of *H. pylori* urease and jack bean urease by targeting the thiols and Ni²⁺[33]. *Atractylodes lancea* is a medicinal plant widely used in treating gastrointestinal diseases with the spleen-deficiency syndrome. In vitro experiments confirmed that *Atractylodes lancea* volatile oils could inhibit the growth of *H. pylori*, reduce the biofilm formation, and decrease the translocation of Cag A, indicating that the volatile oil of *Atractylodes Rhizoma* is a potential inhibitor of *H. pylori* [34]. *Canarium album* Raeusch, belonging to the Burseraceae family, has numerous biological activities, including anti-inflammatory, antioxidative, and antiviral effects [76,77]. An in vitro experiment showed that *Canarium album* Raeusch fruit extracts inhibited *H. pylori* by suppressing growth, destroying the bacterial structure, and down-regulating the virulence factors [35]. Similarly, medicinal mushroom extracts, particularly the Lion's Mane mushroom and *Hericium erinaceus*, have been demonstrated to inhibit the growth of *H. pylori* in vitro [36]. Additionally, many TCM monomers, such as emodin, baicalin, schizandrin, berberine [78], daphnetin [79], palmatine [80], geniposide, and genipin [81], have been proven to have an inhibitory effect against *H. pylori*, providing an additional option for the application of monomers for the treatment of *H. pylori*-related gastrointestinal diseases.

Although TCM extracts have shown promising potential in treating *H. pylori* infections, it is important to note that the current studies have only confirmed their effects through in vitro or in vivo experiments. Therefore, further clinical studies are needed to validate their biological activity against *H. pylori* infection. Such studies will help determine the safety and effectiveness of TCM extracts in humans and pave the way for the development of new treatments for *H. pylori* infections.

3.2. Anti-inflammation

The persistent inflammatory reaction in the gastric mucosa is recognized as an initial driver for the development of CG to gastric cancer. It has been demonstrated that chronic inflammation is sufficient to induce gastric cancer independently of *H. pylori* infection [82]. Clinical trials have revealed that the use of anti-inflammatory drugs such as celecoxib can effectively prevent the development of gastric precancerous lesions [83,84]. However, COX-2 inhibitors have adverse reactions such as abdominal pain, dyspepsia, diarrhea, and gastrointestinal bleeding, which limit their clinical application in the treatment of CG. Therefore, it is necessary to find new anti-inflammatory drugs to treat CG. Here, we summarized the inflammatory modulators derived from TCM and discussed their potential application in the treatment of CG.

Zuojin pill is a classic TCM formula composed of two herbs, *Coptidis Rhizoma* and *Evodiae Fructus*, widely used for treating gastric diseases. A clinical trial involving 14 patients showed that Zuojin Pill effectively reduced erosion and bile reflux in Chronic non-atrophic gastritis patients, and alleviated active chronic inflammation, including COX-2, IL-4, and IL-17 [37]. In vivo and in vitro experiments have demonstrated that Zuojin pill can decrease the serum levels of IL-6, MCP-1, PGE2, TNF- α , and VEGF and improve gastric tissue inflammatory lesions induced by *H. pylori* [38]. Moluodan is a classical TCM patent that has been used in the treatment of CAG. Zhou et al. used network pharmacology to analyze the mechanism of action of Moluodan in the treatment of CAG, and the results suggested that its treatment of atrophic gastritis involves regulating various biological functions, including inflammation. Subsequent experimental studies confirmed that Moluodan can reduce the release of TNF- α and IL-6 to reduce the inflammation level [39]. Similarly, network pharmacology predicted that Banxia Xiexin Decoction could play a role in the treatment of CG through a multi-compound, multi-target, and multi-pathway mechanism. Experimental results have also confirmed that this prescription can play an anti-inflammatory effect by reducing the levels of TNF- α , IL-2, and IL-8 [40]. Qinghuayin, composed of *semen dolichoris album*, *Poria cocos*, *coix seeds*, *herba artemisia scoparia*, *herba eupatorii*, *amomum cardamom*, *rhizoma coptidis*, *cortex magnolia officinalis*, and *radix paeoniae rubra*, is a Chinese formula that has been widely used in the treatment of CAG. Li et al. applied this prescription to treat the CAG rat model, and the results showed that Qinghuayin could reduce the level of serum TNF- α and the expression of TLR4, MyD88, NF- κ B, and COX-2 in gastric mucosa, thereby reducing inflammation [41]. Due to the complexity of the components in TCM compounds, the research of single herb and Chinese medicine monomers has gained much attention. *Atractylodes macrocephala* Koidz. is a widely used Chinese herb for the treatment of gastrointestinal disorders. It is contained in the Sijunzi decoction and Moluodan described in the previous article. Through network pharmacology, Yang et al. analyzed that *Atractylodes macrocephala* Koidz. may treat CG by influencing the inflammatory response. Subsequent experiments confirmed that *Atractylodes macrocephala* Koidz. can regulate the expression of IL-6 and IL-1 β and inhibit inflammation, thus treating CG [42]. *Geranii Herba*, a perennial plant in northeast China and Korea, has long been used for the treatment of gastrointestinal diseases. A study in South Korea demonstrated that *Geranii Herba* could protect against HCl/EtOH-induced gastritis by inhibiting the production of inflammatory proteins in the NF- κ B and MAPK signaling pathways [43]. *Polygonum capitatum* is a traditional Miao-national herb that has been proven to have antibacterial and anti-inflammatory activity. Network pharmacology and experiments confirmed that *Polygonum capitatum* can treat *H. pylori*-associated gastritis by affecting the phosphorylation of I κ B α , NF- κ B p65, p38MAPK, and ERK1/2, as well as the nuclear transposition of NF- κ B p65 and p-p38MAPK [44]. Further research has confirmed that the flavonoid glycosides of *Polygonum capitatum* can reduce the inflammation of gastric tissues infected by *H. pylori* through regulating the levels of IFN- γ and IL-4 [45]. As a natural ingredient abundant in TCM herbs, studies have confirmed that quercetin has a wide range of biological effects, including anti-gastric cancer and anti-inflammatory properties. A large population-based case-control study in Sweden showed that quercetin intake reduced the incidence of non-cardia gastric adenocarcinoma [85]. In vitro experiment confirmed that quercetin could down-regulate the expression of MMP-9 in GES-1 cells induced by TNF- α through the TNFR-c-Src-ERK1/2 and c-Fos or NF- κ B pathways, thereby exerting an anti-inflammatory effect in gastritis [46]. Baicalin, as the main component of *Radix Scutellariae*, can alleviate the inflammatory response of CG by inhibiting the levels of TNF- α , IL-8, and IL-1 β [47]. Taken together, these TCM and their extracts showed good anti-inflammatory activity, which can be used for future anti-gastritis agent discovery and deserve further investigation.

3.3. Regulating the immune response

The gastric mucosal immune system is an essential part of the human body's immune system. It carries out its immune function through both innate and adaptive immunity, which are closely linked to gastric diseases. *H. pylori* infection, as a major cause of gastritis, can activate both innate and adaptive immunity, leading to mucosal damage [86]. For example, a recent study revealed that the CCR6+ subset of CD4⁺ regulatory T cells, which are involved in local immune inhibition, was significantly correlated with increased inflammation in *H. pylori* gastritis [71]. Cold and Hot Syndrome are two typical conditions of TCM Syndrome. A study has found that Cold syndrome and Heat syndrome manifest abnormal immunity and energy metabolism in patients with CG. Specifically, the level of energy metabolism in Cold syndrome is low, while the immune function of Heat syndrome is enhanced [72]. In addition, the Spleen qi deficiency syndrome and Pi-wei damp-heat syndrome are common states of CAG based on TCM theory. A study involving miRNAs showed that Pi-wei damp-heat syndrome-related miRNAs are mainly involved in immune responses, while miRNAs related to Spleen qi deficiency syndrome are involved in inflammatory responses, extracellular matrix (ECM) organization, and collagen

catabolism, both of which are associated with leukocyte function [87]. Similar studies have shown that CG with Spleen qi deficiency has an abnormal immune function, manifested as decreased macrophage activity and decreased lymphocyte proliferation [88]. Therefore, modulating immune function may be a potential way of treating CG.

Weifuchun capsule is a traditional Chinese patent medicine that is utilized to treat CAG by invigorating the spleen and qi, activating blood circulation, and detoxifying the body. Experiments have demonstrated that Weifuchun capsule possesses anti-inflammatory properties and can modulate the immune system by regulating immune cells such as T cells and macrophages, as well as related genes including TLR2 and CD14 [48]. Sijunzi Decoction is a classical Chinese prescription with the effect of invigorating Qi and the spleen, which could activate the innate immune system. According to a clinical study, modified Sijunzi Decoction could effectively relieve CAG symptoms and improve the pathologic changes of CAG. Further study has revealed that this decoction could regulate CAG immune disorders by acting on TCR, a membrane protein that participates in the activation of T-cells [49]. Huangqi Jianzhong Tang is a famous Chinese herbal formula that originated in the Han Dynasty and has been widely used in the treatment of gastritis. A study based on the urine comprehensive metabolome of CAG rats indicated that Huangqi Jianzhong Tang could treat CAG by improving the immune system [50]. Poncirin is a flavanone glycoside found in many Chinese herbs. It has a variety of biological activities, including anticancer, antibacterial, and anti-inflammatory. A study in rats with ethanol-induced gastritis showed that poncirin could treat gastritis by inhibiting the infiltration of immune cells, including neutrophils [51]. These studies suggest that regulating immune function is one of the measures to treat CG. However, related research on the treatment of CG by regulating immune function is still scarce. Therefore, further research on TCM regulating the immune status of CG is needed.

3.4. Regulating apoptosis and proliferation

Gastric epithelial cells maintain a balance between cell proliferation and apoptosis, which is essential for the maintenance of physiological processes. However, as CG progresses to gastric cancer, the balance of proliferation and apoptosis is disturbed. Studies have shown that apoptosis increases in CG but decreases with the progression of CAG and intestinal metaplasia, during which epithelial cell proliferation tends to increase [89]. Consequently, cell proliferation and apoptosis are important therapeutic targets for CG, particularly for precancerous lesions of gastric cancer. The imbalance between proliferation and apoptosis of gastric mucosa is mainly observed in CAG, and related researches mainly focus on the use of TCM to regulate proliferation and apoptosis to treat this disease.

Qilianshupi decoction is an empirical formula used for the clinical treatment of CAG and is composed of *Astragalus membranaceus*, *Fructus ligustri lucidi*, *Scutellaria barbata*, *Zedoary rhizome*, and *Semen coicis*. P53 is a tumor suppressor protein whose activation induces apoptosis. Network pharmacology analysis revealed that Qilianshupi decoction could regulate apoptosis by acting on the p53 signaling pathway. Further animal experiments demonstrated that Qilianshupi decoction prevents gastric precancerous lesions by decreasing the expression of survivin and p53 [52]. The Wnt/ β -catenin pathway plays a critical role in tumorigenesis by facilitating cell proliferation. In an animal study, it has been demonstrated that the Jianpiyiqi formula, which is composed of *Codonopsis pilosula* (Franch.) Nannf., *Atractylis macrocephala* (Koidz.) Hand.-Mazz., *Poria cocos* (Schw.) Wolf, *Glycyrrhiza uralensis* Fisch, *Citrus reticulata* Blanco, *Pinellia ternata* (Thunb.) Makino, *Aucklandia Lappa Decne.*, *Amomum villosum* Lour., *Curcuma aeruginosa* Roxb., *Oldenlandia diffusa* (Willd.) Roxb., *Curcuma wenyujin* Y. H. Chen & C. Ling, and *Yunmushi*, can reduce the protein and gene expression levels of Wnt1, β -catenin, and cyclin D1 and increase the expression of GSK-3 β in CAG rats to inhibit the abnormal proliferation of CAG [53]. Akt1 is a serine/threonine kinase belonging to the AKT family and is a crucial node in the PI3K pathway, playing a pivotal role in modulating cell proliferation and tumorigenesis. Animal experiments have shown that the expression of AKT1 is elevated in the gastric mucosa of CAG. However, the Huazhuojiedu decoction, consisting of *AArtemisiae Capillaris Herba*, *Radix Scutellariae*, *Hedyotis Diffusae Herba*, *Radix Isatidis*, *Lobeliae Chinensis Herba*, *Herba Pogostemonis*, *Herba Scutellariae Barbatae*, *Sophorae Flavescentis Radix*, *Rhizoma Coptidis*, *Pentaphyllum*, *Gynostemmae Pentaphylli Herba*, and *Herba Eupatorii*, has been found to treat CAG by inhibiting AKT1 [54]. Furthermore, additional cell and animal experiments confirmed that the Huazhuojiedu decoction can downregulate the lnc 517368 and effectively inhibit cell proliferation and promote apoptosis in CAG cells [70]. Erianin, the main active ingredient from *Dendrobium chrysotoxum* Lindl., has been found to possess a series of biological effects such as anti-inflammatory, pro-apoptotic, anti-proliferation, and anti-oxidant [90–92], and has an anti-tumor effect by inhibiting the PI3K/Akt/mTOR pathway [93]. In the study of gastric precancerous lesions, it was found that erianin can block the cell cycle in the G2/M phase and induce apoptosis through the PI3K/Akt signaling pathway, thereby treating the disease [56]. *Hericium erinaceus* (Rull ex F.) Pers is a kind of edible mushroom, which is widely used to treat gastrointestinal diseases. Wang et al. observed that EP-1, a polysaccharide isolated from *Hericium erinaceus* (Rull ex F.) Pers, could induce the apoptosis of gastric precancerous cells by regulating the expression of Bax, Bcl-2, and caspase-3 [57]. Quercetin is regarded as one of the main components in the treatment of chronic superficial gastritis in Jinhong tablets [94]. An in vivo and in vitro experiment confirmed that quercetin can regulate the balance of gastric cell proliferation and apoptosis by reducing p38MAPK and BAX levels and increasing BCL-2 [58].

In conclusion, regulating the balance of gastric mucosal apoptosis and proliferation is the key to the treatment of gastric precancerous lesions with TCM.

3.5. Regulating autophagy

Autophagy is an intracellular catabolic process that plays an important role in maintaining intracellular homeostasis. It is a highly regulated process consisting of induction, nucleation, expansion and maturation, fusion, and degradation. Recent studies have found that autophagy has a correlation with the occurrence and development of gastric diseases and plays a vital role in the regulation of

gastric mucosal cells. As a strong risk factor for gastritis, *H. pylori* infection is related to the apoptosis of gastric epithelial cells. Autophagy activation can protect gastric mucosal cells by preventing the apoptosis of human gastric epithelial AGS cells induced by *H. pylori* [95]. IFN- γ is a cytokine that plays an important role in immunity, inflammation, and tumorigenesis. Scholars have confirmed that IFN- γ inhibits gastric carcinogenesis by inducing autophagy to reduce apoptosis of epithelial cells [96]. Therefore, the regulation of autophagy is expected to be a potential target for gastric mucosal protection [97].

As mentioned above, Zuojin Pill is a classic prescription widely used for the treatment of CG. An in vivo and in vitro-based study showed that Zuojin Pill could improve gastric histomorphology of CAG by increasing the expression levels of PTEN, LC3-II, and Beclin-1, which are involved in autophagy induction and autophagosome formation [59]. Berberine is an isoquinoline alkaloid found in many herbs, including *Coptidis Rhizoma* and *Phellodendri Chinensis Cortex*. It can alleviate the inflammatory response of CAG by promoting autophagy-related LC3-II and Beclin-1 and inhibiting the PI3K/AKT signaling pathway [60]. Weipingshu Capsule is a prescription from Xi'an Hospital of TCM for the treatment of precancerous lesions of gastric cancer. It is composed of eleven herbs including *Hedysarum Multijugum Maxim*, *Atractylodes Macrocephala Koidz*, *Paoniae Radix Alba*, *Angelicae Sinensis Radix*, *Panax Notoginseng (Burk.) F. H. Chen Ex C. Chow*, *Curcumae Rhizoma*, *Pollen Typhae*, *Scutellariae Barbatae Herba*, *Hedyotis Diffusae Herba*, *Persicae Semen*, and licorice. Studies have shown that Weipingshu can significantly improve the abnormal morphology of gastric mucosal epithelial cells and gland atrophy, and increase the number of autophagosomes in gastric mucosal epithelial cells [61]. Similarly, Chinese herbal formulas like Huatan Xiaoyu formula and Anwei decoction have been used to interfere with the precancerous lesions of atrophic gastritis, and the experimental results showed that these prescriptions can increase the expression of autophagy-related genes and proteins [62,63].

In summary, these results suggest that the activation of autophagy may be an important way of treating CAG. However, most studies focus on regulating autophagy to treat precancerous lesions of gastritis, and studies on autophagy in CNAG and atrophic gastritis/CAG are still rare. Therefore, it is essential to conduct further research to explore the relationship between autophagy and CG, and to uncover the mechanism of TCM in the treatment of CG.

4. Conclusion

As a multi-step, slowly progressive, and lifelong inflammatory disease, CG brings many physical symptoms to the patient, as well as economic and social burdens to society. With the progression of CNAG to CAG, the risk of gastric cancer increases [98]. Thus, making proactive treatment of CG essential in order to improve the condition of patients and reduce the socio-economic burden.

In recent years, Chinese medicine has garnered significant attention due to its precise efficacy, minimal side effects, and holistic approach. Regarding CG, TCM has conducted extensive research in diagnosis and treatment, such as tongue diagnosis being a crucial component of TCM syndrome diagnosis. According to TCM theory, tongue coating is a reflection of the body's health status. A recent study found that alterations in the microbiota of tongue coating could signal the presence and advancement of gastritis. The researchers identified 21 microbial species that could differentiate between the tongue-coating microbiomes of individuals with and without gastritis. Additionally, they discovered that *Campylobacter concisus*, a bacterium detected in tongue coating and gastric fluid, was associated with the development of gastric precancerous conditions, potentially serving as a non-invasive biomarker for long-term gastritis monitoring [99]. In addition, several scholars have investigated the ultrastructure of gastric mucosa in CG associated with different syndromes. The study discovered distinct mitochondrial abnormalities in the gastric mucosa of patients with different types of chronic gastritis. Specifically, those with spleen-stomach damp-heat syndrome type exhibited obvious mitochondrial edema, irregular arrangement, and rough endoplasmic reticulum aggregation. In contrast, patients with spleen deficiency syndrome showed decreased mitochondrial content, fractured crests, vacuoles accompanying myeloid body, and pool-like rough endoplasmic reticulum extension [100]. These studies offer a fresh perspective for clinical and basic research on diagnosing and treating CG with TCMs, providing valuable insights for further exploration in this field.

In this review, we introduce Chinese herbal compounds, extracts of herbs and compounds used in TCM that have been reported for the treatment of CG. Several clinical evidence-based studies have shown that TCM plays a vital role in the treatment of CG by improving the symptoms, reducing inflammatory damage to the mucosa, and blocking the progression from CG to gastric cancer. Further mechanistic studies have revealed that the mechanisms of TCM for the treatment of CG include eradication of *H. pylori*, anti-inflammatory effects, immune modulation, regulating the level of gastric mucosal cell proliferation, apoptosis, and autophagy. However, there are some challenges in the development of TCM as a treatment for CG. Firstly, more multi-center, double-blind, randomized, and controlled clinical trials should be conducted to validate the efficiency of those classic TCM prescriptions in the treatment of CG. Secondly, many herbal monomers have been found to be effective in the treatment of CG, so clinical studies with herbal monomers can be carried out. Thirdly, due to the complexity of TCM compounding, there is a need to develop new analytical tools and experimental methods to investigate the integrative mechanisms of TCM compounds in the treatment of CG. Fourthly, while the introduction of basic research on related TCM syndromes has provided valuable insights, the absence of relevant TCM prescriptions for intervention and verification has resulted in certain limitations. Therefore, it is imperative that further experimental research be conducted to verify the findings of these studies and provide a more comprehensive understanding of these topics.

In conclusion, Chinese medicine is renowned for its multiple pathways, multiple targets and few side effects. Further exploration of the clinical effects and mechanisms of action of TCM in the treatment of CG is of great significance.

Ethics approval and consent to participate

Not applicable.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of competing interest

No conflict of interest exists in the submission of this manuscript, and all authors have seen the final version of the manuscript and approved to submit to your journal. To the best of our knowledge and belief, this manuscript has not been published in whole or in part nor is it being considered for publication elsewhere.

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