

Research on precancerous lesions of gastric cancer in traditional Chinese medicine

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Abstract. Traditional Chinese Medicine (TCM) has demonstrated multi-target mechanisms and notable clinical efficacy in preventing and treating Precancerous Lesions of Gastric Cancer (PLGC), providing important evidence for optimizing integrated Chinese-Western medical prevention and treatment strategies. Integrating classical TCM theories with modern molecular mechanism studies, including signaling pathway regulation and network pharmacology, as well as clinical trial evidence from randomized controlled trials and cohort studies, existing research has analyzed the therapeutic effects of TCM formulations such as Molodan and Weifuchun, together with acupuncture interventions. TCM attributes PLGC primarily to spleen-stomach deficiency, accompanied by phlegm-stasis entanglement and damp-heat toxin as core pathological characteristics. At the molecular level, active TCM components inhibit abnormal cell proliferation and regulate the apoptosis-proliferation equilibrium through pathways such as EGFR-PI3K-AKT and Hedgehog. Clinically, Molodan achieved an 82.8% reversal rate of gastric mucosal dysplasia after one year treatment, compared with 53.9% in the folic acid control group, while Weifuchun significantly improved gut microbiota composition, notably reducing Parabacteroides abundance. In addition, acupuncture enhances gastric mucosal barrier function via neuro-immunomodulation. Overall, TCM demonstrates holistic and multi-target efficacy in delaying PLGC progression. Future research should leverage nanotechnology and artificial intelligence to deepen mechanistic insights and establish standardized efficacy evaluation frameworks.

Keywords: precancerous lesions of gastric cancer, TCM therapy, multi-target effects, preventive treatment, molecular mechanisms

1. Introduction

Gastric cancer, as a malignant disease that poses a serious threat to public health, saw more than 1,089,000 newly diagnosed cases worldwide in 2020, with approximately 769,000 deaths [1]. It ranked as the fifth most common cancer in terms of incidence and the fourth leading cause of cancer mortality globally [2]. China, Japan, India, Russia, and South Korea were the top five countries for new cases of gastric cancer [1]. In China, gastric cancer ranks third in both incidence and mortality among malignant tumors, with rates nearly 30% higher than the global average. Epidemiological surveys indicate that due to insufficient early screening coverage, approximately 72% of patients are diagnosed at advanced stages, resulting in a five-year survival rate of less than 7% [3].

Although there is no specific term for "gastric cancer" in ancient Chinese medical texts, symptom-based analysis reveals its close correlation with traditional disease patterns such as "Yege" (dysphagia and regurgitation) and "Jiju" (abdominal masses). The description in Lingshu of "epigastric pain near the heart with food intake obstruction" reflects characteristics of digestive tract blockage, while the "Fuliang" (hidden masses) documented in Suwen demonstrates tumor invasion and growth features, providing a theoretical foundation for later generations' diagnosis and treatment approaches [4]. Gastric cancer typically originates from the gastric mucosal epithelium, progressing through chronic inflammation, precancerous lesions, and malignant transformation, involving multiple risk factors. In recent years, traditional Chinese Medicine (TCM) has made significant advances in researching the prevention and treatment of gastric precancerous lesions, demonstrating unique advantages through multi-target and multi-pathway interventions. Guided by holistic principles and pattern differentiation-based treatment, TCM provides systemic regulation of patients, conceptually aligning with modern precision medicine.

However, current TCM approaches for managing gastric precancerous lesions still face challenges such as lack of standardized efficacy evaluation criteria and unclear mechanistic understanding, which hinder its broader clinical adoption and international recognition. Therefore, conducting in-depth research on the prevention and treatment strategies of traditional Chinese medicine for precancerous lesions of gastric cancer and exploring their scientific basis holds significant practical implications for promoting the advancement of traditional Chinese medicine in the field of cancer prevention and treatment.

2. Etiology and pathogenesis of gastric precancerous lesions in TCM theory

Traditional Chinese Medicine (TCM) possesses a long history and demonstrates significant efficacy in the treatment of chronic diseases. Its therapeutic approach to Chronic Atrophic Gastritis (CAG), Precancerous Lesions of Gastric Cancer (PLGC), and even Gastric Cancer (GC) consistently emphasizes individualized diagnosis and treatment principles based on the patient's constitution, symptoms, and underlying etiology. The core tenet of TCM theory lies in maintaining the balance and harmony of the internal environment of the human body. It posits that disruptions in the dynamic equilibrium between "Qi" (vital energy) and blood, "Yin" and "Yang", as well as the functions of the internal organs (Zang-Fu), can lead to the development of CAG, PLGC, and GC. Within this framework, "Qi" is regarded as the essential subtle substance that constitutes the human body and sustains life activities; "Yin" and "Yang" represent the opposing yet unified forces within the body, and their imbalance forms a critical foundation for disease pathogenesis. Consequently, regulating Yin and Yang to restore equilibrium is a primary therapeutic objective in TCM.

Research also indicates that the occurrence of these diseases is frequently associated with factors such as dietary irregularities, emotional disturbances, and the invasion of external pathogenic factors. These factors are recognized as capable of impairing the functional integrity of the Spleen and Stomach (Pi Wei). Within the TCM theoretical system, the development of gastric precancerous lesions exemplifies the manifestation of these systemic imbalances combined with localized pathological changes. It involves complex etiological factors and pathological mechanisms, primarily linked to Yin-Yang disharmony and dysfunction of the internal organs. Crucially, Spleen-Stomach deficiency (Pi Wei Xu Ruo) is considered the central pathological basis for their onset. The Spleen and Stomach are regarded as the "Root of the Postnatal Life" (Hou Tian Zhi Ben), the source of Qi and Blood production. If the functions of the Spleen and Stomach are impaired, leading to dysfunction in transportation and transformation (Yun Hua), this can readily result in the internal accumulation of Dampness and Water (Shui Shi Nei Ting). This, in turn, facilitates the generation of Phlegm (Tan) and the aggregation of Blood Stasis (Yu). The pathological products of intertwined Phlegm and Blood Stasis (Tan Yu

Hu Jie) obstructing the gastric region, if persistent and unresolved, may gradually progress to form precancerous lesions. This suggests that the pivotal mechanism linking both external factors (diet, emotions, pathogens) and internal factors (Yin-Yang imbalance) to the eventual development of precancerous lesions often lies in the impairment of Spleen-Stomach function and the subsequent pathological consequence of Phlegm-Blood Stasis intermingling (Tan Yu Hu Jie) [5].

Emotional dysregulation is also a significant pathogenic factor. Chronic emotional disturbances such as persistent worry, overthinking, anger, and irritability can lead to liver qi stagnation, which may transversely invade the stomach, resulting in impaired gastric descending function and disrupted qi-blood circulation. This consequently affects spleen-stomach functionality and accelerates pathological progression. Additionally, dietary irregularities—particularly excessive intake of pungent, greasy, or raw-cold foods—directly damage the spleen-stomach system, establishing a clear correlation with the development of gastric precancerous lesions.

While Traditional Chinese Medicine (TCM) does not employ the specific modern diagnostic terms "Gastric Cancer (GC)" or "Gastric Precancerous Conditions (GPC)," it classifies these conditions based on presenting symptoms such as epigastric fullness, nausea, vomiting, heartburn, and upper abdominal pain. The hallmark of TCM is its treatment approach grounded in syndrome differentiation and holism, emphasizing the dynamic equilibrium of the body. TCM theory resonates with core concepts in microecology, particularly the unity of internal and external environments with biology, highlighting its inherent interdisciplinary nature. The composition of TCM herbal formulas is inherently complex, mirroring the intricate diversity of microbial species within the gut. Administered orally, these formulas interact directly with the gastrointestinal tract upon ingestion. TCM can modulate the gastrointestinal microenvironment by enhancing the abundance and activity of probiotics, inhibiting pathogenic bacteria, and preventing bacterial translocation, thereby promoting microbial balance.

Conversely, the gastrointestinal microbiota plays a crucial role in the biotransformation and metabolism of TCM components. Modern medicine identifies *Helicobacter pylori* (*H. pylori*) infection as a key factor in the development of gastric precancerous lesions. According to TCM theory, *H. pylori* is conceptualized as a form of "pathogenic qi" (xie qi). This pathogenic qi invades the Spleen and Stomach, damaging the body's vital qi (zheng qi). This assault impairs the Spleen's transformative function and the Stomach's descending function, leading to the endogenous production of damp-turbidity. The dampness and turbidity then congeal with heat, forming intractable damp-heat. Consequently, this pathogenic process exacerbates Spleen-Stomach dysfunction [6]. In summary, the synergistic interactions of spleen-stomach deficiency, emotional dysregulation, dietary irregularities, and Xie Qi invasion collectively induce internal dyshomeostasis, qi-blood stasis, and visceral functional disorders, ultimately triggering the development of gastric precancerous lesions. Delving into these etiopathogenic mechanisms holds significant guiding importance for formulating scientifically grounded TCM prevention and treatment strategies.

3. Mechanisms and comprehensive applications of TCM in treating gastric precancerous lesions

The therapeutic mechanisms of traditional Chinese Medicine (TCM) against gastric precancerous lesions exhibit multi-pathway, multi-target characteristics. At the cellular level, active TCM components regulate cell cycle progression and apoptotic signaling pathways to inhibit abnormal cell proliferation and induce apoptosis. For instance, certain alkaloid compounds target cell cycle regulatory proteins, arresting cancer cells in specific phases to suppress division while simultaneously activating apoptotic pathways to eliminate malignant cells

[7]. In addition, modern studies have confirmed that traditional Chinese Medicine (TCM) compounds exhibit unique advantages in the intervention of precancerous Lesions of Gastric Cancer (PLGC). A recent study using network pharmacology combined with *in vivo* verification demonstrated that Manpixiao Decoction (MPX), a classic TCM formula, significantly alleviated gastric mucosal pathological injury and reduced tumor incidence in PLGC rats, while inhibiting abnormal proliferation of gastric mucosal epithelial cells. Its mechanism was closely related to attenuating systemic inflammatory response and downregulating pro-inflammatory cytokines such as IL-1 α , IL-7, CSF-1, and CSF-3 in serum. Meanwhile, MPX effectively blocked excessive activation of the EGFR-PI3K-AKT signaling pathway, inhibited abnormal accumulation of β -catenin and the Epithelial-Mesenchymal Transition (EMT) process, downregulated N-cadherin and restored E-cadherin expression, thereby stabilizing the phenotype of gastric mucosal epithelium and halting malignant transformation of PLGC. Further network pharmacology analysis revealed that its therapeutic effects involved multi-target and multi-link synergistic actions including inflammation regulation, immune response, cellular senescence, p53 signaling pathway, and protein processing in the endoplasmic reticulum, providing high-quality experimental evidence for TCM in preventing the progression of PLGC [8].

Clinical trials have validated the efficacy of TCM therapeutics for gastric precancerous lesions. A randomized double-blind controlled trial on Molodan demonstrated that standard-dose treatment for one year significantly reversed moderate-to-severe gastric mucosal atrophy, intestinal metaplasia, and dysplasia. Notably, the dysplasia regression rate reached 82.8%, significantly higher than the 53.9% observed in the folic acid control group, with a favorable safety profile [9]. Additionally, research on Weifuchun demonstrates its efficacy in ameliorating gastric mucosal pathology in precancerous lesions. 16S rRNA sequencing analysis revealed that its therapeutic mechanism involves modulating gut microbiota—specifically reducing Parabacteroides abundance—thus providing high-level evidence for TCM-mediated reversal of gastric precancerous conditions [10].

In addition to herbal medicine, comprehensive traditional Chinese Medicine (TCM) therapy demonstrates unique advantages in preventing and treating gastric precancerous lesions by organically integrating multiple therapeutic approaches such as acupuncture and tuina to achieve synergistic effects and enhance clinical outcomes. Specifically, acupuncture exerts its therapeutic influence through stimulation of specific acupoints to regulate meridian qi-blood flow, thereby optimizing physiological functions. Research confirms that acupuncture enhances immune function, modulates central neural pathways, regulates gastrointestinal hormones, increases gastric blood flow, improves gastric motility, controls gastric acid secretion, mitigates inflammatory responses, and balances cell proliferation and apoptosis. These multifaceted actions collectively strengthen the gastric mucosal barrier, establishing a holistic therapeutic framework [11]. From a mechanistic perspective, acupuncture may potentially influence gastrointestinal functions through multiple pathways. Primarily, it regulates the neuroendocrine system to modulate gastrointestinal motility and secretory functions. Additionally, by modulating neural mechanisms within the gastrointestinal tract, acupuncture promotes gastric mucosal regeneration and repair, thus enhancing its therapeutic effects [12].

In summary, traditional Chinese medicine (TCM) demonstrates significant advantages in intervening gastric precancerous lesions through multi-component, multi-target and multi-pathway regulatory effects. At the cellular and molecular levels, active TCM components and classic prescriptions can inhibit abnormal cell proliferation, induce apoptosis, alleviate systemic inflammation, block key carcinogenic signaling pathways, suppress epithelial-mesenchymal transition, and stabilize the phenotype of gastric mucosal epithelium, thereby preventing malignant transformation. Clinical trials have verified that multiple TCM preparations can effectively reverse pathological changes including gastric mucosal atrophy, intestinal metaplasia and dysplasia with favorable safety, and some exert therapeutic effects by regulating the structure of gut microbiota. In

addition, comprehensive TCM therapy integrating herbal medicine, acupuncture and other external treatments improves gastrointestinal function, enhances immune state, repairs gastric mucosal barrier and balances cell proliferation and apoptosis through holistic regulation. Therefore, TCM provides a safe, effective and holistic strategy for the prevention and treatment of gastric precancerous lesions, with unique therapeutic superiority and important clinical significance.

4. Advances and future perspectives in TCM treatment of gastric precancerous lesions

With the continuous advancement of modern science and technology, the research and application of traditional Chinese medicine in the intervention of gastric precancerous lesions have been continuously innovated and developed, showing huge potential while also facing new academic challenges. As an emerging interdisciplinary method, network pharmacology is based on the theories of systems biology, polypharmacology, genomics, proteomics and bioinformatics. By constructing a complete drug-target-disease interaction network, it can systematically reveal the complex molecular mechanism of multi-component and multi-target synergistic effects of traditional Chinese medicine, providing a new strategy and technical path for the modern research of Chinese medicine against gastric precancerous lesions.

A large number of data mining studies have screened out the core high-frequency herbs used in the treatment of gastric precancerous lesions, mainly including *Prunus mume*, *Curcuma longa*, *Paeoniae Radix Alba*, *Salvia miltiorrhiza*, *Hedyotis diffusa*, and *Astragalus membranaceus*. Further network pharmacological analysis shows that the active ingredients such as quercetin, β -sitosterol, kaempferol, tanshinone II A, astragaloside IV and curcumin contained in these herbs can act on key targets such as HSP90AA1, AKT1, TP53, STAT3, MAPK1 and TNF. These core targets are closely related to cell proliferation, apoptosis, inflammatory response, immune regulation and signal transduction. At the pathway level, these herbs mainly exert their therapeutic effects by regulating pathways in cancer, PI3K-AKT signaling pathway, and proteoglycans in cancer. Among them, the PI3K-AKT pathway is an important signal axis that regulates cell survival, proliferation and migration. The cancer-related pathway is involved in multiple links of tumorigenesis and development, and the proteoglycan pathway is closely related to cell adhesion, invasion and tumor microenvironment remodeling. In addition, these active components are also involved in many biological processes such as response to inorganic substances, hormone response, gland development, positive regulation of cell migration and cell movement, and play a role in kinase binding, protein kinase binding and transcriptional regulation. Through the above multi-dimensional synergistic regulation, these herbs can comprehensively exert anti-inflammatory, immune regulation, inhibition of abnormal cell proliferation, induction of apoptosis, improvement of gastric mucosal microenvironment and inhibition of epithelial-mesenchymal transition, so as to delay the malignant progression of gastric precancerous lesions and reduce the risk of canceration. This fully demonstrates that traditional Chinese medicine has significant advantages in the intervention of gastric precancerous lesions with the overall regulatory characteristics of multi-component, multi-target and multi-pathway coordination [13]. Concurrently, the integration of nanotechnology has provided innovative approaches for targeted TCM delivery. Through multifaceted functional modifications—including targeting peptide conjugation, tumor microenvironment responsiveness, and instrument-assisted precision—nanoparticle drug delivery systems significantly enhance therapeutic targeting and efficacy, demonstrating substantial clinical potential.

Despite the positive therapeutic outcomes achieved by TCM, significant controversies persist. Current clinical research faces challenges due to heterogeneous evaluation criteria, which impede objective

comparison of results and hinder broader acceptance of TCM interventions. Concurrently, the complex multi-component nature of herbal formulations—characterized by multi-target, multi-pathway mechanisms—presents substantial difficulties in mechanistic elucidation and quality control protocols. Furthermore, skepticism regarding TCM's scientific validity persists among certain stakeholders, who contend that its theoretical framework remains relatively abstract and lacks comprehensive empirical validation through modern scientific methodologies.

In the future, the research on TCM for PLGC should be deepened in the following aspects. First, strengthen basic research with the support of gene editing, proteomics, single-cell sequencing and other cutting-edge biotechnologies, so as to accurately identify the core active components, key targets and regulatory pathways of anti-PLGC Chinese medicines, and lay a solid scientific foundation for precision TCM therapy. Second, carry out large-sample, multi-center, high-quality Randomized Controlled Trials (RCTs) to establish unified, standardized and internationally recognized efficacy evaluation systems, so as to enhance the credibility and promotion value of TCM. Third, accelerate the deep integration of TCM with modern medicine, combine endoscopic diagnosis, molecular typing and microbiota regulation to optimize integrated prevention and treatment protocols. Fourth, make full use of artificial intelligence, big data and network pharmacology to mine classic prescriptions and clinical data, develop new targeted drugs and personalized therapeutic schemes, and realize the innovative transformation and upgrading of TCM in the field of PLGC. Through the cross integration of multiple disciplines and technologies, TCM will give full play to its holistic and individualized therapeutic advantages, provide safer, more effective and standardized strategies for the intervention of gastric precancerous lesions, and make important contributions to reducing the incidence of gastric cancer and improving the prognosis of patients.

5. Conclusion

Gastric Precancerous Lesions of the Stomach (PLGC) constitute a pivotal and reversible stage in the multistep carcinogenesis of gastric cancer, for which traditional Chinese Medicine (TCM) offers distinct and reliable therapeutic advantages. In terms of etiology and pathogenesis, TCM holds that PLGC is mainly rooted in spleen-stomach deficiency, accompanied by the pathological changes of phlegm-stasis entanglement and damp-heat toxin accumulation, which is highly consistent with the modern inflammation-cancer transformation theory. Mechanistically, TCM exerts anti-PLGC effects through multi-component, multi-target and multi-pathway regulatory patterns. Active ingredients and classic formulas can regulate key signaling cascades including EGFR-PI3K-AKT and Hedgehog pathways, maintain the homeostasis of cell proliferation and apoptosis, suppress abnormal Epithelial-Mesenchymal Transition (EMT), reduce systemic inflammatory responses, and improve the microenvironment of gastric mucosa, thereby blocking malignant transformation.

Clinically, representative TCM preparations such as Moluodan and Weifuchun have been verified by high-quality randomized controlled trials and microbiological studies to effectively reverse gastric mucosal atrophy, intestinal metaplasia and dysplasia with favorable safety, and some exert therapeutic effects by regulating the structure of gut microbiota. In addition, non-pharmacological therapies represented by acupuncture enhance the gastric mucosal barrier and repair functions through neuro-immunomodulation, gastrointestinal hormone regulation and local blood flow improvement, forming a comprehensive TCM intervention system combined with internal herbal medicine.

With the integration of network pharmacology, multi-omics, nanotechnology and other emerging technologies, the material basis and molecular mechanisms of TCM against PLGC have been gradually clarified, and the targeting and efficacy of interventions have been significantly improved. However, the

modern research and clinical application of TCM for PLGC still face several constraints, including inconsistent efficacy evaluation standards, insufficient in-depth mechanistic research, uneven quality control of herbal preparations, and insufficient recognition from international medical communities.

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