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Mechanistic Basis and Research Progress of Spleen-Oriented Therapy for Sjögren's Syndrome Based on the Gut Microbiota-Metabolite-Th17/Treg Axis

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Abstract: ***Sjögren's syndrome (SS), particularly primary Sjögren's syndrome (pSS), is a chronic autoimmune epithelitis characterized by xerostomia, xerophthalmia, lymphocytic infiltration of the exocrine glands, and systemic immune dysregulation. Accumulating evidence indicates that gut microbiota dysbiosis, altered microbial metabolites, intestinal barrier dysfunction, and T-helper 17/regulatory T-cell (Th17/Treg) imbalance are important contributors to disease initiation and progression, although causal relationships still require further confirmation. In traditional Chinese medicine (TCM), SS has long been discussed within the scope of dryness-related disorders. A spleen-oriented interpretation emphasizes impaired transformation and transportation of fluids as an internal basis for persistent dryness and proposes that spleen dysfunction may be linked to modern concepts of gut microecology, mucosal immunity, and metabolic homeostasis. This review summarizes verified clinical, experimental, and multi-omics evidence concerning the gut microbiota-metabolite-Th17/Treg axis in SS and discusses how selected TCM interventions, including modified Zengye Decoction, FuFang Runzaoling, Lushi Runzao Decoction, Qihuang Jianpi Zishen granules, Shaoyao Gancao Decoction, total glucosides of paeony, Dendrobium and Ophiopogon polysaccharides, and Astragalus-Salvia/Ophiopogon-Dendrobium herb pairs, may modulate inflammation, salivary gland injury, gut microbial composition, and related metabolic pathways. Based on the currently available evidence, a chained pathogenesis model is proposed: spleen deficiency, gut microbial and metabolic disorder, intestinal barrier injury, Th17/Treg imbalance, exocrine gland inflammation, and intermingling of dryness and blood stasis. This model may help connect TCM syndrome differentiation with modern immunometabolic mechanisms and support more precise research on TCM-based SS interventions.***

Keywords: Sjögren's syndrome, Spleen-oriented therapy, Gut microbiota, Microbial metabolites, Th17/Treg balance, Traditional Chinese medicine, Pathogenesis**.**

1. Introduction

Sjögren's syndrome is a chronic systemic autoimmune disease that primarily affects the salivary and lacrimal glands and may also involve the joints, lungs, kidneys, nervous system, and other organs. pSS predominantly affects women and follows a persistent, recurrent course that can substantially reduce quality of life. The pathogenesis of SS is multifactorial and includes epithelial cell injury, type I interferon activation, B-cell hyperactivity, T-cell dysregulation, autoantibody production, and mucosal immune disturbance. Current management is mainly symptomatic or immunomodulatory. Although topical treatment, secretagogues, hydroxychloroquine, glucocorticoids, and immunosuppressants may be used in selected clinical settings, existing therapies do not fully reverse glandular dysfunction and must be individualized according to systemic involvement and safety considerations [1].

In TCM theory, SS is commonly classified within dryness-related disorders. Conventional treatment has often emphasized nourishing yin and moistening dryness. However, persistent dryness in SS can also be interpreted as a consequence of impaired spleen function, especially impaired transformation and transportation of body fluids. Spleen deficiency may reduce the generation and distribution of fluids, while long-standing dysfunction can give rise to dampness, stagnation, and blood stasis. Therefore, a spleen-oriented therapeutic framework does not replace yin-nourishing therapy but expands it by emphasizing regulation of fluid metabolism, digestion, intestinal function, and systemic immune balance.

Modern microbiome and metabolomics research provides a plausible biological bridge for this TCM framework. Studies in pSS have reported reduced gut microbial diversity, compositional shifts, altered fecal and plasma metabolites, and changes in immune pathways related to Th17/Treg balance [2-6]. Microbial metabolites, including short-chain fatty acids (SCFAs), tryptophan-derived indoles, and bile acid derivatives, can regulate intestinal barrier function and host immune responses [7-10]. This review therefore examines SS pathogenesis through the gut microbiota-metabolite-Th17 /Treg axis and summarizes verified evidence for TCM interventions that may act on this axis.

2. Theoretical Origin and Modern Interpretation of Treating SS from the Spleen

2.1 Spleen Governing Fluid Transportation as a Basis of Dryness

Classical TCM theory holds that the spleen governs transformation and transportation and participates in the generation and distribution of body fluids. When spleen qi is insufficient or spleen yin is consumed, fluid generation and distribution may become impaired. In the context of SS, this

provides a theoretical explanation for persistent dryness of the mouth, eyes, and other mucosal surfaces. The spleen-oriented view is particularly useful for patients who present not only with dryness but also with fatigue, poor appetite, abdominal distension, loose stools, or a greasy tongue coating, suggesting a mixed pattern of deficiency and stagnation.

2.2 Dynamic Evolution of Spleen Deficiency-Induced Dryness

The spleen-related pathogenesis of SS can be understood as a dynamic process. In early disease, spleen qi and yin deficiency may reduce fluid generation and produce mild xerostomia, xerophthalmia, fatigue, and pale tongue. In the middle stage, impaired transportation may promote dampness accumulation, which hinders fluid distribution and creates the paradoxical coexistence of dampness and dryness. In advanced or refractory disease, prolonged deficiency can involve the kidney and promote blood stasis, leading to more persistent glandular dysfunction and systemic manifestations. This staged interpretation supports the combined use of spleen-tonifying, yin-nourishing, dampness-transforming, and blood-activating strategies according to syndrome differentiation.

2.3 Convergence of Spleen Defense and Gut Microecological Immunity

The TCM concept that the spleen supports defense and maintains internal stability has notable parallels with modern intestinal immune functions. The intestinal tract contains a large immune network and is closely regulated by commensal microbiota, epithelial tight junctions, secretory IgA, and microbial metabolites. Disturbance of this ecosystem may impair immune tolerance and promote low-grade systemic inflammation. In SS, both human and animal studies support the presence of gut microbial dysbiosis and metabolic abnormalities, suggesting that gut microecology is a meaningful target for interpreting and modernizing spleen-oriented therapy [2-7].

3. The Gut Microbiota-Metabolite-Th17/Treg Axis in SS Pathogenesis

3.1 Characteristics of Gut Microbiota Dysbiosis in SS

A systematic review and meta-analysis of 22 case-control studies involving 915 pSS patients and 2,103 healthy controls found reduced alpha diversity in pSS, including lower Shannon-Wiener, Chao1, and ACE indices, and also reported differences in beta diversity [2]. Clinical studies further indicate that patients with pSS may show decreased beneficial or SCFA-producing bacteria and enrichment of opportunistic or pro-inflammatory taxa [3-5]. These findings suggest that gut dysbiosis is not merely a peripheral observation but may be linked to inflammatory activity, mucosal immune changes, and disease heterogeneity.

At the taxonomic level, reported findings vary across cohorts, sequencing platforms, diet, geography, medication exposure, and disease stage. Nevertheless, several studies converge on reduced microbial diversity, altered Firmicutes/Bacteroidetes patterns, increased Proteobacteria or pathobiont abundance, and decreased SCFA-producing genera. Recent multi-omics studies have further connected microbial shifts with fecal and plasma metabolite changes, strengthening the rationale for examining pSS as an immunometabolic disease involving the gut-gland axis [4-6].

3.2 Microbial Metabolites as Bridges between Dysbiosis and Immune Imbalance

SCFAs, especially butyrate, acetate, and propionate, are important microbial metabolites that regulate intestinal epithelial integrity and immune tolerance. In experimental SS, butyrate increased salivary flow, reduced inflammatory damage in salivary glands, and promoted IL-10-producing B cells while suppressing IL-17-producing B cells through circadian-clock-related pathways [8]. These data support the idea that depletion of SCFA-producing bacteria may weaken anti-inflammatory regulation and favor autoimmune inflammation.

Tryptophan-derived indole metabolites represent another important immunoregulatory pathway. Indole-3-propionic acid (IPA), a gut-derived aryl hydrocarbon receptor (AhR) ligand, has been shown to promote polymorphonuclear myeloid-derived suppressor cell responses and attenuate experimental SS [10]. Rather than proving a single linear mechanism, these findings indicate that tryptophan metabolism may influence immune tolerance through AhR-dependent and myeloid-cell-mediated pathways.

Bile acid metabolism also connects gut bacteria with host immunity. Bile acid derivatives such as 3-oxo-lithocholic acid and isoallo-lithocholic acid can directly regulate Th17 and Treg cell differentiation [9]. In SS models, recent studies of Lushi Runzao Decoction and related metabolomic work suggest that bile acid and SCFA pathways may participate in the improvement of glandular injury and inflammatory status [16].

3.3 Th17/Treg Imbalance and Glandular Injury

Th17/Treg imbalance is an important downstream immune event in SS. Experimental data show that Th17 cells contribute to the development of SS-like disease, while Treg insufficiency or impaired regulatory function may fail to restrain inflammatory damage [11]. Overactivation of Th17-related pathways can increase IL-17 and other inflammatory mediators, promote lymphocytic infiltration, and aggravate epithelial and acinar cell injury. Conversely, restoration of Treg function, IL-10 signaling, and mucosal tolerance may help reduce glandular inflammation [8,11,12].

The gut microbiota-metabolite-Th17/Treg axis therefore provides a mechanistic framework for linking intestinal dysbiosis with exocrine gland injury. In this framework, microbial imbalance and metabolite deficiency weaken barrier integrity and immune tolerance, intestinal inflammatory signals amplify systemic immune activation, and dysregulated Th17/Treg responses contribute to salivary and lacrimal gland damage. This pathway is compatible with, but does not fully replace, other established mechanisms of SS such as epithelial activation, type I interferon signaling, B-cell hyperactivity, and genetic or epigenetic susceptibility [12].

4. Research Progress of Spleen-Oriented TCM Interventions

4.1 Compound Prescriptions with Verified SS-Related Evidence

Modified Zengye Decoction has clinical and experimental evidence in pSS. A clinical study reported improvement in symptoms and changes in plasma exosomal proteins after treatment with modified Zengye Decoction [13]. A network pharmacology and animal study further explored Zengye Decoction against SS and provided mechanistic support involving inflammatory and immune pathways [14]. These findings support the use of fluid-generating and yin-nourishing therapy, while also suggesting that its action may extend beyond simple moistening effects.

FuFang Runzaoling has been investigated in NOD mouse models of SS. Combined gut microbiota and fecal metabolomics analysis showed that FuFang Runzaoling reduced inflammatory responses, decreased IL-6, TNF-alpha, and IL-17A, increased IL-10, and altered microbial and metabolic profiles [15]. These data are directly relevant to the gut microbiota-metabolite-immune axis and provide stronger mechanistic support than unsupported extrapolation from non-SS models.

Lushi Runzao Decoction has also been studied in NOD/LtJ mice. The formula improved submandibular gland injury, reduced inflammation, and regulated gut flora, SCFA levels, and bile acid-related metabolites [16]. Because this study simultaneously assessed microbiota, SCFAs, and metabolomics, it offers a useful model for future research on spleen-oriented and dryness-moistening prescriptions.

Qihuang Jianpi Zishen granules are particularly relevant to the spleen-kidney deficiency framework. Network pharmacology, transcriptomics, and experimental validation suggest that Qihuang Jianpi Zishen granules may act through immune-inflammatory and epithelial injury-related pathways in SS [17]. Although additional randomized clinical trials are still needed, this formula provides a modern example of how spleen-tonifying and kidney-supporting strategies can be evaluated using systems biology.

Shaoyao Gancao Decoction has evidence related to glandular secretion. Experimental work showed that it regulated aquaporin 5 and muscarinic receptor 3 through the cAMP-PKA pathway in SS models [18]. This mechanism is directly related to salivary secretion and provides a molecular explanation for the use of sour-sweet yin-nourishing formulas in dryness disorders.

4.2 Active Components and Herb Pairs

Total glucosides of paeony (TGP) have comparatively stronger SS-related evidence than many other single components. In NOD mice, TGP altered gut microbiota composition based on 16S rRNA sequencing [19]. Clinical evidence also supports the effectiveness and safety of TGP in pSS, although study quality and heterogeneity should be considered [20]. Additional experimental data indicate that TGP may alleviate intestinal inflammation associated with SS-like disease [21].

Polysaccharide-containing yin-nourishing herbs may also improve SS-related dryness and inflammation. Dendrobium officinale polysaccharides improved aquaporin 5 abnormalities, inflammatory cytokines, and apoptosis in experimental SS mice [23]. Ophiopogon japonicus polysaccharides showed preventive effects in an autoallergic SS model by regulating Th1/Th2 cytokine imbalance [24]. A meta-analysis of nourishing yin formulas as adjunctive therapy to hydroxychloroquine also suggested potential clinical benefit, but the evidence base remains limited by trial quality [22].

Astragalus-Salvia and Ophiopogon-Dendrobium herb pairs have recently been evaluated in NOD/LtJ mice. The combination improved salivary flow, reduced autoantibody levels and lymphocyte infiltration, lowered the Th17/Treg ratio, and inhibited JAK1/STAT3 and PI3K/AKT signaling pathways [25]. This study supports a combined strategy of tonifying qi, nourishing yin, and activating blood, which is consistent with the complex deficiency-excess pattern often seen in chronic SS.

4.3 Evidence Gaps in Classic Spleen-Tonifying Formulas

Classic spleen-tonifying formulas such as Sijunzi Decoction, Buzhong Yiqi Decoction, and Shenling Baizhu San are frequently discussed in TCM theory and have evidence in digestive, immune, and gut microecological contexts. However, direct SS-specific evidence showing that these formulas regulate the gut microbiota-Th17/Treg axis remains limited. Therefore, strong mechanistic claims should be avoided unless supported by primary studies in SS patients or validated SS models. These prescriptions are better presented as theoretically plausible candidates for future SS-specific research rather than as confirmed gut-immunometabolic interventions.

5. Pathogenesis Model, Limitations, and Future Prospects

5.1 Updated Pathogenesis Model

Integrating TCM spleen theory with modern microbiome and immunology evidence, this review proposes an updated chained model of SS: spleen deficiency, gut microbial and metabolic disorder, intestinal barrier injury, Th17/Treg imbalance, exocrine gland inflammatory injury, and intermingling of dryness and blood stasis. In this model, spleen deficiency represents the macroscopic syndrome basis, while gut dysbiosis, SCFA reduction, tryptophan and bile acid metabolic changes, mucosal barrier impairment, and immune imbalance represent measurable microscopic mechanisms. The model is intended as a research framework rather than a proven causal chain.

5.2 Research Limitations

Several limitations should be emphasized. First, most microbiome studies in SS are observational and cannot fully distinguish cause from consequence. Second, diet, geography, medication exposure, disease activity, sample type, and

sequencing methods create substantial heterogeneity. Third, many TCM studies remain based on animal experiments or small clinical cohorts, and high-quality randomized controlled trials with standardized outcome measures are still insufficient. Fourth, not all classical TCM formulas have direct SS-specific microbiome or Th17/Treg evidence. Fifth, objective biomarkers for spleen deficiency or spleen-kidney deficiency in SS have not yet been fully established.

5.3 Future Prospects

Future research should prioritize large-scale, prospective clinical cohorts and randomized controlled trials that combine TCM syndrome differentiation with modern clinical endpoints such as ESSDAI, ESSPRI, salivary flow, ocular tests, autoantibody titers, inflammatory cytokines, and safety outcomes. Multi-omics approaches should be used to link gut microbiota, fecal and plasma metabolites, intestinal barrier markers, and Th17/Treg indices. Mechanistic studies should distinguish formula-specific effects from general anti-inflammatory effects and should verify whether microbiota changes are necessary for therapeutic benefit. Finally, standardized reporting of formula composition, dosage, preparation, quality control, and patient syndrome patterns will be essential for reproducibility and international publication.

6. Conclusion

The gut microbiota-metabolite-Th17/Treg axis offers a useful modern framework for interpreting spleen-oriented TCM therapy in SS. Verified evidence supports the involvement of gut dysbiosis, altered SCFAs, tryptophan-derived metabolites, bile acid metabolism, and immune imbalance in SS pathogenesis. Several TCM prescriptions and components have shown potential to improve glandular injury, inflammatory responses, microbial composition, and metabolic pathways. However, the evidence remains uneven, and claims must be carefully matched to verifiable references. A cautious but integrated model connecting spleen deficiency, gut microecology, metabolic immunity, and glandular inflammation may guide future basic and clinical studies and promote more precise TCM-based interventions for Sjögren's syndrome.

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