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Mechanisms and Research Advances of Traditional Chinese Medicine Intervention for Primary Sclerosing Cholangitis Based on the Gut-Liver Axis Theory

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Abstract: ***Background & Objective:*** ***Primary sclerosing cholangitis (PSC) is a refractory chronic cholestatic liver disease with limited disease-modifying therapies. Gut-liver axis dysregulation, characterized by gut microbiota dysbiosis, intestinal barrier impairment and bile acid metabolism disorder, serves as the core pathological driver of PSC progression. This review aims to systematically elucidate the pharmacological mechanisms and clinical staged strategies of traditional Chinese medicine (TCM) for PSC targeting the gut-liver axis, and to provide theoretical references for integrative PSC management.*** ***Methods:*** ***Relevant domestic and international studies on TCM interventions for PSC and cholestatic liver diseases were retrieved and synthesized. The pathological mechanisms of the gut-liver axis in PSC were summarized, and the scientific consistency between the gut-liver axis network and TCM theory of concurrent liver and intestinal disorders was analyzed. The multi-target mechanisms and clinical application strategies of TCM formulas, active components and extracts were sorted out from three dimensions: microbiota regulation, barrier repair and anti-fibrosis.*** ***Results:*** ***TCM exerts holistic therapeutic effects via multi-target regulation: it remodels gut microbiota structure and modulates bile acid metabolism to activate FXR/TGR5 receptors; upregulates tight junction proteins (ZO-1, Occludin) to repair the intestinal mucosal barrier and block endotoxin translocation; and inhibits the TLR4/NF-κB and TGF-β1/Smad pathways to suppress intrahepatic inflammatory cascade and biliary fibrosis. Clinically, a three-stage integrative strategy can be established: intestine-clearing and choleretic therapy in the early stage, spleen-fortifying and intestine-securing therapy in the middle stage, and stasis-resolving and collateral-dredging therapy in the late stage.*** ***Conclusion:*** ***TCM intervention targeting the gut-liver axis exerts unique multi-component and multi-target advantages against PSC, which compensates for the limitations of Western medicine monotherapy. Future studies should adopt multi-omics technologies to clarify the causal relationship between TCM-modulated microbiota and host metabolism, and carry out high-quality clinical trials to support precision integrative therapy.***

Keywords: Primary sclerosing cholangitis, Gut-liver axis, Integrative Chinese and Western medicine, Gut microbiota, Bile acid metabolism.

1. Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by diffuse biliary inflammation and idiopathic fibrosis, which may ultimately progress to liver cirrhosis and even cholangiocarcinoma [1-3]. Epidemiological data show that approximately 70%–80% of PSC patients are complicated with inflammatory bowel disease (IBD) such as ulcerative colitis, suggesting a critical role of the intestinal microenvironment in PSC pathogenesis [4,5].

To date, effective pharmacological agents capable of reversing the natural course of PSC remain lacking in modern medicine. The long-term efficacy of ursodeoxycholic acid (UDCA), the first-line agent, remains controversial. Novel single-target agents such as obeticholic acid are frequently associated with adverse reactions including aggravated pruritus, while liver transplantation is limited by donor shortage and postoperative recurrence [6-8]. Therefore, exploring integrative therapeutic strategies with enhanced efficacy and reduced toxicity holds important clinical value.

In recent years, the gut-liver axis theory has emerged as a research hotspot for unraveling PSC pathogenesis [9]. During PSC progression, gut microbiota dysbiosis and impaired intestinal mucosal barrier drive translocation of enteric pathogens and their metabolites (e.g., lipopolysaccharide) to the liver, which subsequently activate macrophages and hepatic stellate cells and induce peribiliary inflammation and fibrosis [10]. Meanwhile, microbiota dysregulation combined with impaired bile excretion triggers bile acid metabolism disorders, leading to accumulation of toxic bile acids in the liver and exacerbating epithelial injury [11].

Traditional Chinese medicine emphasizes a holistic perspective. The gut-liver axis pathological mechanism in PSC aligns closely with the TCM pathogenesis concept of “simultaneous liver and intestinal disorders” and “disease transmission from the intestine to the liver”. Guided by therapeutic principles such as “treating the liver by regulating the intestine” and “unblocking the fu-organ to discharge turbidity”, TCM serves as an effective complement to conventional Western therapy [12–14]. TCM exerts holistic multi-component, multi-target advantages by improving gut microbiota, repairing the intestinal mucosal barrier, and regulating bile acid enterohepatic circulation (e.g., activating FXR/TGR5 receptors).

On this basis, this review synthesizes domestic and international evidence to discuss the molecular mechanisms of TCM intervention in the PSC gut-liver axis and

corresponding clinical syndrome differentiation strategies, aiming to provide references for integrative PSC management.

2. Modern Medical Understanding of the Gut-Liver Axis Pathological Mechanism in PSC

The gut-liver axis refers to the bidirectional anatomical and physiological interaction network between the intestine and liver, established via the portal vein and biliary system. Under physiological conditions, the liver maintains gut microbiota homeostasis by secreting bile acids and antimicrobial peptides, while the intact intestinal mucosal barrier effectively blocks abnormal translocation of intestinal microorganisms and their metabolites. In PSC, this bidirectional crosstalk is severely disrupted, evolving into a pathological cascade centered on "microbiota dysbiosis – barrier impairment – cholestasis" [9,15,16].

2.1 Gut Microbiota Dysbiosis and Pathogenic Bacterial Overgrowth

Multiple 16S rRNA and metagenomic sequencing studies have confirmed significant structural disturbances in the gut microbiota of PSC patients. Compared with healthy individuals and patients with isolated IBD, PSC patients exhibit markedly reduced α-diversity of intestinal flora [17,18]. The core signature is a sharp decline in short-chain fatty acid (SCFA)-producing beneficial bacteria (e.g., Faecalibacterium prausnitzii, Bifidobacterium), alongside pathological overgrowth of potential pathogens (e.g., Klebsiella, Enterococcus). Excessive pathogenic proliferation not only directly disrupts the local intestinal immune microenvironment, but also alters luminal physicochemical properties via abnormal metabolites, acting as the initiating trigger for persistent intrahepatic biliary inflammation [11,19,20].

2.2 Impaired Intestinal Mucosal Barrier ("Leaky Gut") and Enteric Pathogen Translocation

Intestinal mucosal barrier integrity depends critically on epithelial tight junction proteins (e.g., ZO-1, Occludin). In PSC, the combination of microbiota dysbiosis and locally elevated pro-inflammatory cytokines (e.g., TNF-α, IL-6) disrupts tight junction architecture, causing pathological hyperpermeability — the clinical "leaky gut" syndrome [21,22].

Breakdown of the mechanical barrier allows lipopolysaccharide (LPS, a core component of the Gram-negative bacterial cell wall) and other pathogen-associated molecular patterns (PAMPs) to cross the intestinal wall and reach the liver via the portal vein. This translocation rapidly and persistently activates intrahepatic Kupffer cells, triggering an inflammatory cascade that drives hepatic stellate cell (HSC) activation and excessive extracellular matrix (ECM) deposition, accelerating biliary stricture and fibrosis in PSC [23–25].

2.3 Disordered Bile Acid Metabolism Network and Impaired Receptor Signaling

PSC progression is accompanied by severe dysregulation of bile acid (BA) enterohepatic circulation. Progressive biliary stricture impairs bile excretion, and highly cytotoxic hydrophobic bile acids accumulate in the liver, directly inducing oxidative stress and apoptosis of biliary epithelial cells [26].

Concurrently, gut microbiota dysbiosis severely impairs the conversion of primary to secondary bile acids, markedly reducing activation of key nuclear receptors: farnesoid X receptor (FXR) and G protein-coupled bile acid receptor 1 (TGR5). Inhibited FXR signaling relieves negative feedback on cholesterol 7α-hydroxylase (CYP7A1), driving sustained hepatic bile acid synthesis and worsening cholestatic toxicity.

Taken together, microbiota dysbiosis, barrier impairment, and bile acid metabolism disorder form an interwoven vicious cycle driving PSC deterioration. The microecological and immunometabolic differences of the gut-liver axis between physiological status and PSC are schematically illustrated in Figure 1.

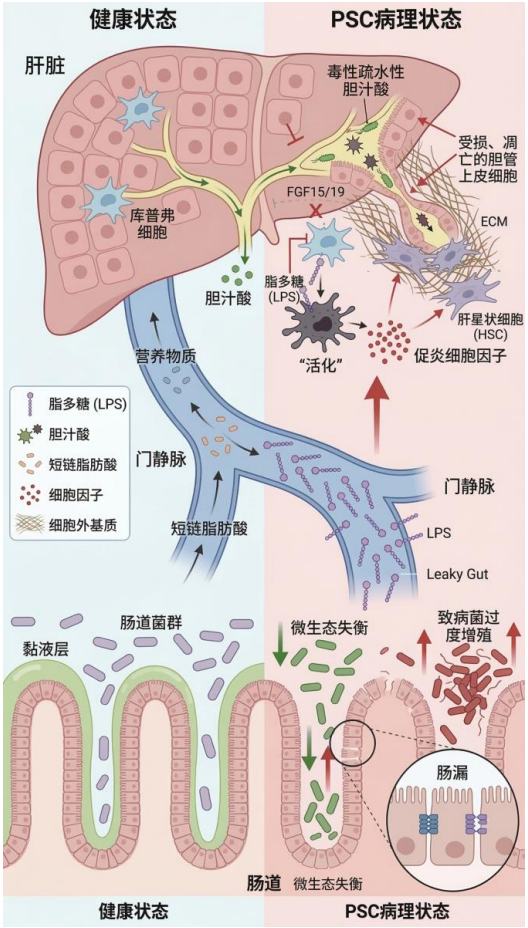

Figure 1: Schematic diagram of the gut-liver axis pathological mechanism in PSC

Note: PSC, primary sclerosing cholangitis; LPS, lipopolysaccharide; SCFAs, short-chain fatty acids; ECM, extracellular matrix; HSC, hepatic stellate cell; FGF15/19, fibroblast growth factor 15/19.

3. Scientific Consistency Between the Gut-Liver Axis Network and TCM "Liver-Intestinal Co-Disease" Theory

The modern gut-liver axis microecological and immunometabolic network shows high consistency with the

TCM theory of meridian connection and visceral interdependence between the liver-gallbladder and spleen-stomach (large intestine). PSC progression maps clearly to the TCM pathological trajectory of "damp-heat accumulation, disease spreading from intestine to liver". Within this framework, "treating the liver via the intestine" is the core clinical strategy for halting PSC progression.

3.1 Physiological Synergy: Liver Governing Free Flow of Qi and Large Intestine Governing Conduction

In TCM physiology, the liver and intestine (spleen-stomach and large intestine) maintain a dynamic balance of qi movement based on the harmonious wood-earth interaction. Li Chan, a Ming Dynasty physician, explicitly proposed the theory of "mutual communication between the liver and large intestine" in Introduction to Medicine (Yi Xue Ru Men), laying the foundational principle for intestinal-based liver therapy [28].

Liver free flow of qi regulates systemic qi movement and drives bile secretion and excretion — a prerequisite for gut microbiota homeostasis. Bile descending into the intestine assists the spleen and stomach in food digestion, enabling normal large intestine conduction and waste excretion [29]. Unobstructed large intestine qi and waste elimination in turn support smooth liver-gallbladder qi flow. As Qing Dynasty physician Tang Zonghai stated in Treatise on Blood Syndromes (Xue Zheng Lun): "Wood governs free flow and dispersion; food digestion in the stomach depends entirely on liver wood qi to disperse it" [30]. This bidirectional regulation corresponds to the modern gut-liver axis physiological crosstalk mediated by the bile acid pool and microbiota-regulated intestinal motility [31].

3.2 Pathogenesis Evolution: Damp-Heat Accumulation, Intestine-to-Liver Spread, and Toxin-Stasis Intermingling

PSC onset typically originates from spleen deficiency with impaired transportation, leading to internal damp-heat accumulation in the intestinal fu-organ, which corresponds to gut microbiota dysbiosis and mucosal barrier impairment in modern medicine [32,33]. As the disease advances, intestinal damp-heat toxins ascend to fumigate the liver and gallbladder, impeding liver qi flow and causing bile overflow. With chronic progression, damp-heat congeals into toxin, and qi stagnation with blood stasis develops, culminating in intermingled toxin and stasis in the liver-gallbladder collaterals [34], which forms the pathological basis of excessive HSC activation and biliary sclerosis [35,36].

3.3 Therapeutic Principles: Multi-Dimensional "Intestine-Based Liver Treatment" Strategy

Based on the liver-intestinal co-disease transmission pattern, Zhang Zhongjing stated in Synopsis of the Golden Chamber (Jin Gui Yao Lue): "When encountering liver disease, one must recognize that the liver transmits to the spleen, and therefore first fortify the spleen" [37]. In PSC, liver-soothing and bile-promoting therapy alone is often insufficient to reverse disease course; a holistic multi-dimensional intestine-based liver treatment approach is essential:

Unblocking fu-organ to discharge turbidity: For damp-heat stagnation ascending to the liver-gallbladder, classical formulas such as Dachaihu Decoction and Yinchenhao Decoction are used to unblock fu-organs, clear heat and relieve jaundice. Accelerated large intestine conduction promotes fecal excretion of toxic turbidity, corresponding to enhanced toxic bile acid excretion and microbiota regulation, which reduces hepatic inflammatory load [38].

Fortifying earth to subdue wood: Spleen-invigorating and qi-tonifying herbs including Astragali Radix, Atractylodis Macrocephalae Rhizoma and Codonopsis Radix are applied to repair the intestinal mucosal mechanical barrier and fundamentally block the intestine-to-liver endotoxin transmission pathway [39,40].

Activating blood and resolving stasis: For advanced biliary sclerosis, collateral-entering blood-activating herbs such as Paeoniae Radix Rubra, Salviae Miltiorrhizae Radix et Rhizoma and Trionycis Carapax are added to improve hepatic microcirculation and delay irreversible biliary fibrosis [41,42].

These three therapeutic principles correspond precisely to the three core pathological links of the gut-liver axis cascade.

4. Molecular Pharmacological Mechanisms of TCM Targeting the PSC Gut-Liver Axis

With advances in multi-omics technologies, the pharmacological mechanisms of TCM for PSC and related cholestatic liver diseases have been increasingly clarified. Evidence shows that TCM formulas and active monomers act not on a single target, but through a cascade network of "gut microbiota – metabolites – hepatic immunity". The core mechanisms involve three interrelated pathways, as summarized in Table 1.

4.1 Synergistic Regulation of Gut Microbiota and Bile Acid Metabolism

Intestinal flora and bile acid metabolism engage in bidirectional crosstalk. TCM formulas and extracts modulate gut microbiota structure, indirectly reshaping the bile acid pool and activating key nuclear receptors. For example, Si-Ni-San ameliorates cholestatic liver injury in mice by promoting colonization of the anti-inflammatory bacterium Parabacteroides goldsteinii [43]. Genipin, an active monomer from Gardeniae Fructus, has been shown to delay cholestasis and liver fibrosis in the classic PSC Mdr2-/- mouse model via gut microbiota modulation [44].

In bile acid metabolism regulation, monomers such as paeoniflorin [27, 47] and rhein [48-50] target and activate FXR, downregulate CYP7A1 to reduce primary bile acid synthesis, and upregulate bile salt export pump (BSEP) to promote toxic bile acid excretion, alleviating intrahepatic cholestatic injury. In addition, astragaloside IV enhances TGR5 signaling to exert anti-inflammatory and choleretic effects [12,51]. This microbiota-bile acid synergistic regulation is a core pathway by which TCM restores gut-liver axis metabolic homeostasis.

Table 1: Summary of pharmacological mechanisms of TCM active components and formulas targeting the PSC gut-liver axis

Drug category	Representative agents	Core targets and mechanisms	Corresponding TCM principle
Formulas / extracts	Si-Ni-San	Remodel gut microbiota, promote colonization of probiotics (e.g., Parabacteroides goldsteinii), suppress pathogens	Soothing liver and regulating spleen
Polysaccharides	Artemisia capillaris polysaccharide, Gardenia jasminoides polysaccharide	Upregulate tight junction proteins (ZO-1, Occludin), reduce intestinal permeability, repair mucosal barrier	Fortifying earth to subdue wood; securing spleen and intestine
Monomeric compounds	Paeoniflorin, rhein, genipin	Activate FXR, downregulate CYP7A1 to inhibit bile acid synthesis, promote toxic bile acid excretion; modulate gut microbiota and delay biliary fibrosis	Clearing heat and eliminating dampness; activating blood and resolving stasis
Herbal extracts	Astragalus membranaceus extract	Enhance TGR5 signaling, exert anti-inflammatory and choleretic effects	Tonifying qi and elevating yang
Classical formulas	Dahuang Xiaoshi Decoction, Sanhuang Xiexin Decoction	Inhibit Kupffer cell activation, downregulate pro-inflammatory cytokines (TNF-α), block inflammatory cascade	Unblocking fu-organ and clearing heat; resolving stasis and dredging collaterals

Note. PSC, primary sclerosing cholangitis; ZO-1, zonula occludens-1; FXR, farnesoid X receptor; CYP7A1, cholesterol 7α-hydroxylase; TGR5, G protein-coupled bile acid receptor 1; TNF-α, tumor necrosis factor-α.

4.2 Repairing the Intestinal Mucosal Barrier and Blocking Endotoxin Translocation

In PSC, microbiota dysbiosis and local inflammation increase intestinal mucosal permeability, driving massive translocation of LPS and other PAMPs to the liver via the portal vein. Maintaining barrier integrity is critical to interrupting this pathological cascade.

Studies demonstrate that polysaccharides from Artemisia capillaris and Gardenia jasminoides upregulate intestinal tight junction proteins ZO-1 and Occludin, reversing abnormal intestinal permeability [45,46]. By restoring mechanical barrier function, TCM effectively cuts off the portal translocation route of enteric endotoxin, reducing secondary hepatic immune stimulation and lowering serum endotoxin and D-lactate levels.

4.3 Inhibiting Intrahepatic Inflammatory Cascade and Delaying Fibrosis

Reduced enteric endotoxin translocation and activated bile acid receptors (FXR/TGR5) collectively create an intrahepatic microenvironment that suppresses excessive immune activation. When endotoxin influx is reduced, Kupffer cell activation is markedly blunted. Formulas such as Dahuang Xiaoshi Decoction and Sanhuang Xiexin Decoction further downregulate the TLR4/NF-κB pathway, reducing release of TNF-α, IL-6 and other pro-inflammatory cytokines, and alleviating peribiliary inflammatory cascade [38,52].

With reduced inflammatory load, blood-activating TCM monomers (e.g., salvianolic acid B from Salvia miltiorrhiza) directly target the TGF-β1/Smad pathway, inhibiting HSC proliferation and ECM deposition [53,54]. This intestine-to-liver cascade regulation ultimately delays PSC progression to fibrosis and cirrhosis. The multi-target regulatory network of TCM targeting the PSC gut-liver axis is detailed in Figure 2.

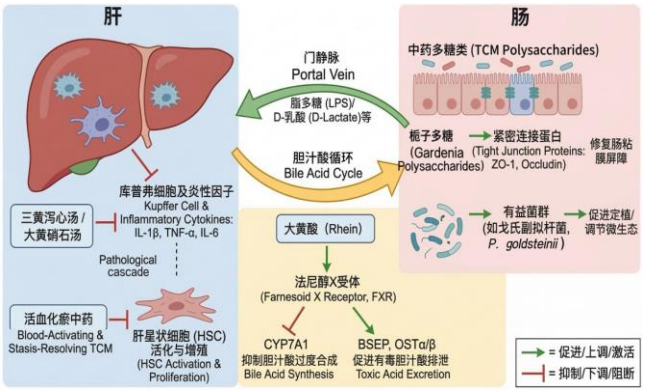

Figure 2: Multi-target mechanism of TCM targeting the gut-liver axis in PSC

Note. PSC, primary sclerosing cholangitis; LPS, lipopolysaccharide; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; HSC, hepatic stellate cell; FXR, farnesoid X receptor; CYP7A1, cholesterol 7α-hydroxylase; BSEP, bile salt export pump; OSTα/β, organic solute transporter α/β; ZO-1 / Occludin, tight junction proteins; P. goldsteinii, Parabacteroides goldsteinii; TCM, traditional Chinese medicine. Green arrows indicate promotion, upregulation or activation; red T-bars indicate inhibition, downregulation or blockade.

5. Clinical Integrative Medicine Strategies for PSC Based on the Gut-Liver Axis

Guided by the holistic liver-intestinal co-disease concept, PSC clinical management should integrate holistic thinking with staged syndrome differentiation. Given the limitations of UDCA in reversing disease progression and improving intestinal symptoms, a staged integrative strategy is widely

adopted in clinical practice. This strategy embeds intestinal conditioning and gut-liver axis homeostasis restoration throughout standard UDCA treatment to achieve synergistic efficacy (Table 2).

Table 2: Staged integrative clinical protocol for PSC based on the gut-liver axis

Disease stage	Core TCM pathogenesis	Therapeutic principle	Representative formulas	Key medication features	Gut-liver axis mechanism
Early / acute stage	Damp-heat accumulation, liver-gallbladder stagnation	Clear intestine and promote bile, discharge heat and detoxify	Modified Yinchenhao Decoction + Dachaihu Decoction	Rhei Radix et Rhizoma, Aurantii Fructus Immaturus (purgative, descending large intestine qi)	Synergistic burden reduction: compensates for slow UDCA onset; accelerates fecal excretion of toxic bile acids and LPS via purgation, rapidly reducing endotoxemia.
Middle / remission stage	Liver stagnation and spleen deficiency	Invigorate spleen and soften liver, fortify spleen and secure intestine	Shenling Baizhu San, Sijunzi Decoction	Astragali Radix, Codonopsis Radix, Atractylodis Macrocephalae Rhizoma (spleen-invigorating, qi-tonifying)	Barrier consolidation: targets intestinal lesions, upregulates tight junction proteins, blocks secondary endotoxin translocation, maintains gut-liver immune tolerance.
Late / progressive stage	Toxin-stasis intermingling, liver collateral obstruction	Resolve stasis and dredge collaterals, soften hardness and dissipate masses	Huoxue Qingjie Ling, Gexia Zhuyu Decoction	Trionycis Carapax, Hirudo (animal-derived collateral-entering herbs)	Anti-fibrosis gap filling: improves hepatic microcirculation, inhibits HSC activation, promotes ECM degradation, delays biliary sclerosis progression.

Note. PSC, primary sclerosing cholangitis.

5.1 Early / Acute Active Stage: Synergistic Intestine-Clearing and Choleretic Therapy

In early or acute inflammatory PSC, patients typically present with fatigue, intractable pruritus, and markedly elevated hepatobiliary biomarkers (ALP, GGT). The pathogenesis falls under "damp-heat accumulation with liver-gallbladder stagnation".

Integrative strategy: On top of standard UDCA for bile excretion promotion, purgative heat-clearing formulas (e.g., modified Yinchenhao Decoction combined with Dachaihu Decoction) are added [33]. UDCA modifies bile acid pool physicochemical properties, while TCM purgation facilitates the physical elimination of retained biliary toxins and bacterial metabolites. Purgative herbs such as Rhei Radix et Rhizoma and Aurantii Fructus Immaturus accelerate fecal excretion of retained toxic hydrophobic bile acids and bacterial metabolites (e.g., LPS), rapidly reducing enteric endotoxemia and alleviating acute Kupffer cell inflammatory load.

5.2 Middle / Chronic Remission Stage: Spleen-Fortifying and Intestine-Securing Therapy for Barrier Repair

With chronic disease progression, patients develop "liver stagnation and spleen deficiency" patterns. Given the high IBD comorbidity in PSC patients, this stage is often accompanied by diarrhea, mucopurulent bloody stool and other intestinal symptoms. UDCA monotherapy cannot address intestinal lesions.

Integrative strategy: For leaky gut and microbiota dysbiosis, treatment focus shifts to "fortifying the spleen and securing the intestine", typically using Shenling Baizhu San or Sijunzi Decoction as base formulas [40]. Mechanistically, spleen-invigorating herbs improve digestive function and significantly upregulate intestinal tight junction proteins. By repairing the mucosal barrier, TCM blocks secondary enteric pathogen translocation, compensating for Western medicine's limitations in maintaining intestinal immune tolerance and controlling IBD complications [55].

5.3 Late / Fibrotic Stage: Stasis-Resolving and Collateral-Dredging Therapy to Delay Biliary Stricture

Advanced PSC features diffuse biliary stricture and severe fibrosis, with pathogenesis shifting to "toxin-stasis intermingling and liver collateral obstruction". No approved pharmacotherapy can effectively reverse established biliary fibrosis.

Integrative strategy: At this stage, collateral disease theory-guided treatment is essential, emphasizing blood-activating, collateral-dredging agents (e.g., modified Huoxue Qingjie Ling or Gexia Zhuyu Decoction, often combined with animal-derived herbs) [35,42]. The core advantage of stasis-resolving collateral-dredging therapy is its well-documented anti-fibrosis targets. By improving hepatic microcirculation, inhibiting sustained HSC activation, and promoting ECM degradation, TCM fills the Western medicine anti-fibrosis gap and provides a clinically feasible approach to delay progression to end-stage cirrhosis [56].

6. Conclusion and Perspectives

Grounded in the gut-liver axis theory, the holistic TCM concept of concurrent liver-intestinal disorders and intestine-based liver treatment offers a new perspective to address the limitations of single-target Western therapy for PSC.

Current evidence demonstrates that TCM achieves comprehensive regulation of the PSC pathological network by modulating gut microbiota, repairing the intestinal mucosal barrier, activating bile acid nuclear receptors (FXR/TGR5), and inhibiting macrophage and hepatic stellate cell activation. This multi-target holistic mode not only compensates for the deficiencies of UDCA monotherapy in microbiota regulation and anti-fibrosis, but also provides a theoretical foundation for developing precise integrative intervention regimens.

Nevertheless, research in this field remains limited. Clinical evidence is mostly derived from expert experience and small retrospective studies; high-quality multicenter randomized double-blind controlled trials are needed to confirm the efficacy and safety of integrative regimens. Mechanistic studies remain largely phenotypic and correlation-based; causal relationships between specific TCM-modulated microbial niches and host immunometabolic outcomes

require further validation using germ-free and gene knockout animal models.

Future research should integrate metagenomics, untargeted metabolomics and other multi-omics approaches to delineate the precise targets and dose-effect relationships of TCM on the "drug-microbiota-metabolite-host" axis. Clinically, given the promise of fecal microbiota transplantation (FMT) for refractory hepatobiliary diseases, novel integrative models — such as TCM acting as prebiotics combined with functional bacterial strains or sequential TCM-FMT therapy — may improve microbial colonization and long-term outcomes, further enriching therapeutic strategies for PSC [57].

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