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Research progress of TCM intervention in gastric mucosal barrier function in chronic atrophic gastritis

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Abstract. Chronic Atrophic Gastritis (CAG) is recognized as a precancerous condition of gastric cancer, characterized by a prolonged course and complex pathogenesis. Increasing evidence suggests that gastric mucosal barrier dysfunction plays a central role in the onset and progression of CAG, typically manifested by thinning of the mucus layer, destruction of epithelial cell junctions, increased microvascular permeability, and sustained mucosal inflammation. Traditional Chinese Medicine (TCM) has shown unique advantages in the prevention and treatment of CAG through its multi-target, multi-level regulatory actions, particularly in restoring gastric mucosal barrier integrity. Recent studies have demonstrated that TCM formulations exert protective effects by promoting mucin secretion, enhancing the expression of tight and adherens junction proteins, suppressing inflammatory signaling pathways, and improving microvascular circulation. These interventions contribute to the repair and maintenance of gastric mucosal structure and function, thereby reducing the risk of further pathological progression. This review summarizes recent research progress on the role of TCM in modulating gastric mucosal barrier function in CAG, thereby providing new insights and a theoretical foundation for future research and clinical application of TCM in the management of this disease.

Keywords: chronic atrophic gastritis, gastric mucosal barrier, Traditional Chinese Medicine

1. Introduction

Chronic Atrophic Gastritis (CAG) is a chronic disease characterized by the gradual reduction and loss of gastric mucosa glands. It often occurs as a result of ongoing inflammation and can be accompanied by intestinal metaplasia and pseudo-pyloric gland metaplasia. This disease lacks specific clinical manifestations, but common symptoms include upper abdominal pain, burning sensation, belching, acid reflux, and loss of appetite. Its cause is complex and includes Helicobacter pylori (H. pylori) infection, bile reflux, and Autoimmune Gastritis (AIG) [1]. The prevalence of CAG is relatively high in China and tends to increase gradually with age. Meanwhile, studies have shown that there is a positive correlation between the incidence of this disease and the incidence of gastric cancer, suggesting that it has a significant role to play in the development of gastric cancer [2]. Therefore, early diagnosis and intervention of CAG not only help to alleviate patients' symptoms and improve their quality of life, but also provide an important opportunity for early screening and timely treatment of gastric cancer and other malignant tumours, which is of great clinical significance.

The concept of the Gastric Mucosal Barrier (GMB) was initially proposed by Ivey and KJ, and subsequently by Silen [3, 4]. The gastric mucosal barrier is comprised of a complex network of structures, including the gastric mucus layer, the gastric epithelium, the gastric mucosal microvascular network, the gastric glands, and the immune cells. These layers work in a coordinated manner to establish a crucial defensive system that maintains the structural integrity and functional stability of the stomach. The integrity of the gastric mucosa is a pivotal factor in the progression and development of gastritis. Its impairment not only reduces the mucosa's capacity to resist noxious agents but also exacerbates the inflammatory response and the damage to the epithelial cells, resulting in persistent mucosal injury and impaired repair [5].

In modern medicine, the treatment of CAG primarily focuses on *H. pylori* eradication, promotion of gastric mucosal repair, and alleviation of clinical symptoms. Commonly used medications include Proton Pump Inhibitors (PPIs) to suppress gastric acid secretion and gastric mucosal protectants to enhance mucosal barrier function. However, the clinical efficacy of these treatment strategies remains relatively limited, with frequent disease recurrence and prolonged treatment duration, posing

ongoing challenges in the management of CAG [6]. In recent years, studies have shown that traditional Chinese Medicine (TCM) offers unique therapeutic advantages in the treatment of CAG by employing syndrome differentiation and flexible, individualized treatment strategies tailored to various clinical patterns. This review highlights recent research on the role of TCM in treating CAG, with a particular focus on its regulatory effects on gastric mucosal barrier function.

2. Mechanisms of gastric mucosal barrier involvement in chronic atrophic gastritis

2.1. Mechanisms of the gastric mucus layer in chronic atrophic gastritis

The gastric mucus layer, primarily composed of water, glycoproteins, and mucins, covers the surface of the gastric mucosa and serves as an essential component of the gastric mucosal barrier. It provides a fundamental line of defence by protecting against the corrosive effects of gastric acid and digestive enzymes and by preventing the penetration of exogenous harmful substances into the subepithelial tissues. Although most current studies focus on the role of mucins in gastric cancer, their altered expression may already occur at the stage of CAG, given that gastric cancer often arises from persistent inflammation associated with CAG. Experimental results from animal models of CAG demonstrate a significant reduction in gastric mucus secretion [7, 8]. This decrease weakens the protective function of the mucus layer, leading to direct exposure of the superficial epithelial cells and exacerbating mucosal barrier damage. Mucin 5 Subtype AC (MUC5AC) and Mucin 6 (MUC6) are the primary mucins that constitute the gastric mucus layer, secreted by surface mucous cells and glandular cells, respectively. Previous studies indicate that the loss of MUC6 activates the MAPK signalling pathway, thereby promoting tumour-associated changes. In contrast, the absence of MUC5AC is linked to the presence of atypical glandular cells in the gastric mucosa. These findings suggest that both mucins play a critical role in the development and progression of gastric cancer [9]. At the same time, patients with CAG often exhibit imbalances in gastrointestinal hormones, leading to reduced bicarbonate secretion in the gastric mucosa. This decrease weakens the buffering capacity of the mucus layer against gastric acid, thereby further impairing the integrity and function of the gastric mucosal barrier [10].

2.2. Mechanisms of the gastric epithelial layer in chronic atrophic gastritis

The gastric epithelial layer consists primarily of surface mucous cells and glandular epithelial cells, which function cooperatively to regulate mucosal integrity and permeability—key factors in maintaining gastric homeostasis. Cell Junctions (CJs) are essential for maintaining the stability, permeability, and repair of the gastric epithelial layer. Among them, Tight Junctions (TJs) and Adherens Junctions (AJs) play key roles in regulating epithelial barrier integrity and intercellular adhesion. Representative proteins of tight junctions include claudins, occludin, and zonula occludens proteins such as ZO-1. Claudin-1 maintains selective permeability of the gastric mucosa, while occludin regulates cell adhesion and preserves epithelial polarity. ZO-1 links transmembrane proteins to the actin cytoskeleton. Together, these proteins are essential for preserving the integrity of intercellular junctions [11-13]. H. *pylori* eradication has been shown to upregulate the expression of occludin and ZO-1 in the gastric mucosa of patients with chronic gastritis, thereby promoting mucosal healing [14]. Adherens junctions, mediated by calcium-dependent cadherins (e.g., E-cadherin), are essential for maintaining intercellular adhesion and tissue structural integrity. Under chronic inflammatory conditions, the expression of E-cadherin is often downregulated, thereby compromising mucosal barrier function and impairing gastric mucosal repair. This dysfunction contributes to the persistence of CAG-associated lesions and promotes progression toward intestinal metaplasia or dysplasia [15, 16]. During the progression of CAG, chronic inflammation persistently activates multiple signalling pathways, leading to downregulation or mislocalization of epithelial junction proteins such as ZO-1, occludin, and claudin. These alterations increase mucosal permeability and exacerbate gastric mucosal injury [17, 18]. In addition, studies have shown that H. pylori infection in CAG can activate the CXCR2–p53 signalling pathway, leading to premature senescence of gastric epithelial cells. This process impairs mucosal regeneration and accelerates glandular atrophy and structural disorganization in the gastric mucosa [19].

2.3. Mechanisms of the gastric mucosal microvascular network in chronic atrophic gastritis

The gastric mucosal microvascular network is in the lamina propria and consists of arterioles, capillaries, and venules. It serves as the primary pathway for nutrient delivery and metabolic exchange within the gastric mucosa and contributes to the maintenance of local acid–base balance. During the progression of CAG, the gastric mucosal microvascular network undergoes pathological changes such as subepithelial capillary loss, increased vascular permeability, and abnormal angiogenesis. These alterations impair local nutrient supply and disrupt mucosal barrier integrity, thereby promoting inflammation and the development of precancerous lesions. Meanwhile, insufficient microvascular perfusion may lead to localized hypoxia in the gastric mucosa, inducing upregulation of Hypoxia-Inducible Factor 1α (HIF-1α) and subsequent activation of the Vascular Endothelial Growth Factor (VEGF) signalling pathway. This cascade promotes abnormal angiogenesis and creates a permissive environment for pathological remodelling of the gastric mucosa [20]. During the pathological progression of CAG, *H. pylori* infection triggers chronic inflammation, leading to extensive infiltration of immune cells within the gastric mucosa and the release of pro-inflammatory cytokines such as IL-6 and TNF-α. These mediators induce endothelial dysfunction and increase

vascular permeability, thereby compromising the stability of the gastric mucosal microvascular network [21]. Therefore, disruption of the gastric mucosal microvascular network promotes inflammation and the development of precancerous lesions, representing a critical factor in the persistent injury and impaired repair of the gastric mucosa in CAG.

3. Traditional Chinese medicine intervention in the gastric mucosal barrier of chronic atrophic gastritis

3.1. Protective effects of traditional Chinese medicine on the gastric mucus layer in chronic atrophic gastritis

During the progression of CAG, reduced mucin secretion and thinning of the gastric mucus layer are key features of gastric mucosal barrier dysfunction. Therefore, regulating the composition of the mucus layer through TCM intervention represents an important therapeutic strategy for restoring gastric mucosal barrier function in CAG. The gastric mucus layer serves as a physical barrier that reduces mechanical injury to the gastric mucosa from coarse food particles. It also functions as a chemical barrier by preventing the binding of adhesins to gastric epithelial cells, thereby lowering the risk of invasion by external harmful factors. Several studies have confirmed that certain traditional Chinese medicines exert protective effects on the gastric mucus layer. Mineral-based traditional Chinese medicines such as calcined oyster shell (Duan Muli) and clam shell (Hai Ge Ke) exhibit gastroprotective effects by directly neutralizing gastric acid and inhibiting pepsin activity. These actions help regulate the composition of the gastric mucus layer and protect the gastric mucosa [22]. Cuttlebone (Hai Piao Xiao), a commonly used traditional Chinese medicine for gastrointestinal disorders, has been shown to inhibit gastric acid secretion, increase bicarbonate levels in gastric fluid, and promote the synthesis of prostaglandin E2, thereby protecting the gastric mucus layer [23]. Bletilla striata (Bai Ji), a traditional Chinese medicine known for its astringent and hemostatic properties, is commonly used in the treatment of gastric ulcers. Its viscous nature enables it to form a protective film over damaged gastric mucosa, thereby promoting mucosal healing [24]. Mechanistic studies have further demonstrated that Bletilla striata polysaccharides protect the gastric mucosa by inhibiting the abnormal secretion of cytokines such as IL-2R and other related inflammatory mediators [25]. Astragaloside IV, one of the major active components of Astragalus membranaceus (Huang Qi), has been shown to exert therapeutic effects on the gastric mucus layer. Wang et al. [26] demonstrated that Astragaloside IV protects against gastric injury in a rat model of spleen-deficiency type diabetic gastropathy. The protective mechanism may involve the regulation of mucin-related molecules, including iNOS, COX-2, and MUC1, thereby contributing to the preservation of gastric mucosal integrity. In addition to the protective and regulatory effects of individual Chinese medicinal herbs, several TCM compound formulas have also been shown to repair the gastric mucosal barrier by modulating glycoproteins and mucins in the gastric mucus layer through multi-target mechanisms. For instance, treatment with Bu-Zhong-Yi-Qi-Tang has been shown to enhance the expression of gastric mucins such as MUC5AC, thereby promoting the repair of the gastric mucosal barrier in spleen deficiency–related gastric mucosal injury [27]. Jian-Pi-Yi-Qi-Fang has been shown to upregulate the expression of mucins MUC5AC and MUC6, thereby enhancing the integrity of the gastric mucus barrier and increasing resistance to acidic conditions and external harmful factors [28].

3.2. Regulatory effects of traditional Chinese medicine on the gastric epithelial cell layer in chronic atrophic gastritis

In the context of chronic inflammation, aberrant expression of epithelial junction proteins is a key factor contributing to increased gastric mucosal permeability. Ma Q.H. et al. found that combining Shu-Gan-He-Hei-Tang with conventional modern medicine significantly increased E-cadherin expression in patients with CAG, compared to treatment with modern medicine alone [29]. In addition, Xiang-Lian-Hua-Zhuo-Fang has also been shown to upregulate E-cadherin expression in a rat model of CAG [30]. Shu-Gan-He-Wei-Fang has been shown to act on PAR-2–related targets, modulating the expression of Claudin-1 and Claudin-4, thereby promoting the repair of damaged mucosal barriers [31]. Tongxinluo, a traditional Chinese patent medicine, has been shown to upregulate Krüppel-Like Factor 5 (KLF5), thereby enhancing the expression of tight and adherens junction proteins—including occludin, claudin, VE-cadherin, and β-catenin—in vascular endothelial cells, thus exerting endothelial protective effects [32]. Berberine, the primary active component of Coptis chinensis (Huang Lian), has been shown to inhibit the TGF-β1/Smad3 signalling pathway, upregulate E-cadherin expression, and prevent the loss of cell–cell adhesion. These effects contribute to the suppression of Epithelial–Mesenchymal Transition (EMT), thereby exerting anti-fibrotic and anti-tumour effects [33]. These findings suggest that TCM contributes to the repair of damaged gastric epithelial structures in CAG by regulating the expression of cell junction proteins and related signalling pathways, thereby enhancing mucosal barrier function. In addition to strengthening epithelial cell junctions, TCM can inhibit Epithelial–Mesenchymal Transition (EMT) and apoptosis, thereby reducing epithelial cell shedding and necrosis while promoting cell proliferation and differentiation. The Chinese patent medicine Weierning preserves the structural integrity of the gastric epithelial layer by downregulating pro-inflammatory cytokines, inhibiting mitochondrial pathway–mediated apoptosis in gastric epithelial cells, and reversing intestinal metaplasia mediated by CDX2 and MUC2 [34]. In addition to its regulatory effects on gastric mucin expression, Jian-Pi-Yi-Qi-Fang has also been shown to activate proliferation-related proteins such as Ki67 and PCNA in gastric stem cells. This effect is achieved by upregulating Wnt/β-catenin pathway–related factors, including Wnt3A and R-spondin 1 (Rspo1), thereby promoting stem cell proliferation and differentiation and enhancing the repair capacity of the gastric epithelial layer [28].

3.3. Regulatory effects of traditional Chinese medicine on the gastric microvascular network and inflammation in chronic atrophic gastritis

Certain active components of traditional Chinese medicine directly target inflammatory signalling pathways and help regulate local inflammation. Studies have shown that total saponins from Codonopsis pilosula (Dang Shen) and polysaccharides from Astragalus membranaceus (Huang Qi) can inhibit the activation of the NF-κB signalling pathway, thereby downregulating pro-inflammatory cytokines such as TNF-α and IL-6. This reduces inflammatory cell infiltration in the gastric mucosa, alleviates local inflammation, and improves the inflammatory microenvironment of the gastric microvasculature [35]. Astragaloside IV, an active component of Astragalus membranaceus (Huang Qi), has been shown to modulate immune responses and reduce the release of inflammatory mediators by regulating the JAK/STAT signalling pathway. These effects help alleviate gastric mucosal inflammation and restore microenvironmental balance in CAG [26, 36]. Tanshinone IIA, an active compound from Salvia miltiorrhiza (Dan Shen), alleviates gastric mucosal inflammation by inhibiting the NF-κB signalling pathway. Meanwhile, salvianolic acid B, another major constituent of Salvia miltiorrhiza, exhibits antioxidant properties that help mitigate CAG-related oxidative stress and improve local microcirculation in the gastric mucosa [37]. The total flavonoids extracted from Smilax glabra (Tu Fu Ling) have been shown to inhibit NLRP3 inflammasome activation, thereby reducing the expression of multiple pro-inflammatory cytokines. This effect contributes to the improvement of localized inflammatory responses in the gastric mucosa of CAG and may also help alleviate microvascular inflammatory damage [38]. Xiao et al. reported that combining Wu-Zhu-Yu-Tang with conventional western medicine more effectively reduces the expression of inflammatory mediators such as IL-6 and COX-2 in the gastric mucosa of patients with CAG. These results suggest that this traditional formula exerts notable anti-inflammatory effects and may help improve the local inflammatory microenvironment associated with CAG [39].

4. Conclusion

CAG is a pathological condition characterized by the atrophy of gastric glands under chronic inflammatory conditions. It is closely associated with H. pylori infection, bile reflux, immune dysregulation, and other contributing factors. CAG can progress to gastric cancer, posing a serious threat to patients‘ health and quality of life. Recent studies have shown that gastric mucosal barrier dysfunction plays a central role in the onset and progression of CAG. This dysfunction is primarily characterized by thinning of the mucus layer, disruption of epithelial cell junctions, increased microvascular permeability, and persistent mucosal inflammation. Impairment of the gastric mucosal barrier not only reduces the stomach’s defence against endogenous aggressors such as gastric acid and digestive enzymes, but also facilitates the entry of exogenous irritants like H. pylori and bile acids. This promotes a vicious cycle of “injury–inflammation–impaired repair,” further aggravating the progression of CAG.

TCM exhibits a unique advantage in holistic regulation, particularly in restoring gastric mucosal barrier function in the management of CAG. Both individual herbs and classical formulas in TCM exert synergistic effects through multiple mechanisms, including the regulation of mucin secretion, restoration of epithelial cell junctions, inhibition of inflammatory cytokine release, improvement of microcirculatory dysfunction, and modulation of key signalling pathways. These coordinated actions contribute to multi-dimensional, targeted regulation of the pathological progression of CAG.

Despite recent progress in clinical research on gastric mucosal barrier function in CAG, high-quality, large-scale clinical trials are still lacking to provide robust evidence-based support. In addition, mechanistic studies on TCM formulas have predominantly focused on single signalling pathways, which limits a comprehensive understanding of their inherently multi-component, multi-target, and synergistic therapeutic effects. Future research could prioritize evidence-based clinical studies to systematically evaluate the efficacy and mechanisms of TCM in modulating gastric mucosal barrier function in chronic atrophic gastritis CAG. Moreover, the integration of advanced technologies, such as multi-omics, spatial transcriptomics, and single-cell sequencing, will be essential to further elucidate the complex, multi-dimensional regulatory networks through which TCM influences mucosal barrier integrity and associated signalling pathways.

TCM shows great promise in restoring gastric mucosal barrier function in CAG. Uncovering the mechanisms underlying TCM intervention in CAG may not only enrich its theoretical foundation in the treatment of chronic gastric disorders but also provide novel insights into the early prevention and intervention of gastric cancer.

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