

***World Journal of Gastrointestinal Oncology***

5 December 2022

Re: Manuscript Number: 80215

Title: Traditional Chinese Medicine for Transformation of Gastric Precancerous Lesions to Gastric Cancer: A Critical Review

Dear editor,

Please find attached a revised version of our manuscript “ Traditional Chinese Medicine for Transformation of Gastric Precancerous Lesions to Gastric Cancer: A Critical Review ”, which we would like to resubmit for publication as a review article in ***World Journal of Gastrointestinal Oncology***.

The comments of reviewers were extremely insightful and enabled us to greatly improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers.

We revised the manuscript with red color and made thorough revisions to the article in accordance with reviewers' suggestions. We hope that with these revisions and our accompanying responses, our manuscript is now suitable for publication in ***World Journal of Gastrointestinal Oncology***.

We shall look forward to hearing from you at your earliest convenience.

Yours sincerely,

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**Reviewer #1:** This paper covers a very important topic. Traditional Chinese Medicine (TCM) plays a certain role in reversing the transformation from Gastric precancerous lesion (GPL) to Gastric cancer (GC). However, there are several issues that need to be addressed:

1. In addition to the mechanism, you should supplement relevant clinical studies that TCM can regulate the changes from GPL to GC.

**Response:** Thank you very much for the valuable comments and constructive suggestion. In the "Introduction", we added a background introduction to the clinical research of TCM for the treatment of GPL and GC, and provided a table of relevant clinical research: Clinical trial of traditional Chinese medicine in treating gastric cancer and precancerous lesions (Table 1), as follows:

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 formulas (fangjis) were documented in Treatise on Febrile Diseases, and Prescriptions of the Pharmacy Bureau, 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<sup>[25, 26]</sup> and GC<sup>[27, 28]</sup>. Currently, a variety of traditional Chinese patent medicines (CPM), such as the Weiqi decoction(WQD)<sup>[29]</sup>, WeiFuChun(WFC)<sup>[30]</sup>, and Weipixiao (WPX)<sup>[31]</sup> 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 gastric cancer, and improve the progression of advanced gastric cancer (Table1). For instance, WFC is a Chinese herbal compound approved by the National Medical Products Administration (NMPA) 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<sup>[16]</sup>. Moreover, with the advantages of TCM in precancerous lesions and gastric cancer, TCM has received increasing attention, and a growing number of clinical studies have been registered at ClinicalTrials.gov, such as the Jianpi Yangzheng Xiaozheng decoction ([NCT03823248](#)) and Yiqi Wenyang Jiedu decoction ([NCT05229809](#)).

Table 1: Clinical trials of TCM in treating gastric cancer and precancerous lesions

pathological stages	Authors and year	Clinical drugs	Clinical Sample Size	Intervention	Control	Treatment duration	Outcome measures
Gastric precancerous lesions (GPL)	Deng et al[123], 2012	Weining Granules	120	Weining Granules	Weifuchun tablets	6 months	Overall response; gastroscopically-determined response; pathologically-confirmed response; eradication of Hp; microvessel density in the gastric mucosa; expression of vascular endothelial growth factor; IL-2; IL-6; T lymphocyte subsets; immunoglobulins; symptom scores; QOL; and adverse reactions.
	Bian et al[16], 2021	Weifuchun (WFC)	120	WFC tablets	Vitacoenzyme tablets	6 months	Histopathology of gastric tissues; intestinal microbiota; sensitivity and specificity of different intestinal microbiota
	Li et al[124], 2006	Weiansan (WAS)	76	Weiansan	Weifuchun tablets	24 weeks	Inflammation of gastric mucosa; degree of glandular atrophy; IM and dysplasia; Hp infection
	NCT0382324	MoLuoDa	480	Moluodan	Folic acid	24 weeks	The disappearance rate of dysplasia; Histopathological

	8	n and Sanchi powder		combined with Sanchi powder	tablets		score; Endoscopic Findings score; Main symptom score; The patient-reported outcome scale integrals
gastric cancer (GC)	Pan et al[126], 2020	Jianpi Yangzheng Xiaozheng decoction	210	Chemotherapy combined with JPYZXZ decoction	Chemotherap y	24 weeks	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 [127], 2013	Wei Chang'An	399	Chemotherapy combined with Wei Chang'An decoction	Continuously	3 months or more	Survival trends; Survival time
	Shu et al [128], 2019	Yiqi Huayu Jiedu decoction	489	Chemotherapy combined with YHJD	Chemotherap y	6 months or more	disease-free survival rate; 5-year survival rate; QOL; TCM symptoms
	NCT0522980 9	Yiqi Wenyang Jiedu	212	Yiqi Wenyang Jiedu prescription	Simulation agent of Yiqi Wenyang	24 weeks	2-year disease-free survival rate; disease-free survival; overall survival; cumulative annual recurrence and metastasis rate for 1-3 years; cumulative annual

		prescription			Jiedu prescription		survival rate for 1-3 years; Indexes related to fat distribution; visceral adiposity Index; tumor marker; peripheral blood inflammatory index; prognostic nutritional index; QOL of the patient; evaluation of the patient's symptoms; medication compliance; percentage of participants with adverse events
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2. In the Discussion section, it would be better if clinical studies involving those reversing the GPL to GC and what need to be done in the future could be supplemented.

**Response:** Thank you very much for the valuable comments and constructive suggestion. In the "Discussion" section, we supplemented the discussion and analysis of clinical studies related to GC and GPL, and gave our opinions on the current situation

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<sup>[10]</sup>. However, for patients with advanced GPL, such as the IM stage, whether eradication of *H. pylori* have therapeutic effects remain controversial<sup>[124]</sup>. 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 gastric cancer<sup>[125, 126]</sup>. 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% and 23.33%, respectively. The total effective rates of relieving IM in the WFC and Vit groups were 73.33% and 26.67%, respectively<sup>[16]</sup>. 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.

3. This study only reviewed the three parts of proliferation, apoptosis, inflammatory pathways and angiogenesis, the limitations of this review are required. It will also be more significant to summarize the aspects of metabolism, epithelial-mesenchymal transition, immune regulation and so on.

**Response:** Thank you very much for the valuable comments and constructive suggestion. According to your suggestion, we have added relevant contents about the three mechanisms aspects of metabolism, epithelial-mesenchymal transition and immune regulation

## **OTHER MECHANISMS OF ACTION IN THE TREATMENT OF GPL**

### ***Regulate GPL related metabolism***

Metabolic disorder is a hallmark of gastric cancer, the most significant of which are disorders of glucose metabolism<sup>[60]</sup>. In contrast to normal cells, gastric cancer cells preferentially choose glycolysis as the main way to obtain energy, even under conditions of sufficient oxygen<sup>[61]</sup>. The rapid proliferation of GC cells depends largely on glycolysis<sup>[62]</sup>. 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<sup>[63]</sup>. Ginsenoside Rg3(GRg3) blocks glycolysis by inhibiting the PI3K/AKT pathway and downregulating downstream miRNA-21<sup>[63]</sup>, whereas WPX inhibits the PI3K/AKT/mTOR pathway by upregulating upstream miRNA-34a, and then blocks glycolysis<sup>[64]</sup>. Interestingly, both WPX and As-IV can regulate LDHA, MCT4, HIF-1 $\alpha$ , and CD147 targets inhibits glycolysis<sup>[65]</sup>.

### ***Reverse GPL related epithelial-mesenchymal transition (EMT)***

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<sup>[66]</sup>. 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 gastric cancer<sup>[67]</sup>. 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. found that GA can inhibit the EMT process by downregulating the Wnt/ $\beta$ -catenin signaling pathway, thereby inhibiting the malignant proliferation of MC cells and finally achieving the goal of treating GPL<sup>[68]</sup>. The Manpixiniao Decoction is a compound used in Chinese medicine. Li et al. 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<sup>[69]</sup>.

## **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<sup>[93, 94]</sup>. Current research has shown that many TCMs can inhibit abnormal metabolic processes. Licochalcone A (Lic A) is an important active compound extracted from licorice that has anti-inflammatory, antibacterial, antioxidant, antitumor, and other activities. Wu et al. found that Lic A inhibits glycolysis by blocking the Akt/HK2 pathway. In nature, baicalein mainly exists in *Scutellaria baicalensis* Georgi and has anti-inflammatory, antibacterial, and other effects. Chen et al. found that baicalein can inhibit glycolysis by regulating the PTEN/Akt/HIF-1 $\alpha$  signaling pathway<sup>[95]</sup>.

### ***Reverse GC related epithelial-mesenchymal transition (EMT)***

In the malignant progression of gastric cancer, tumor cells use the process of EMT to change their cell morphology to improve their invasiveness, metastatic ability, and drug resistance<sup>[96, 97]</sup>. Therefore, the inhibition of EMT is a key factor in the treatment of gastric cancer. Wang et al. 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 gastric cancer cells<sup>[98]</sup>. Babaodan (BBA) 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. found that BBD can inhibit the TGF- $\beta$ /Smad signaling pathway, thereby inhibiting TGF- $\beta$ -induced EMT<sup>[99]</sup>.

### ***Improved GC related immune regulation***

Compared with other therapies, immunotherapy has the characteristics of lasting remission, improving the quality of life (QOL) of patients, and prolonging survival<sup>[100]</sup>, which brings new hope to most patients with gastric cancer<sup>[101]</sup>. Modern experimental studies have found that many TCMs regulate immunity and eliminate immune disorders<sup>[102]</sup>. Oleanolic acid is widely found in many TCMs, such as hawthorns and black plums. Lu et al. found that OA destroyed IL-1 in gastric cancer cells  $\beta$ /NF- $\kappa$  B/TET3 axis, leading to DNA hypomethylation and downregulation of PD-L1. This suggests that OA can be used as an epigenetic modulator in gastric cancer immunotherapy<sup>[103]</sup>. In addition, sophoridine, a monomer of TCM, regulates immune function and can act on macrophages and CD8<sup>+</sup>T cells, thus reshaping the immune microenvironment of GC<sup>[104]</sup>.

4. The format of references is not uniform, journals have full names and abbreviations.

**Response:** Thank you very much for the valuable comments and constructive suggestion. We re proofread the format of the literature and standardized the names of all journals.

**Reviewer #2:** Specific Comments to Authors: In this paper, the authors reviewed the use of traditional Chinese medicine (TCM) in treating transformation from gastric precancerous lesion to gastric cancer. The paper is interesting and suitable for the journal.

**Response:** Thank you very much for your comments.

## Round 2

It is mentioned in the review “the existence of the same TCM compound with obvious therapeutic effect both on GPL and GC indicate that TCM shows a dual-directional regulation”, but the effect of treating GC and its precancerous lesions and reversing transformation to GC and recovery of GPL is in the same direction. The word “dual-directional regulation” may not be appropriate here.

### *World Journal of Gastrointestinal Oncology*

14 December 2022

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