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Research Progress on the Mechanism of Sanren Decoction in Treating Slow-Transit Constipation

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Abstract: ***Slow transit constipation (STC) is a prevalent functional gastrointestinal disorder characterized by impaired intestinal motility, prolonged fecal retention, and difficult defecation. Its pathological mechanisms may involve multiple factors, including enteric nervous system dysfunction, interstitial cell of Cajal impairment, gut microbiota dysbiosis, and neuroimmune dysregulation. Accumulating evidence-based medical research indicates that Sanren Decoction demonstrates significant therapeutic efficacy in treating slow transit constipation with spleen-stomach damp-heat syndrome, accompanied by a low recurrence rate. This article systematically reviews recent advances in mechanistic studies on Sanren Decoction for managing STC with damp-heat syndrome: analyzing its multi-target, multi-component, and multi-pathway regulatory mechanisms through the "regulating Sanjiao" theory, elucidating the pathogenesis of STC, and providing evidence-based foundations for clinical treatment and novel drug development.***

Keywords: Slow Transit Constipation, Sanren Decoction, Gastrointestinal Function, Treatment**.**

1. Introduction

Slow Transit Constipation (STC) is a chronic functional gastrointestinal disorder whose pathogenesis remains incompletely understood. Its primary clinical manifestations include impaired defecation sensation, reduced bowel movement frequency, hard stools, straining or requiring manual assistance during defecation, and often accompanied by anal heaviness, discomfort, or a sensation of incomplete evacuation. Severe cases may trigger cardiovascular diseases and psychological disorders [1,2]. Studies indicate [3, 4] that the prevalence of this condition remains consistently high, with a global incidence rate around 30%. In China, the prevalence among adults ranges from 3.19% to 11.6%, lower than the global rate. Globally, its incidence typically increases with age. Simultaneously, due to its chronic nature, recurrent episodes, and treatment challenges, slow-transit constipation significantly disrupts patients' daily lives and psychological well-being, severely impairing quality of life.

The pathogenesis of STC remains unclear, though it is widely believed to be associated with the brain-gut axis, intestinal microenvironment, genetics, immunity, and psychological factors. Consequently, modern medical approaches to treating STC often involve laxatives, prokinetic agents, probiotics, immunosuppressants, and enemas. While these methods may yield short-term efficacy, they present significant limitations, including high recurrence rates, frequent adverse reactions, substantial costs, and the potential for drug resistance [5]. Traditional Chinese Medicine (TCM) offers distinct advantages in treating STC through holistic patient assessment, comprehensive management, syndrome differentiation-based treatment, and stage-specific intervention. This paper analyzes the mechanisms of Sanren Decoction in treating STC based on TCM's "syndrome differentiation and treatment" principle, focusing on spleen-stomach damp-heat pattern and constipation - predominant patter. The findings aim to inform future basic research, clinical applications, and proprietary Chinese medicine development.

2. Pathogenesis of Slow Transit Constipation

Traditional Chinese medicine generally attributes slow-transit constipation to abnormal spleen and stomach function, compounded by damp-heat pathogens obstructing qi circulation and impairing intestinal transmission. With accelerating societal development, people's lifestyles have become increasingly fast-paced. Common unhealthy habits—such as excessive consumption of rich, greasy, or cold foods, staying up late, drinking alcohol, and smoking—severely impair spleen-stomach transport and transformation functions. The spleen, one of the five zang organs, resides in the middle jiao and governs the transformation of food essence. The stomach, one of the six fu organs, is paired with the spleen and governs the reception and digestion of food essence. The spleen governs ascending energy, while the stomach governs descending energy. Their coordinated reception and transportation ensure smooth qi circulation. The spleen prefers dryness and dislikes dampness, while the stomach prefers dampness and dislikes dryness. Their mutual regulation of dryness and dampness is crucial for maintaining normal transformation of food essence, providing nutrients for the body's vital functions. When the spleen and stomach fail to transform and transport properly, qi circulation throughout the body becomes obstructed, leading to food stagnation. Combined with dampness pathogens that cannot be properly transformed, this can accumulate internally over time, forming damp-heat. Simultaneously, dietary preferences can also damage the spleen and stomach. Excessive consumption of rich and sweet foods allows damp-heat pathogens to linger internally. The sticky nature of dampness descends into the intestines, causing intestinal obstruction and stagnation of impurities. This results in infrequent bowel movements (sometimes days apart), foul-smelling stools that are sticky, dry, or hard to pass, a thick yellow tongue coating, and a slippery, forceful pulse. This pattern indicates damp-heat accumulation in the spleen and stomach [6].

Modern medicine generally holds that STC development is

associated with gastrointestinal dysfunction, which can result from multiple contributing factors leading to abnormal peristalsis in gastrointestinal tissues such as the stomach, small intestine, colon, and rectum. Recent studies indicate [7] that abnormalities in the brain-gut axis are closely associated with gastrointestinal dysfunction. The enteric nervous system (ENS), central nervous system (CNS), and autonomic nervous system (ANS) form key components of this axis, with abnormalities in any segment potentially triggering gastrointestinal disorders. The ENS, primarily distributed within the intestinal wall, serves as the command center regulating colonic and rectal peristalsis. It modulates the secretion of neurotransmitters such as serotonin (5-HT), nitric oxide (NO), vasoactive intestinal peptide (VIP), and substance P (SP). Interstitial cells of Cajal (ICC) within colonic tissue function as carriers for these neurotransmitters. ICC serves as the natural pacemaker for gastrointestinal slow-wave reflexes. Abnormal ICC apoptosis and autophagy may disrupt the cellular reticular structure, alter cell phenotypes, and cause smooth muscle cell (SMC) dysfunction. This leads to damage of the intestinal mucosal barrier, impaired intercellular and inter-organ substance transport, disruption of the intestinal microenvironment, and ultimately gastrointestinal dysfunction [8, 9]; The CNS primarily transmits signals to the gastrointestinal tract via the vagus nerve to regulate the intestinal mucosal barrier and maintain intestinal microenvironment homeostasis. Concurrently, abnormalities in the intestinal microenvironment and related signals are also fed back to the CNS through the vagus nerve [10]; The ANS regulates gastrointestinal function by mediating sympathetic and parasympathetic nerve activity. For instance, reduced sympathetic activity inhibits gastrointestinal motility, while parasympathetic excitation promotes it [11]. Therefore, the bidirectional regulation of the brain-gut axis is the primary mechanism influencing gastrointestinal function. Gastrointestinal disorders frequently co-occur with central nervous system diseases, jointly impacting human physiological activities.

3. Mechanisms of Sanren Decoction in Treating Damp-Heat Type Slow Transit Constipation

3.1 Mechanisms in Traditional Chinese Medicine

Sanren Decoction is a representative formula of the Warm Disease School, created by Qing Dynasty physician Wu Jutong based on the academic ideas of Ye Tianshi's Clinical Guide to Medical Cases. It was first recorded in the Upper Burner Chapter of Treatise on Warm Diseases. The formula combines eight herbs: Apricot Kernel, Coix Seed, White Cardamom Seed, Pinellia Rhizome, Tongcao, Magnolia Bark, Talcum, and Bamboo Leaf. As stated in Treatise on Warm Diseases: "If dampness does not combine with heat, its force remains isolated." The formula design of Sanren Decoction is ingenious, simultaneously opening the gate of the upper burner, regulating the qi of the middle burner, and draining water from the lower burner. Apricot kernel, the foremost of the three kernels, promotes the ascending lung qi of the upper burner and transforms dampness through qi movement. White cardamom seed, with its aromatic nature, transforms dampness, regulates qi, broadens the chest, and harmonizes the middle burner's spleen qi. Coix seed drains damp pathogenic factors, fortifies the spleen, clears heat, expels pus, and reduces swelling, facilitating the elimination of damp-heat from the lower burner. Combined, these three herbs achieve the effects of dispersing the upper, unblocking the middle, and draining the lower, comprehensively dispersing, transforming, and draining dampness to eliminate pathogenic factors from all three burners, serving as the sovereign herbs. Talcum clears heat, drains dampness, promotes urination, relieves dysuria, and alleviates summer heat; Tongcao clears heat, promotes urination, and regulates qi; Bamboo Leaf clears heat, purges fire, promotes urination, and relieves dysuria. Together, these three serve as minister herbs, enhancing the heat-clearing and dampness-draining power of the "Three Kernels." Pinellia rhizome dries dampness, transforms phlegm, descends counterflow to stop vomiting, and disperses fullness and nodules. Magnolia bark promotes qi circulation, dries dampness, eliminates food stagnation, and calms wheezing. These two herbs serve as auxiliary agents, supporting the sovereign and minister herbs in regulating qi, transforming dampness, and eliminating fullness. The combined action of these herbs enables pathogenic factors in the Triple Energizer to dissipate through distinct pathways: qi movement transforms dampness, heat clearance resolves summer heat, and harmonized qi mechanism restores balance. This formula stands as a classic exemplar of the later-developed method of "separating and dispersing".

3.2 Modern Medical Mechanisms

Modern pharmacology indicates that Sanren Decoction significantly improves gastric mucosal inflammation and glandular damage in rats with spleen-stomach damp-heat patterns. NOD-like receptor protein 3 (NLRP3), a major cytoplasmic pattern recognition receptor, is activated upon sensing external danger signals. NLRP3 activation catalyzes the production of the key protein caspase-1, which induces inflammatory responses and inflammatory necrosis. The release of necrotic cell contents further triggers inflammatory cascade reactions [12, 13]. Peng Linjia et al. demonstrated that Sanren Decoction may inhibit Caspase-1 and NLRP3 protein expression in rats with spleen-stomach damp-heat syndrome, thereby reducing pyroptosis rates in gastric mucosal cells and mediating gastric mucosal inflammatory responses [14].Cui Cui et al. [15] demonstrated that Modified Sanren Decoction repairs the colonic mucosal barrier by elevating sIgA levels; modulates intestinal substance metabolism by downregulating AQP4 expression; regulates immune function by adjusting inflammatory factor activity (including IL-2, TNF-α, and IFN-γ); and enhances overall resistance. Cao Wenbin et al. [16] Research indicates that after Sanren Decoction intervention, rat colon tissues exhibited decreased levels of the MAPK system (c-Jun N-terminal kinase, extracellular signal-regulated kinase, and p38MAPK), NF-κB, IL-6, TNF-α levels decreased in rat colon tissue, AQPs expression was downregulated, intestinal motility frequency increased, and colonic transit time improved. This suggests Sanren Decoction may treat constipation by inhibiting the MAPK/NF-κB signaling pathway.

Modern pharmacological research indicates that Sanren Decoction primarily exerts its therapeutic effects through the

active components of its constituent herbs. Among these, bitter apricot kernel (is rich in volatile oils, flavonoids, cyanogenic glycosides, amino acids, fatty acids, and trace elements. It possesses anti-inflammatory and analgesic properties, promotes bowel regularity, and modulates immune function. Coix seed contains active components including fatty acids, flavonoids, proteins, polysaccharides, sterols, and alkaloids. It exhibits analgesic and anti-inflammatory effects, lowers blood pressure, regulates blood lipids, and enhances immune function. (White Cardamom Rich in volatile oils, diarylheptanes, and flavonoids, it exhibits anti-inflammatory, antibacterial, antitumor, and hepatoprotective/ nephroprotective effects. Bitter Apricot Kernel, Coix Seed, and White Cardamom collectively serve as the principal herbs in Sanren Decoction, significantly enhancing its ability to regulate qi. This enables the decoction to fully exert its anti-inflammatory and anti-infective effects, promote intestinal peristalsis, regulate immunity, and repair the intestinal mucosal barrier. Talcum, combined with bitter apricot kernel, coix seed, and white cardamom, achieves the functions of dispersing upward, promoting central flow, and draining downward, thereby resolving damp-heat pathogens from the interior to the exterior and from the upper to the lower regions [20]. Talcum protects gastrointestinal mucosa. When ingested, it adheres to mucosal surfaces, obstructing absorption of intestinal toxins, reducing inflammatory responses, and alleviating pain. It addresses conditions like gastric heat accumulation and damp-heat diarrhea [21]. Magnolia officinalis, a key herb for descending stomach qi, possesses effects of relieving distension, promoting digestion, resolving food stagnation, and eliminating fullness. Rich in active components like magnolol, it stimulates contraction of gastric and intestinal smooth muscles, accelerates gastrointestinal emptying rates, and plays a significant role in gastrointestinal motility disorders [22]. Pinellia (Banxia) possesses warming, dispersing, and knot-resolving properties, while also descending rebellious qi to stop vomiting and aiding spleen transformation. Research indicates that Pinellia can enhance vagal nerve sensitivity, increase gastrointestinal motility, and improve gastrointestinal function. Additionally, it can regulate the intestinal microbiota to improve the intestinal microenvironment for treating related diseases [23, 24].

4. Clinical Studies

Zhang Wenxiu et al. [25] Clinical studies indicate that patients with spleen-damp-heat pattern functional constipation treated with modified Sanren Decoction for 14 days showed a lower overall efficacy rate compared to the control group. However, their defecation difficulty improved significantly, with high patient acceptance. This effectively alleviated psychological stress, confirming that Sanren Decoction improves constipation and enhances quality of life by mediating defecation ease and regulating psychological stress. Cui Yangyang [26] Clinical research confirms that after 30 days of treatment with modified Sanren Decoction, patients with spleen-damp-heat pattern functional constipation demonstrated significantly superior clinical efficacy compared to the control group. Patients exhibited markedly elevated motilin levels, gastric emptying rate was effectively accelerated, stool passage difficulty scores were markedly reduced, and quality of life was significantly improved. This indicates that Sanren Decoction can effectively alleviate clinical symptoms, enhance gastrointestinal motility, improve patients' quality of life, and effectively treat constipation. JIANG H et al. [27] Clinical studies confirm that after 30 days of Sanren Decoction treatment, patients with spleen-damp-heat pattern functional constipation exhibited softer stools, smoother bowel movements, and longer defecation times compared to the control group. This indicates that Sanren Decoction softens stools, prolongs defecation time, promotes bowel movements, effectively relieves constipation, and improves patients' quality of life.

5. Issues and Outlook

Although Sanren Decoction demonstrates significant efficacy and unique advantages in treating STC, several challenges remain. (1) Its mechanism of action remains incompletely elucidated. Current research primarily focuses on intestinal motility, gut microbiota, anti-inflammatory, and antioxidant effects, lacking deeper investigations into molecular mechanisms and signaling pathways. Future studies should strengthen research in molecular mechanisms and signaling pathways to provide scientific evidence for its action. (2) Large-scale, multicenter clinical trial evidence for Sanren Decoction remains insufficient. Future large-scale, multicenter clinical trials are needed to validate its efficacy and safety. (3) Individualized treatment protocols for Sanren Decoction require further refinement. Due to variations in disease severity and patient constitution among STC patients, personalized diagnosis and treatment are essential. Future efforts should focus on precision medicine tailored to individual patient conditions, offering more effective treatment options for STC patients.

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