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RECEIVED 30 May 2025

ACCEPTED 22 August 2025

PUBLISHED 11 September 2025

CITATION

Zhan J, Fu Y, Liu Z, Zhang S and Wu C (2025)
Modulating the gut-immune axis to
alleviate rheumatoid arthritis: mechanistic
insights and therapeutic potential of
traditional Chinese medicine.
Front. Immunol. 16:1637942.
doi: 10.3389/fimmu.2025.1637942

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Modulating the gut-immune axis to alleviate rheumatoid arthritis: mechanistic insights and therapeutic potential of traditional Chinese medicine

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Rheumatoid arthritis (RA), a chronic autoimmune disorder marked by systemic inflammation and joint destruction, remains challenging to treat due to the limitations of conventional therapies, including side effects and diminishing efficacy. Emerging research underscores the gut-immune axis—a dynamic interplay between gut microbiota, immune responses, and inflammation—as a pivotal contributor to RA pathogenesis. Traditional Chinese Medicine (TCM), recognized for its established safety and accessibility, has been shown to synergistically alleviate symptoms of RA when used alongside conventional treatments, while significantly reducing drug-related toxicity. Pre-clinical models and clinical trials have demonstrated that TCM formulations, bioactive phytochemicals, and their metabolites can modulate the gut-immune axis by restoring gut microbiota balance and regulating immune-inflammatory pathways. This review summarizes the multi-target effects of TCM, including microbiota modulation and immune system regulation, and proposes a microbiota-centered therapeutic strategy for RA. Although the role of Traditional Chinese Medicine in regulating gut microbiota and immune modulation supports its clinical translatability, rigorous mechanistic studies remain essential to facilitate its integration into mainstream rheumatology treatment strategies. This involves research on its pharmacokinetic-pharmacodynamic characteristics, validation of microbiome-dependent mechanisms, and investigation into mechanisms involving microbial metabolites. By integrating millennia of empirical knowledge with cutting-edge systems biology, TCM presents a microbiota-centered holistic strategy for RA management.

KEYWORDS

rheumatoid arthritis (RA), traditional Chinese medicine (TCM), gut microbiota, immunomodulation, gut-immune axis

1 Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by synovial inflammation and hyperplasia, leading to cartilage and bone destruction, as well as systemic manifestations such as pulmonary, cardiovascular, skin, psychological, and skeletal disorders. RA arises from disrupted immune tolerance and sustained immune activation, driving inflammation and tissue remodeling (1). It affects approximately 0.46% of the global population, with a higher prevalence in industrialized countries (2). RA develops as a result of both genetic predispositions and environmental factors, such as specific gene variants like human leukocyte antigen-DR beta chain 1 (HLA-DRB1) and lifestyle triggers including smoking, pollutant exposure, and viral infections. Risk factors modulate gene expression via epigenetic mechanisms, contributing to disease onset and progression. These factors can influence post-transcriptional modifications (PTMs) of specific genes or affect susceptibility genes via epigenetic mechanisms. The burden of RA is substantial due to its recurrent nature and high disability rate (1, 3).

The human gut microbiota (GM) represents a complex and dynamic ecosystem of microorganisms residing within the gastrointestinal tract (4). This microbial community includes diverse subgroups of bacteria, viruses, fungi, and archaea, all coexisting within the gastrointestinal environment. The gastrointestinal tract hosts a substantial proportion of the body's immune cells and continuously interacts with the GM, thereby shaping their functions and properties (5). The gut microbiome, which includes microbiota, microbial structural components such as nucleic acids, metabolites, and environmental factors, plays a fundamental role in the priming and development of the immune system (6). The GM serves as an innate immune modulator, drug and diet metabolizer, and producer of biologically active metabolites. It is vital for modulating immune cell activities and inflammatory cytokines, thus helping to maintain balanced immune responses (5).

Increasing evidence and reports have demonstrated that there is an intricate and dynamic interaction between the GM and the immune system, forming what is known as the gut-immune axis (7–9). Numerous studies highlighted a critical role of the gut-immune axis in the pathogenesis of RA (5, 10–12). Dysbiosis of specific bacterial lineages and metabolic alterations in gut microbiota resulted in modifications to the host immune profile, which contribute to the development of RA (13). Extensive investigations have demonstrated that GM composition on fecal samples differs between RA patients and healthy controls (HCs), implying gut dysbiosis may contribute to RA pathogenesis (14–17). Recent research highlights that dysbiosis and compositional variations of GM in RA patients are key factors contributing to abnormal systemic immunity (18–20). It has been suggested that the mechanism through which gut dysbiosis leads to RA might be associated with the regulation of immune function by metabolites generated by GM (21–24). Intestinal barrier dysfunction precedes RA, which further supports the “gut-immune axis” in RA pathogenesis (25–27).

Despite efforts to develop anti-RA drugs, there is no safer and more sustainable therapeutic agent for RA in humans. Conventional

treatments for RA include glucocorticoids (GCs), non-steroidal anti-inflammatory drugs (NSAIDs), and disease-modifying anti-rheumatic drugs (DMARDs). etc. NSAIDs, DMARDs and GCs could effectively relieve the pain of RA patients and inhibit the inflammatory reaction *in vivo*, but they fail to restore the native function of joints. Moreover, current therapeutic options are limited by deleterious side effects, high costs, inadequate control of disease progression in many patients, and diminishing therapeutic efficacy over time.

Traditional Chinese medicines (TCMs) have been used to treat various diseases since ancient times and shown to be safe and accessible to the general population in treating RA (28–30). Accumulating evidence have revealed that TCMs, their extracts, and bioactive compounds have anti-inflammatory, cartilage-protective, and immunoregulation properties and exhibit promising anti-RA activities (31–33). Clinical studies show TCMs are more effective with fewer side effects compared to conventional treatments. Combining TCM with synthetic DMARDs can reduce adverse effects of conventional therapies (34–39). TCMs offer advantages in modulating the gut-immune axis through multi-target regulation and lower toxicity (39–44). Notably, DMARDs such as methotrexate and leflunomide often cause gastrointestinal toxicity, whereas TCM can mitigate toxicity (45, 46).

However, due to their complex compositions and multiple targets, TCMs necessitate further investigation to elucidate the active ingredients and mechanisms of action in treating RA. Natural products derived from TCMs, characterized by their remarkable chemical diversity and bioactivity, hold significant potential as a foundation for developing novel pharmacological agents for RA treatment (47). Therefore, upon validation of their pharmacological potential, these TCM-derived natural products may provide promising leads for the development of modern anti-RA drugs.

Investigating the mechanisms by which TCMs regulate the gut-immune axis in RA treatment holds significant importance, as this identifies potential target for developing RA therapeutics. Consequently, this paper provides a comprehensive review of TCMs with anti-RA activities that specifically target the gut-immune axis, thereby paving the way for future research and development endeavors.

2 Overview of immune response in RA

RA pathogenesis is initiated by PTMs, such as citrullination, carbamylation, and glycosylation, which generate neoepitopes recognized as autoantigens. Citrullination, mediated by peptidyl arginine deiminases (PADs), converts arginine to citrulline, triggering anti-citrullinated protein antibody (ACPA) production. Genetic susceptibility enables T-cell recognition of modified peptides and disrupts T-cell signaling, promoting autoimmunity (1).

Antigen-presenting cells (APCs) present these autoantigens to autoreactive T cells. Metabolic reprogramming and DNA repair defects drive abnormal T-cell differentiation into short-lived effector T cells (SLECs), contributing to premature senescence and skewed differentiation into proinflammatory subsets at the expense of regulatory T (Treg) cells and T helper-2 (Th2) cells. Senescent T cells acquire cytotoxic/NK-like properties, resisting

apoptosis and sustaining inflammation (1, 48, 49) (Figure 1). Proinflammatory subsets include Th1, Th17, follicular helper T cells (Tfh) and peripheral helper T cells (Tph). Th1 cells produce interferon (IFN)- γ , tumor necrosis factor (TNF)- α , and interleukin (IL)-2, and amplify macrophage activation (50), whereas Th2 cells generally secrete IL-4, IL-10, and IL-13, cytokines, and reduce macrophage activation (51). Th17 cells release proinflammatory cytokines such as IL-17, IL-21, and TNF- α , which affect chondrocytes, fibroblasts, osteoclasts, and neutrophils (52). Chondrocytes undergo apoptosis and pyroptosis and can be induced to release pro-inflammatory proteins, such as TNF- α , IL-6, collagenolytic enzymes, and matrix metalloproteinases (MMPs) (53). Treg cells, which secrete anti-inflammatory cytokines such as IL-10 and transforming growth factor- (TGF-) β 1, are essential in controlling RA (54). Abnormal Th1/Th2 and Th17/Treg ratio have been detected in RA patients (55, 56) (Figure 2). Tfh and Tph cells expand in synovium, supporting B-cell maturation and autoantibody diversification (e.g., IgG ACPA) (1, 57, 58) (Figure 1).

Autoreactive B cells, stimulated by Tph/Tfh-derived chemokine (C-X-C) motif ligand 13 (CXCL13) and IL-21, differentiate into plasma cells secreting ACPA, rheumatoid factor (RF), and anti-PAD4 antibodies. B cells also secrete proinflammatory cytokines (IL-6, TNF- α), sustaining synovitis and ectopic lymphoid structures formation in joints (49, 57).

Macrophages, synoviocytes and neutrophils play important roles in RA innate immune activation and joint destruction. M1-polarized macrophages dominate RA synovium, releasing TNF- α , IL-1 β , and MMPs that drive cartilage degradation. M2 macrophages, which secrete anti-inflammatory cytokines such as IL-4, IL-10, and TGF- β , are critical for tissue repair, become depleted, thereby impairing the resolution of inflammation (1, 59). Macrophage-like synoviocytes (MLSs) produce such cytokines as IL-1 β , IL-6, and TNF- α to stimulate Fibroblast-like synoviocytes (FLSs) to secrete MMPs and receptor activator of nuclear factor κ B ligand (RANKL) (60, 61). FLSs acquire an invasive phenotype, secrete cytokines (e.g., IL-6, IL-17, and IL-33)

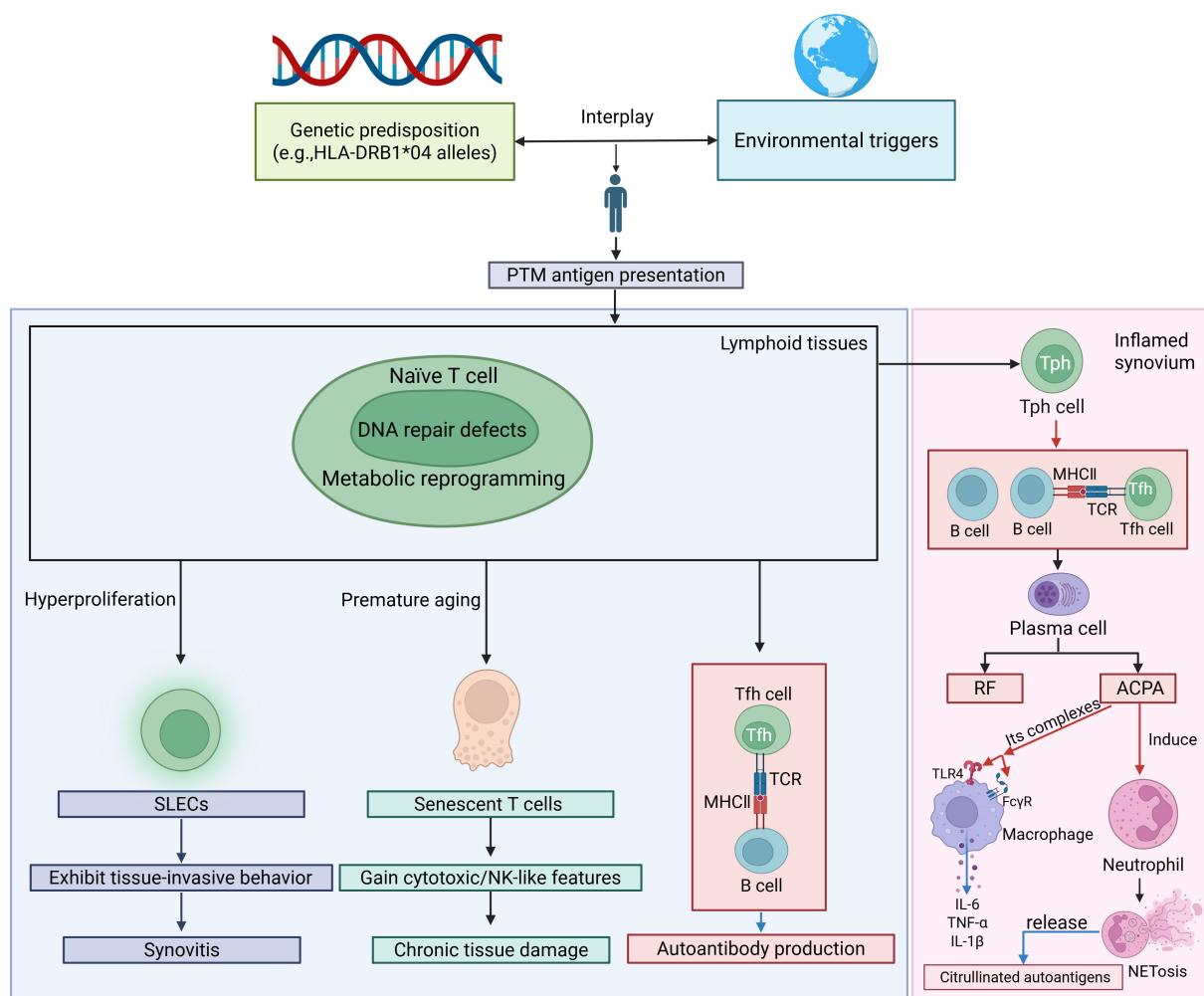


FIGURE 1

The crosstalk between T cells, neutrophils, and macrophages creates a vicious cycle in RA. SLECs, short-lived effector T cells; PTM, posttranslational modification; TCR, T cell receptor; MHC, major histocompatibility complex; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibody; TLR, Toll-like receptor; Fc γ R, Fc gamma receptor. Red arrows indicate activation, facilitation or stimulation, whereas blue arrows represent the secretion of cytokines or release of autoantigens/autoantibodies.

and chemokines (e.g., C-C motif ligand 2/CCL2), and recruit immune cells such as monocytes/macrophages, neutrophils, and T cells. Moreover, these cells release growth factors and pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) and heparin-binding epidermal growth factor-like growth factor (HB-EGF), thereby promoting FLS invasiveness, macrophage activation, angiogenesis, and sustaining synovial hyperplasia (61). Neutrophils produce pro-inflammatory proteins and neutrophil extracellular traps (NETs), which release citrullinated antigens and induce CD14⁺ monocytes to differentiate into osteoclasts through a RANKL-independent pathway (Figure 1). ACPAs further directly activate neutrophils and induce NETosis (NETs) (62, 63). Citrullinated fibrinogen-ACPA complexes in the RA synovium synergistically activate macrophages through dual engagement of Toll-like receptor 4 (TLR-4) and Fc gamma receptors (FcγR). This co-stimulation triggers robust TNF-α production (64, 65) (Figures 1, 3).

In summary, a self-reinforcing cycle of innate-adaptive crosstalk, cytokine storms, and tissue destruction underpins RA progression.

3 The gut-immune axis in RA

The gut-immune axis represents a burgeoning concept that elucidates the bidirectional interactions between the gut microbiome and the immune system. Accumulating evidence highlights the critical role of the gut-immune axis in the pathogenesis of RA (10, 39, 48, 66). This axis operates through four primary mechanisms: (1) gut dysbiosis-driven immune dysregulation, (2) microbial metabolite-mediated immunomodulation, (3) intestinal barrier dysfunction, and (4) molecular mimicry of autoantigens. Below, we summarize current evidence linking these mechanisms to RA progression (Figure 2).

GM and their metabolites contribute to RA development through immunomodulatory effects. Gut dysbiosis, characterized by alterations in microbial diversity and abundance, is linked to RA pathogenesis in both patients and animal models (22, 67–71). The GM generates a variety of metabolites, including trimethylamine N-oxide, tryptophan derivatives, short-chain fatty acids (SCFAs), indole-3-acetate, bile acids, peptidoglycan, amines, polyamines, vitamins, and other small molecules (72). A growing body of evidence indicates that these microbial metabolites possess immunomodulatory properties and affect the development of RA (14, 73–75).

3.1 Gut dysbiosis in RA: microbial shifts and pathogenic drivers

Gut dysbiosis contributes to the occurrence of RA in both patients and animal models, with increased prevalence of *Prevotella* spp. in pre-clinical and diagnosed RA cases. While multiple *Prevotella* species other than *P. copri* are associated with RA etiology, *P. copri* itself is most abundant in new-onset RA and correlates with reduced *Bacteroides fragilis* levels (14, 71).

Animal models do not fully replicate human RA, but they provide valuable mechanistic insights despite differences in GM (12, 76). SKG mice develop arthritis when colonized with *Prevotella*, while germ-free or antibiotic-treated mice remain disease-free. Collagen-induced arthritis (CIA) mice show altered GM composition with reduced Bacteroidetes and increased Firmicutes and Proteobacteria during early arthritis onset (77). Germ-free (GF) L-1 receptor antagonist (IL-1Ra) knockout mice do not develop arthritis unless colonized with *Lactobacillus bifidus*, which induces rapid disease onset similar to conventional mice (78).

Additionally, GM affects the development of RA. Early RA patients show higher levels of *Lactobacillus* and *Blautia gnavus*, while *Acetanaerobacterium elongatum*, *Cristiansella massiliensis*, and *Gracilibacter thermotolerans* were significantly enriched in the control group (79, 80). TNF transgenic (TNF-Tg) mice overexpress human TNF-α, leading to spontaneous arthritis similar to human RA. Key mechanisms include TNF-α-driven inflammation via the Nuclear Factor kappa B (NF-κB) and Mitogen-activated protein kinase (MAPK) pathways, synovial hyperplasia, and bone erosion. These mice show increased *Prevotella*, *Aerococcus*, and *Staphylococcus* but reduced *Parasutterella* and *Clostridium_XIVa*. Dysbiosis promotes systemic inflammation via altered metabolites and increased gut permeability (81).

During the active phase of RA patients, *Haemophilus* and *Bacteroides* were reduced, while *Lactobacillus salivarius*, *Streptococcus*, *Akkermansia*, *Klebsiella*, and *Escherichia coli* were increased (21, 82, 83). Probiotic genera such as *Faecalibacterium* are decreased, while pathogenic bacteria including *Porphyromonas gingivalis*, *Collinsella*, and *Aggregatibacter actinomycetemcomitans* are more abundant in RA (83–85).

Taken together, these microbial shifts disrupt immune and metabolic homeostasis, contributing to the onset and exacerbation of autoimmunity. The findings highlight GM as a critical therapeutic target, emphasizing the need to restore microbial balance to attenuate RA progression.

3.2 Interactions between the GM and the immune system in RA

Substantial evidence indicates that gut dysbiosis in RA is a key factor contributing to systemic immune dysregulation. It is plausible that local tissue stress induces PTMs of peptides, which subsequently trigger antibody formation, serving as a common mechanism in RA (86). Certain GM such as *Collinsella* and *Porphyromonas gingivalis* encode functional microbial PADs which can leak into the human intestinal epithelium under conditions of increased intestinal permeability, leading to citrullination of peptides within the human gut. Citrullinated peptides from both human and bacterial proteins trigger loss of immune tolerance, especially in genetically predisposed individuals (85). For example, *Aggregatibacter actinomycetemcomitans* activates citrullinating enzymes in neutrophils, promoting autoantigen

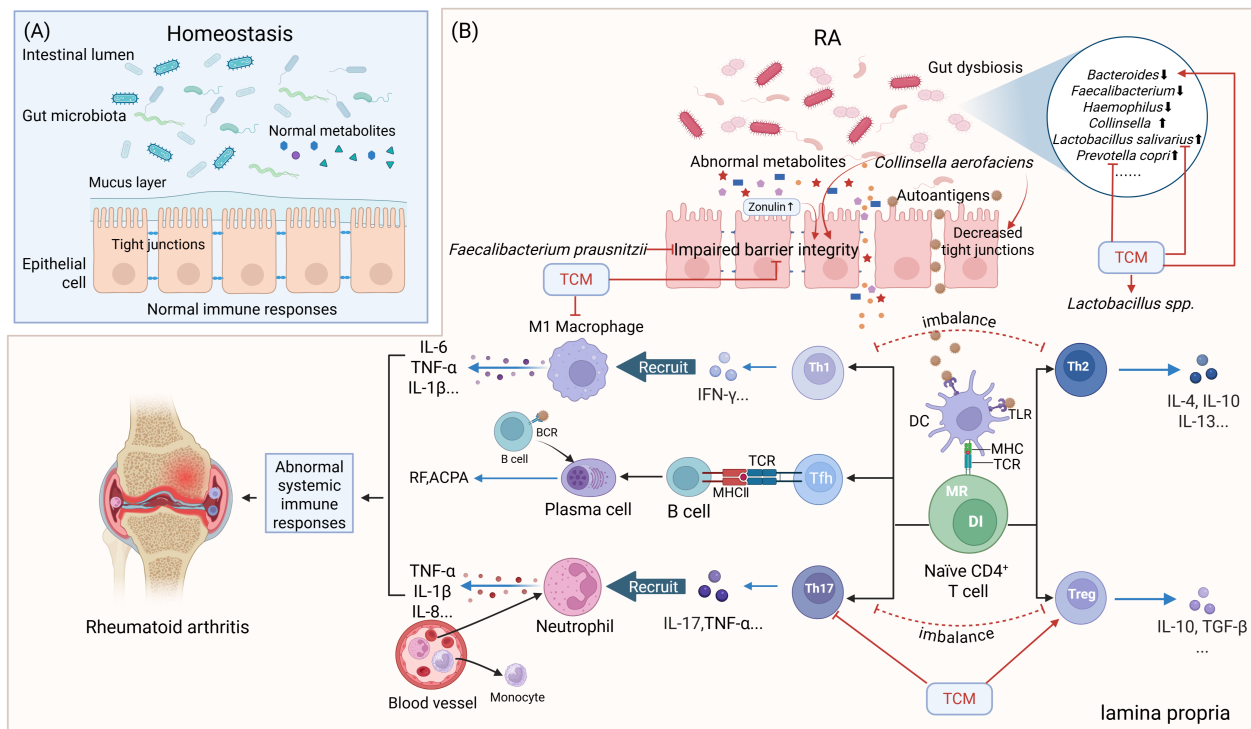


FIGURE 2

Simplified scheme of the gut-immune axis in the pathogenesis of RA and its TCM modulation. (A) The normal gut microbiota and their metabolites maintain the integrity of the intestinal epithelial cell layer and the homeostasis of gut immunity. (B) Impact of gut dysbiosis on gut barrier integrity and immune responses in RA and TCM interventions. Elevated Zonulin secretion leads to impaired gut barrier integrity. APCs recognize autoantigens and present them to T and B lymphocytes within lymphoid tissues, triggering an autoimmune response, ultimately leading to RA. DC=dendritic cell, BCR, B-cell receptor; DI, DNA instability; MR, Metabolic reprogramming. Red arrows indicate activation or facilitation, whereas red blocked lines indicate inhibition. Blue arrows represent the secretion of cytokines/autoantibodies.

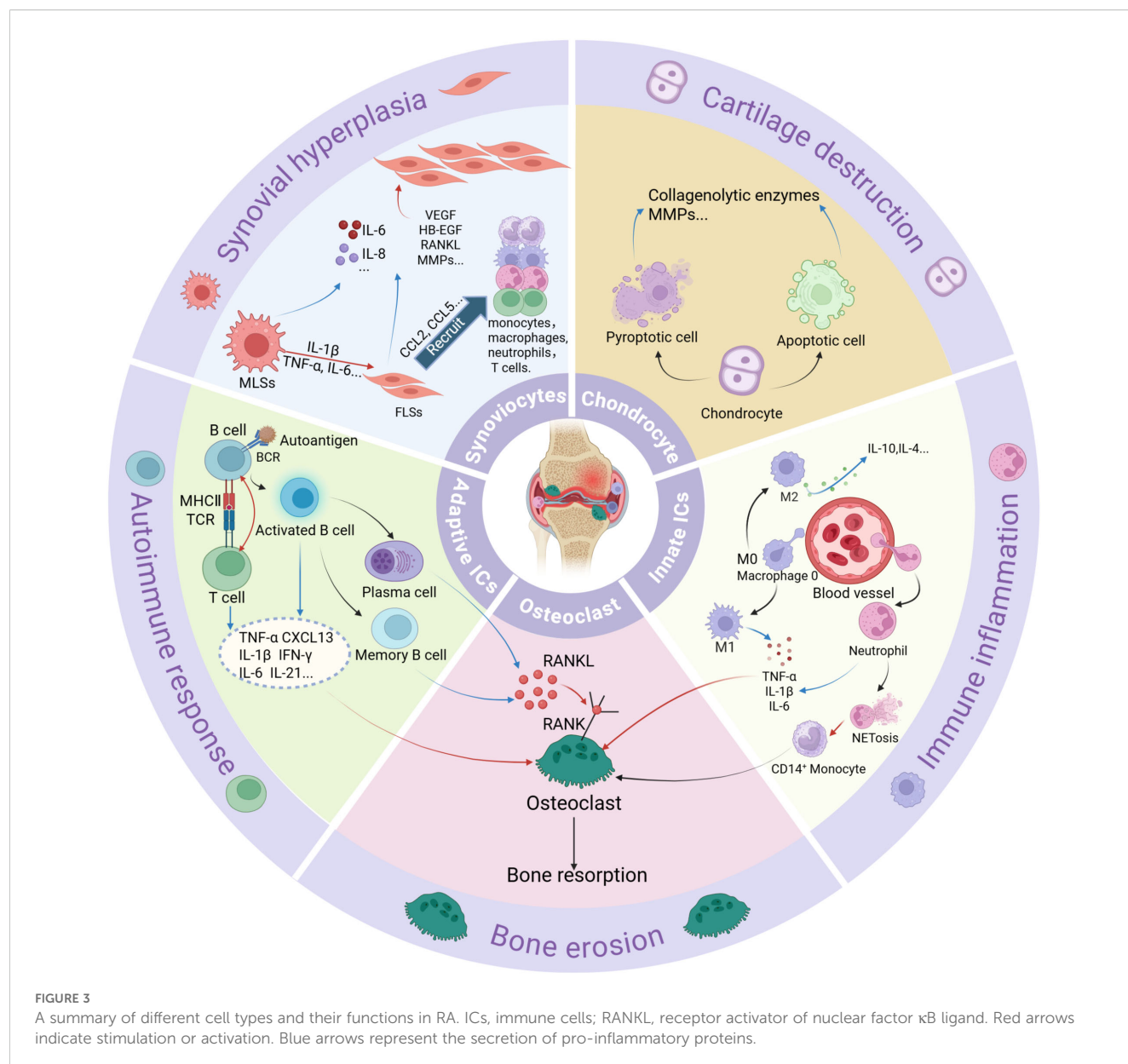
citrullination in RA joints. Specific citrullinated antigens such as vimentin, fibrinogen- α , and actin are targeted by ACPAs, suggesting the colon mucosa as a potential site for autoimmunity initiation (87). The Pc-p27 protein, a citrullinated peptide from *Prevotella copri*, induces Th1 immune responses in RA patients via binding to human leukocyte antigen (HLA)-DR (25). This association is further supported by the presence of IgA antibodies against Pc-p27 in both acute and chronic RA patients, which are linked to the production of Th17 cytokines and ACPA.

Autoantigens can be presented to CD4⁺ T cells by dendritic cells (DCs) and macrophages, driving inflammatory T cell differentiation and disrupting the Th17/Treg balance. Th17 cells promote B cell activation and antibody production, while Treg cells maintain immune tolerance and homeostasis by suppressing aberrant immune responses. *Lactobacillus* and *Bifidobacterium infantis* exert anti-inflammatory effects by inducing the expansion of Treg cells (88). The Th17/Treg ratio is significantly increased in advanced RA patients, highlighting the role of GM and metabolites in modulating this imbalance (10, 89) (Figure 2). *Lactobacillus bifidum* exacerbated arthritis by promoting Th17 and Th1 responses via TLR2/TLR4 signaling (78). *Lactobacillus plantarum* strain TIFN101 enhances intestinal mucosal immunity by increasing IL-17-producing memory Th cells and upregulating major histocompatibility complex (MHC)-IIa expression (90).

Moreover, *Lactobacillus helveticus* SBT2171 suppresses T/B cell proliferation and lymphoma cell cycle progression through JNK pathway inhibition *in vitro* (91). The phylum *Firmicutes* was negatively correlated with Th17 cell counts, while *Verrucomicrobiota* (e.g., *Akkermansia muciniphila*) were positively correlated with Treg numbers (13). Additionally, the accumulation of Treg cells in the colonic lamina propria can also be induced by *Clostridia* (92).

In contrast, the colonization of *Bacteroides fragilis* is associated with increased activity of regulatory T (Tregs), potentially mitigating the severity of autoimmune diseases (93, 94). The reduction in *Bacteroidetes* in CIA mice is thought to impair the differentiation of CD4⁺ T cells into Tregs, thereby contributing to an overall pro-inflammatory environment (95).

GF mice serve as a powerful and widely utilized model for investigating the impact of the microbiome on the immune system. *Segmented Filamentous Bacteria* (SFB) monocolonization in GF K/BxN mice induces autoantibody production, pathogenic Th17 cells, and arthritis (96). Additionally, SFB promotes Th17 cell accumulation in the gut via DC-presented antigens and IL-1 β secretion induced by reactive oxygen species (ROS) (97, 98). SFB can induce autoimmune arthritis by promoting the differentiation and migration of gut Tfh to systemic lymphoid tissues, increasing autoantibody production (99). In contrast, depletion reduces Tfh



cells and antibody levels, indicating that microbiota regulate arthritis via Tfh cells independently of Th17 cells (100).

Other studies employed the K/BxN model, in which mice co-expressed the T-cell receptor (TCR) transgene KRN and MHC class II molecule A (g7), leading to the development of autoantibodies against glucose-6-phosphate and subsequent severe inflammatory arthritis. GF conditions markedly reduce arthritis severity due to lower autoantibody levels and fewer Th17 cells (101). *Prevotella* and *Monoglobus* abundance correlates positively with Th1/Th2 cell counts and cytokine levels including IL-4, IL-2, IL-10, TNF- α , and IFN- γ (13).

Disrupted GM can also interact with other kinds of immune cells and their cytokines to modulate immune responses and inflammatory reactions, contributing to RA. Injection of *colonic E. coli* or *Enterococcus* into autoimmune-prone Dark Agouti rats caused a reduction in macrophages, an increase in activated

neutrophils, and inflammatory polarization of peritoneal cells (102). Tanoue et al. found 11 bacterial strains, including *Bacteroides clarus* 82C1, *Bacteroides uniformis* st. mat-281 81A2, *Anaerostipes caccae* 81B4, *Bacteroides eggerthii* 82B11, *Bacteroides fragilis* 82A12, *Bacteroides cellulosilyticus* 82B7, *Bacteroides salyersiae* 82A3, *Clostridium* sp. AUH-JLC39 82D29, *Hungatella hathewayi* 81G1, *Clostridium* sp. AT5 83F2, and *Clostridium innocuum* 81A1, from healthy human donor faces that could induce IFN- γ -producing CD8⁺ T cells without intestinal inflammation (103).

A novel intestinal immune regulatory pathway involves macrophage sensing of microbes via myeloid differentiation primary response 88 (MyD88) and Nucleotide-binding oligomerization domain 2 (Nod2), leading to IL-1 β production and innate lymphoid cells (ILC) 3-derived IL-2, essential for intestinal Treg induction (104). Clinically, the abundance of *P.*

goldsteinii correlates negatively with NETs indices and RA disease activity (105). CD8⁺ T cells displayed notable alterations in RA patients characterized by dysregulation of both *Prevotella* and *Bacteroides* microbiota (106) (Figure 4).

The overactivation of Th1 cells and Th17 cells, induced by a disrupted GM, results in the excessive production of pro-inflammatory cytokines such as TNF, IL-6, and IL-17. This triggers systemic inflammation and immune dysregulation, playing a critical role in autoimmune diseases like RA. Specifically, the disruption of GM within the *Enterobacteriaceae* family activates the NF- κ B signaling pathway, promoting the release of pro-inflammatory cytokines and thereby contributing to inflammation (107).

In contrast, some strains, such as *Lactobacillus casei* and *Lactobacillus acidophilus* exhibit significant anti-inflammatory and antioxidant effects, protecting against CIA (108). *Faecalibacterium prausnitzii* induces the secretion of IL-10 by CD4⁺ T cells and exhibits substantial anti-inflammatory effects (109). A previous study indicated that *L. helveticus* SBT2171 could up-regulate the expression of A20, a negative regulator of NF- κ B/ MAPK signaling, via TLR2 signaling, thereby suppressing IL-6 and IL-1 β production by APCs (110).

Collectively, the interplay between gut dysbiosis and RA pathogenesis is underscored by mechanisms linking microbial activity to systemic immune dysregulation. These findings highlight the therapeutic potential of targeting GM through

probiotics, dietary interventions, or microbial transplants to restore immune balance. However, the complexity of microbial-immune interactions necessitates further research to delineate strain-specific effects and optimize translational strategies for RA management.

3.3 Interactions between the gut microbial metabolite and the immune system in RA

Dysfunctional GM can lead to alterations in fecal metabolites and compromise gut barrier integrity, permitting metabolites to enter the circulatory system, thereby inducing inflammatory processes and immune responses (23, 24). The primary SCFAs produced by GM in the human gut are acetate, propionate, and butyrate. Other SCFAs include pentanoate, hexanoate, and heptanoate (111). The concentrations of acetate, propionate, butyrate, and valerate were found to be reduced in RA patients (22, 80, 112). These SCFAs correlate positively with B cell frequency and can inhibit B cell differentiation and autoantibody production (113). Some immunomodulatory properties of SCFAs are attributed to their influence on both innate and adaptive immune system cells through the inhibition of histone deacetylases (HDACs) (114). Specifically, SCFAs enhance IL-10 production in T-helper 1 cells via the G protein-coupled receptor 43 (GPR43) pathway and inhibit HDAC activity during T helper 1 and Th17 differentiation (115).

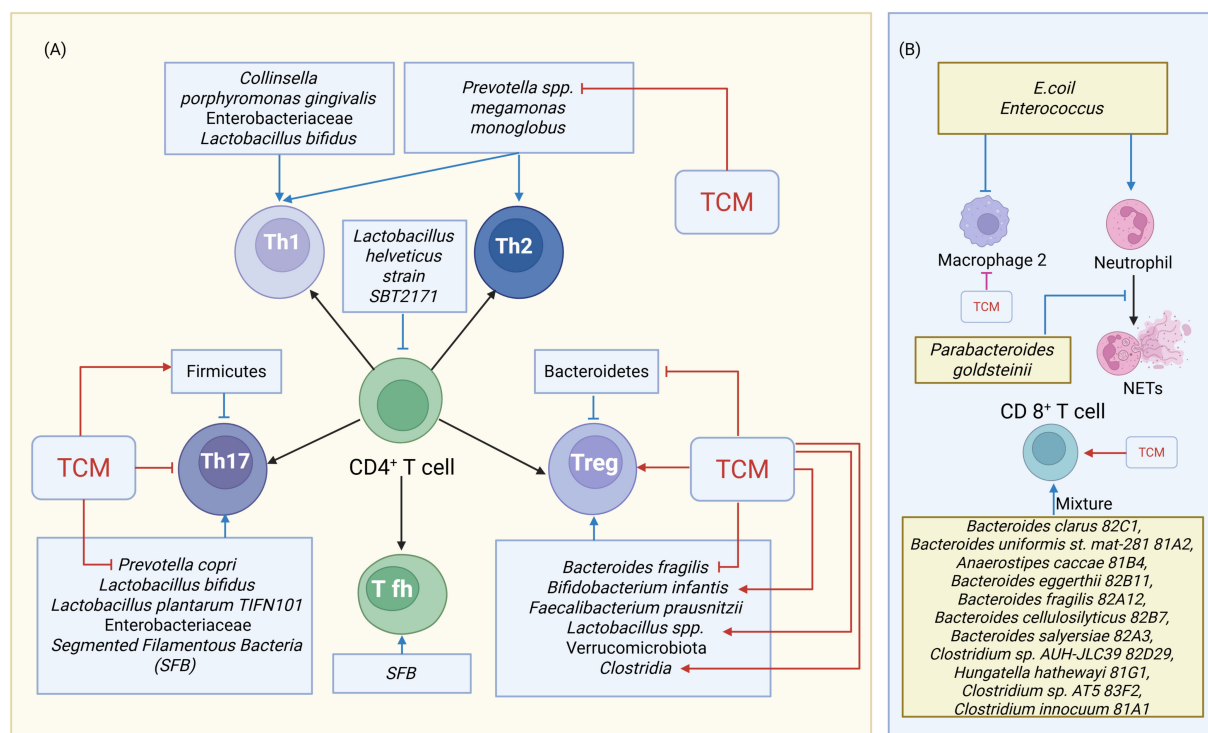


FIGURE 4

TCM's Modulation of Disrupted Gut Microbiota and Immune Cell Crosstalk. (A) TCM's Modulation of Gut Microbiota and T Cell Crosstalk. (B) TCM's Modulation of Gut Microbiota and other immune Cell Crosstalk. Blue indicators represent the actions of gut microbiota on immune cells, while red indicators represent the effects of TCM on immune cells or gut microbiota. Arrows indicate activation or facilitation, whereas blocked lines indicate inhibition. NETs=neutrophil extracellular traps.

They also stimulate IL-22 production in CD4⁺ T cells through a GPR41-dependent pathway and reduce HDAC activity (115). SCFAs play crucial roles in regulating the balance between anti-inflammatory Tregs and pro-inflammatory Th17 cells by targeting key transcription factors. They promote Treg differentiation through multiple mechanisms. Butyrate inhibit HDACs, increasing histone acetylation at the Forkhead box P3(Foxp3) promoter. This enhances the transcription of Foxp3 which is the master transcription factor for Tregs (72). Additionally, SCFAs bind to GPR43 and GPR109A, inhibit HDAC, activate signal transducer and activator of transcription 3 (STAT3) signaling pathways, and boost Foxp3 expression (72, 116, 117). Moreover, SCFAs induce retinal dehydrogenase, facilitating the conversion of vitamin A into retinoic acid, which promotes Treg differentiation (72). In contrast, SCFAs suppress Th17 cell activity. For instance, butyrate inhibits retinoic acid-related orphan receptor gamma t (ROR γ t) via HDAC inhibition and IL-6/STAT3 blockade, reducing Th17 gene expression (117).

Butyrate-treated DCs enhance Treg differentiation and suppress Th1 cell differentiation by upregulating the expression of immunosuppressive enzymes, including indoleamine 2,3-dioxygenase 1 and aldehyde dehydrogenase 1 family member A2 via an SLC5A8-dependent mechanism. SCFAs have been shown to regulate neutrophils and macrophages, thereby modulating the intensity of inflammatory responses (118–120). Specifically, acetate and propionate activate the cell surface receptor GPR43, promoting neutrophil chemotaxis (121). SCFAs promote M2 macrophage polarization and reduce pro-inflammatory cytokine expression (122). They also maintain colonic Treg homeostasis, reduce B cell IgG, IgA, and IgE secretion, and suppress plasma cell differentiation (72). SCFAs correlate with increased Tregs and decreased IL-17A, IL-6, and TNF- α in CIA rats, and their administration alleviates arthritis severity by expanding Foxp3⁺ IL-10⁺ Tregs (123, 124). Furthermore, the production of SCFAs is proposed as one of the mechanisms through which GM influences Treg cell differentiation (125).

SCFAs block NF- κ B via HDAC inhibition or peroxisome proliferator-activated receptor gamma (PPAR γ) activation and exert anti-inflammatory effects. This leads to reduced expression of inflammatory mediators such as cytokines, chemokines, inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and adhesion molecules (126, 127). Butyrate specifically decreases LPS-induced proinflammatory mediators like nitric oxide (NO), IL-6, and IL-12 in macrophages (128). These cytokines enter circulation and affect the joints.

Microbial tryptophan metabolites, such as indoles and their derivatives, engage with aryl hydrocarbon receptors (AhRs) to influence B cell development, differentiation, cytokine production, and regulation via AhR signaling pathways. Furthermore, bile acids and their metabolites modulate immune responses by regulating signaling pathways and maintaining the balance between Th17 and Treg cells (11). The bile acids derived from live *P. distasonis* (LPD), including lithocholic acid (LCA), deoxycholic acid (DCA), isolithocholic acid (isoLCA), and 3-oxolithocholic acid (3-oxoLCA), exhibited both similar and synergistic effects in

mitigating RA. Notably, 3-oxoLCA and isoLCA not only directly inhibited the differentiation of Th17 cells but were also identified as TGR5 agonists that promoted the M2 polarization of macrophages. Furthermore, a specific synthetic inhibitor of bile salt hydrolase diminished the antiarthritic effects of LPD by reducing the production of these four bile acids (129).

LPS activates TLR4 and the NF- κ B pathway, triggering inflammation and activating the complement alternative pathway, which contributes to arthritis (129, 130). *Bacteroides fragilis* secretes polysaccharide A (PSA), which stimulates Th1 responses, affects epithelial IL-17A production (15), corrects systemic T cell deficiencies, restores Th1/Th2 balance, and promotes lymphoid organogenesis (131). Colonization with *Bacteroides* in GF mice increases the population of Tregs via CD4⁺ T cell stimulation by PSA (93, 132).

In conclusion, GM metabolites (SCFAs, BAs, tryptophan derivatives) are critical regulators of immune cells, especially T cell subsets. Their dysregulation in RA disrupts the Th17/Treg equilibrium, driving inflammation and joint damage. Targeting these metabolites offers promising strategies to restore immune balance and mitigate RA progression.

3.4 Intestinal barrier dysfunction

The gut mucosal barrier, comprised of a monolayer of intestinal epithelial cells interconnected by tight junctions (TJ), separates the host from dietary and microbial antigens. Zonulin regulates TJ function by altering the expression of proteins like Zonula Occludens-1, occludin, claudin-1, claudin-2, and claudin-15, increasing intestinal permeability (20). In murine models, elevated zonulin levels lead to TJ disruption, promoting T-cell-mediated inflammation and migration of autoreactive Th1/Th17 cells from the gut to joints, contributing to RA development (133). Zonulin antagonists such as larazotide acetate reduce arthritis onset in mice (26). Flak et al. found increased gut permeability due to reduced numbers of TJ compared to HCs (27).

The gut integrity is compromised in RA patients, resulting in translocation of microbiota or their metabolites across the gut barrier into the lamina propria. The interaction between TLRs and pathogen-associated molecular patterns on these microbes can potentially activate the immune system, inducing pro-inflammatory cytokines like IL-6, TNF- α , or IL-1 β (134, 135).

Furthermore, dysbiosis of the GM also instigate the migration of autoreactive cells to the joints, leading to local inflammation and damage (136). *Collinsella aerofaciens* increases intestinal permeability and worsens arthritis by reducing TJ protein expression (15). In contrast, *Faecalibacterium prausnitzii* preserves intestinal barrier integrity, maintain the balance between Th17 and Treg cells, and exhibit substantial anti-inflammatory effects (137). Loss of beneficial bacteria like *Akkermansia muciniphila* also impairs epithelial barrier function; its protein Amuc_1000 enhances Claudin-3 and Occludin via TLR2 signaling (138). It is worth noting that *A. muciniphila* is classified as a mucin-degrading bacterium, which can influence the integrity of the mucin barrier (139, 140). These findings suggest that alterations

in gut microbiota diversity may impair intestinal mucosal permeability, thereby facilitating the onset of RA (26, 141).

Microbial metabolites function as exogenous regulators of the TJ barrier. For example, butyrate enhances the expression of Cldn1 (encoding Claudin-1) and Ocln (encoding occludin) via hypoxia-inducible factor 1 (HIF-1), conferring resistance to barrier disruption and bacterial translocation following *Clostridium difficile* infection (142). In intestinal epithelial cells, indole-3-propionic acid down-regulates TNF- α and up-regulates TJ-related proteins through pregnane X receptor (PXR) signaling (143). Urolithin A, derived from polyphenols, modulates TJs through AhR signaling (144). *Lactobacillus* species generate hydroxy fatty acids like 10-hydroxy-cis-12-octadecenoic acid (HYA), which activates MAPK/extracellular signal-regulated kinase (ERK) signaling and upregulates TJ-related proteins (145, 146).

Collectively, these findings suggest that specific symbionts influence epithelial barrier function through the provision of beneficial metabolites and proteins.

3.5 The GM derived molecular mimicry of autoantigens

Molecular mimicry is a mechanism implicated in the pathogenesis of RA, characterized by the structural similarities between bacterial peptides and host antigens or receptors, leading to immune cross-reactivity and autoimmunity. GM produces metabolites resembling host molecules, and peptides from species like Firmicutes and Proteobacteria show homology with human proteins such as N-Acetyl-glucosamine-6-sulfatase (GNS) and filamin A (FLNA), which are targeted in RA (147, 148). HLA-DR-presented GNS and FLNA peptides also exhibit sequence homology with bacterial epitopes from *Prevotella* sp., *Parabacteroides* sp., and *Butyrivibrio* sp. (148). Additionally, shared sequences between *Collinsella* and DRB1*0401 suggest that *Collinsella* may induce RA through molecular mimicry (15). These findings provide evidence for molecular mimicry as a potential mechanism linking disrupted mucosal immune tolerance and systemic immunity in RA patients.

In summary, the gut-immune axis in RA underscores the interplay between dysbiosis, metabolite dysregulation, barrier defects, and autoantigen mimicry. Future therapies aimed at modulating GM or their metabolites hold promise for restoring immune equilibrium and halting RA progression.

4 TCM therapy via modulating the gut-immune axis

TCM therapy targets the gut-immune axis for RA through multiple mechanisms, including modulating microbial composition, regulating GM-derived metabolites, and enhancing intestinal barrier function

4.1 TCM formulas

Table 1 summarizes TCM formulas that demonstrate anti-RA activities through modulation of gut-immune axis.

4.1.1 Wu-tou decoction

WTD, a classical TCM formula, was originally recorded in the “Jin Kui Yao Lue” by the renowned Chinese medical sage Zhang Zhongjing. This decoction is composed of five primary herbs: *Aconitum carmichaelii* Debeaux, *Ephedra sinica* Stapf, *Astragalus membranaceus* (Fisch.) Bunge, *Paeonia lactiflora* Pall., and *Radix Glycyrrhizae* Preparata. It is widely manufactured in China following the quality control standards set by the Chinese Pharmacopoeia. Clinically, WTD has been extensively applied for treating conditions such as RA, constitutional hypotension, and hemiparesis (149, 150). Compared with the MTX, WTD significantly decreased the 28-joint disease activity score (DAS28) and the levels of TNF- α and IL-6 in RA patients with cold-damp syndrome, furthermore, it can improve clinical symptoms and significantly reduce the serum levels of pro-inflammatory cytokines in RA patients (34).

WTD effectively alleviates arthritis in adjuvant-induced arthritis (AIA) rats by modulating GM composition. Specifically, WTD significantly reduces the abundance of *Akkermansia*, *Prevotella*, *Bacteroides*, *Enterococcus*, *Dorea*, and *Jeotgalicoccus*, while increasing *Oscillospira* and *Lactobacillus* populations. Correlation analysis further reveals that WTD's therapeutic effects are partially mediated by up-regulating microbial metabolites, including SCFAs, lactate, and tryptophan derivatives (indole-3-acetic acid/IAA, indole-3-propionic acid/IPA, and indole-3-aldehyde/IALd), which collectively regulate inflammatory responses and enhance intestinal barrier function, furthermore, IAA, IPA, and IALd possess anti-inflammatory properties and can serve as ligands for the AhR. The activation of AhR can modulate innate and adaptive immune responses in a ligand-specific manner (151).

WTD significantly decreased the expression of TNF- α , IL-1 β , monocyte chemoattractant protein-1 (MCP-1), and MMP-3 in the synovium, mitigating arthritis. WTD suppressed M1-type macrophage polarization while promoting M2-type polarization both *in vitro* and *in vivo*. Additionally, WTD inhibited NF- κ B and p38 phosphorylation in CIA rats and LPS-induced RAW264.7 macrophages, enhanced PPAR γ nuclear translocation, and consequently alleviated synovial inflammation (152). It regulates immune responses by altering CD4⁺/CD8⁺ ratios in the AIA rats (153). The five constituent herbs in WTD have synergistic anti-arthritis effects on RA. *Radix Aconite* is the main anti-inflammatory component. *Herba Ephedrae* inhibits NF- κ B mediated inflammation. *Radix Astragali* enhances the NF-E2-related factor 2 (Nrf2) expression. Collectively, WTD inhibits NF- κ B phosphorylation and increases Nrf2 expression (154). These findings suggest WTD as a promising microbiota-targeted therapy for RA.

TABLE 1 The effects and mechanisms of anti-RA TCM formulas on the gut–immune axis.

TCM formulas	Main Ingredients	GM Modulation (↓↑)	Effects and mechanisms	References
Wu-tou decoction	<i>Aconitum carmichaelii</i> Debeaux, <i>Ephedra sinica</i> Stapf, <i>Astragalus membranaceus</i> (Fisch.) Bunge, <i>Paeonia lactiflora</i> Pall., and <i>Radix Glycyrrhizae</i> Preparata	↓ <i>Akkermansia</i> , <i>Prevotella</i> , <i>Bacteroides</i> ↑ <i>Oscillospira</i> , <i>Lactobacillus</i>	↓ Inflammation, TNF- α , IL-1 β , MCP-1, MMP-3, NF- κ B/p38; ↑ PPAR γ ; ↓ CD4 ⁺ /CD8 ⁺ T cell ratio, ↑ M2 macrophage polarization, ↑ SCFAs, lactate, IAA, IPA, IAla, activate AhR, ↑ gut barrier	(34, 149–152; (153, 154)
Qing-re-huo-xue decoction	<i>Smilax glabra</i> Roxb., <i>Lonicera japonica</i> Thunb., <i>Atractylodes lancea</i> (Thunb.) DC., stir-fried, <i>Phyllodendron chinense</i> C.K.Schneid., <i>Paeonia veitchii</i> Lynch, <i>Medicago sativa</i> L., <i>Salvia miltiorrhiza</i> Bunge, <i>Curcuma phaeocaulis</i> Valetton, <i>Sinomenii Caulis</i> , <i>Scolopendra subspinipes mutilans</i> , <i>Nidus Vespae</i>	↑ Increased the abundance and species evenness of GM	↑ Treg cells, ↓ Th17 cells, rebalances the Th17/Treg axis, anti-inflammatory immune regulation	(29, 44, 155)
Dang-gui-nian-tong Decoction	<i>Notopterygium incisum</i> K.C. Ting ex H.T. Chang, <i>Atractylodes macrocephala</i> Koidz., <i>Artemisia capillaris</i> Thunb., <i>Panax ginseng</i> C. A. Mey., <i>Radix Glycyrrhizae</i> Preparata, <i>Sophora flavescens</i> Aiton, <i>Angelica sinensis</i> (Oliv.) Diels, <i>Actaea cimicifuga</i> L., <i>Polyporus umbellatus</i> (Pers.) Fries, <i>Puerariae Lobatae</i> Radix, <i>Scutellaria baicalensis</i> Georgi, <i>Atractylodes lancea</i> (Thunb.) DC., <i>Alisma plantago-aquatica</i> L., <i>Anemarrhena asphodeloides</i> Bunge, <i>Saposhnikovia divaricata</i> (Turcz.) Schischk.	↑ <i>Lactobacillus</i> , <i>Prevotella</i> , and <i>Alloprevotella</i> ↓ <i>Bacteroides</i>	↓ The hyperplasia and inflammation of synovial tissue; ↓ the arthritis index(AI)	(156–160)
Jin-wu-jian-gu Capsules	<i>Cibotium barometz</i> (Linn.) J. Sm., <i>Periploca forrestii</i> Schltr., <i>Sabia parviflora</i> Wall. ex Roxb., <i>Homalomena occulta</i> (Lour.) Schott, <i>Curcuma longa</i> L., <i>Zaocys dhumnade</i> , <i>Panax notoginseng</i> (Burkill) F. H. Chen ex C. Y. Wu & K. M. Feng, <i>Radix Paeoniae Alba</i> , and <i>Glycyrrhiza uralensis</i> Fisch.	↑ <i>Lachnospira</i> <i>Bryantii</i> , <i>Small_NK4A136_group</i> ; ↓ <i>Prevotella</i> <i>Shan</i> & <i>Collins</i> , <i>Helicobacter</i>	↓ Immune response, inflammation, ↓ pro-inflammatory cytokines, IL-1 β & IL-18, NLRP3/Caspase-1, IL-33/ST2 binding; ↓ Pyroptosis	(14, 161, 162; (74, 163, 164)
Li-jie Capsule	<i>Astragalus membranaceus</i> (Fisch.) Bunge, <i>Atractylodes lancea</i> (Thunb.) DC., <i>Arisaema cum Bile</i> , <i>Coix lacryma-jobi</i> L., <i>Angelicae pubescentis</i> radix, <i>Paeonia veitchii</i> Lynch, <i>Ligusticum chuanxiong</i> Hort, <i>Atractylodes macrocephala</i> Koidz., <i>Pericarpium Citri Reticulatae</i> , <i>Gentiana macrophylla</i> Pall., <i>Lonicerae Japonicae</i> Caulis, <i>Rehmannia glutinosa</i> Libosch, <i>Anemarrhena asphodeloides</i> Bunge, <i>Angelica dahurica</i> (Fisch. ex Hoffm.) Benth. & Hook. f. ex Franch. & Sav., <i>Saposhnikovia divaricata</i> (Turcz.) Schischk., <i>Glycyrrhiza uralensis</i> Fisch.	↑ <i>Barnesiella</i> , <i>Bifidobacterium</i> , <i>Allobaculum</i> , and <i>Erysipelotrichace</i> ↓ <i>Desulfovibrio</i> , <i>Streptococcus</i> , and <i>Clostridium</i> <i>XIVa</i>	↑ CD3+, CD8+ cell counts ; ↓ the CD4+/CD8+ ratio	(165, 166)
New-bi-tong-ling	<i>Cinnamomi Ramulus</i> , <i>Sinomenii Caulis</i> , <i>Saposhnikovia divaricata</i> (Turcz.) Schischk., <i>Aconiti radix</i> , <i>Ephedrae herba</i> , and <i>Nidus Vespae</i>	↑ <i>Mycoplasma</i> <i>taceae</i> , <i>Metamycoplasma_sualvi</i> . ↓ <i>Prevotellaceae</i> <i>_Ga6A1_group</i>	↓ Inflammatory Cytokines (TNF- α , IL-17, IL-6); ↓ VEGF, VEGFR1, VEGFR2, HIF-1 α ; ↑ miR-20a-5p, miR-223-3p	(68, 167, 168)
Zhu-bi decoction	<i>Curculigo orchoides</i> Gaertn., <i>Epimedium brevicornu</i> Maxim., <i>Morinda officinalis</i> How, <i>Angelica sinensis</i> (Oliv.) Diels, <i>Anemarrhena asphodeloides</i> Bunge, <i>Cortex Phellodendri</i> <i>Chinensis</i> , <i>Buthus martensii</i>	↑ Firmicutes, <i>Clostridia</i> , <i>Bacilli</i> . ↓ <i>Prevotella</i> <i>_9</i> , <i>Ligilactobacillus</i> ,	Restore GM diversity, balance metabolic and immune pathways (PI3K/AKT)	(169–171)

(Continued)

TABLE 1 Continued

TCM formulas	Main Ingredients	GM Modulation (↓↑)	Effects and mechanisms	References
	<i>Karsch</i> , and <i>Scolopendra subspinipes mutilans</i>	<i>Prevotellaceae</i> and <i>Tuzzerella</i>		
Jing-fang Granule	<i>Schizonepeta tenuifolia</i> (Benth.) Briq., <i>Notopterygium incisum</i> K.C. Ting ex H.T. Chang, <i>Saposhnikovia divaricata</i> (Turcz.) Schischk., <i>Heracleum hemsleyanum</i> Diels, <i>Bupleurum chinense</i> DC., <i>Ligusticum striatum</i> DC., <i>Citrus aurantium</i> L., <i>Poria cocos</i> (Schw.) Wolf., <i>Peucedanum praeruptorum</i> Dunn, <i>Platycodon grandiflorus</i> (Jacq.) A.DC., and <i>Glycyrrhiza uralensis</i> Fisch.	↑ <i>Bacteroidota</i> , <i>Norank_f_Muribaculaceae</i> , <i>Butyricicoccus</i> , <i>Adlercreutzia</i> and <i>Enterorhabdus</i> ; ↓ <i>Firmicutes</i> and <i>Lactobacillus</i>	↓ <i>TNF-α</i> , <i>IL-1β</i> , <i>IL-6</i> , <i>NLRP3</i> , <i>TLR4/NF-κB</i> pathways, lipid oxidative stress-induced ferroptosis, ↑ <i>AMPK</i> signaling, <i>Claudin 5</i> and <i>ZO-1</i>	(42, 172, 173)

↑=Increase/Promote/Uregulate, ↓=Decrease/Inhibit/downregulate.

4.1.2 Qing-re-huo-xue decoction

QRHDX is made up of eleven TCMs: *Smilax glabra* Roxb., *Lonicera japonica* Thunb., *Atractylodes lancea* (Thunb.) DC., stir-fried, *Phyllocladon chinense* C.K.Schneid., *Paeonia veitchii* Lynch, *Medicago sativa* L., *Salvia miltiorrhiza* Bunge, *Curcuma phaeocaulis* Valetton, *Sinomenii Caulis*, *Scolopendra subspinipes mutilans* Nidus Vespaee. A five-year radiological study demonstrated that QRHDX exhibits a significant therapeutic effect on RA patients, primarily by slowing the long-term progression of bone destruction (29). A multicenter, double-blind, randomized controlled trial (RCT) demonstrated that QRHDX was effective in alleviating symptoms of active RA, although its efficacy was slightly lower compared to csDMARDs. Notably, QRHDX has fewer side effects (44). In a rat CIA model, QRHDX significantly alleviated pathological lesions in synovium and cartilage, increased the abundance and species evenness of GM, elevated Treg levels, and concurrently reduced Th17 levels. These findings suggest that QRHDX may alleviate RA symptoms by improving intestinal microecological imbalance and modulating the immune dysregulation of the Th17/Treg axis (155).

4.1.3 Dang-gui-nian-tong decoction

DGNTD, a well-established TCM formula, is widely acknowledged for its efficacy in alleviating dampness and treating RA. Originating from the Qing Dynasty, DGNTD is currently listed in the National Health Insurance Directory of China (174). This decoction comprises fifteen distinct TCMs, including *Notopterygium incisum* K.C. Ting ex H.T. Chang, *Atractylodes macrocephala* Koidz., *Artemisia capillaris* Thunb., *Panax ginseng* C. A. Mey., *Radix Glycyrrhizae Preparata*, *Sophora flavescens* Aiton, *Angelica sinensis* (Oliv.) Diels, *Actaea cimicifuga* L., *Polyporus umbellatus* (Pers.) Fries, *Puerariae Lobatae Radix*, *Scutellaria baicalensis* Georgi, *Atractylodes lancea* (Thunb.) DC., *Alisma plantago-aquatica* L., *Anemarrhena asphodeloides* Bunge, *Saposhnikovia divaricata* (Turcz.) Schischk. Previous clinical study indicated DGNTD has good therapeutic effects on early RA patients with damp-heat obstruction syndrome (156, 157). DGNTD effectively mitigates the hyperplasia and inflammation of synovial tissue in AIA model rats, thereby inhibiting pannus formation. DGNTD increased the abundance of *Lactobacillus*, *Prevotella 9*, and *Alloprevotella*, while reducing the abundance of *Bacteroides*. *Bacteroides* and *Helicobacter*

positively correlated with the arthritis index (AI), while *Prevotella 9* and *Candidatus Saccharimonas* negatively correlated with AI. *Prevotella 9* abundance showed significant negative correlations with paw volume and spleen index (158), whereas *Ruminococcaceae_NK4A214_group*, *Christensenellaceae_R-7_group*, and *Bacteroides* were positively associated with spleen index. *Ruminococcaceae* exhibits pro-inflammatory effects by activating immune cells and stimulating pro-inflammatory cytokine secretion (159), while *Christensenellaceae_R-7_group* modulates lipid metabolism and SCFA levels, both of which are closely linked to immune regulation (160). The results suggest that these microbial changes may be linked to immune response modulation.

4.1.4 Jin-wu-jian-gu (JWJG)Capsules

JWJG Capsules, a renowned Chinese Miao medicinal formula, is widely recognized for its efficacy in promoting bone repair and treating RA. JWJG Capsule in combination with leflunomide can effectively alleviate joint and systemic symptoms in RA patients with cold-dampness obstruction syndrome, reduce inflammatory markers, demonstrate superior efficacy compared to leflunomide monotherapy, and maintain good safety (161). The formula comprises nine traditional herbs: *Cibotium barometz* (Linn.) J. Sm., *Periploca forrestii* Schltr., *Sabia parviflora* Wall. ex Roxb., *Homalomena occulta* (Lour.) Schott, *Curcuma longa* L., *Zaocys dhumnade*, *Panax notoginseng* (Burkill) F. H. Chen ex C. Y. Wu & K. M. Feng, *Radix Paeoniae Alba*, and *Glycyrrhiza uralensis* Fisch. JWJG-medicated serum significantly suppresses the expression of Nod-like receptor pyrin domain-containing 3(*NLRP3*) and caspase in RA synovial fibroblasts (SF), inhibiting the maturation of *IL-1β* and *IL-18*, mitigating pyroptosis (162). JWJG also modulates immune-inflammatory responses by down-regulating pro-inflammatory cytokines, including *TNF-α*, *IL-6*, *IL-13*, *IL-17*, and *IL-1β*, as well as by inhibiting inflammatory cell infiltration. Liquiritigenin, identified as the key component through network pharmacology, inhibits the *IL-33/Suppression of Tumorigenicity 2* (*ST2*) receptor complex, reducing inflammation (163). JWJG capsules significantly altered the GM composition in CIA model rats, specifically up-regulating *Lachnospira* Bryant & Small_NK4A136_group while down-regulating the relative

abundances of *Prevotella* Shan & Collins and *Helicobacter* Gest & Favinger (93, 175). Clinical studies show higher *Prevotella* levels in untreated RA patients, suggesting its role in disease development (14), while *Lachnospira* may be beneficial. Notably, JWJG capsules reduced *Prevotella* abundance in CIA rats, further supporting its therapeutic effect through microbiota regulation. Collectively, these combined actions on molecular inflammatory mechanisms and gut dysbiosis underpins JWJG's effectiveness in alleviating RA symptoms and pathology.

4.1.5 Li-jie Capsule

Li-jie Capsule has been used in the treatment of RA for many years because of its better therapeutic effects and lower incidence of side effects (96). The main ingredients of *Li-jie Capsule* are *Astragalus membranaceus* (Fisch.) Bunge, *Atractylodes lancea* (Thunb.) DC., *Arisaema cum Bile*, *Coix lacryma-jobi* L., *Angelica sinensis* (Oliv.) Diels, *Paeonia veitchii* Lynch (Chi Shao), *Ligusticum chuanxiong* Hort, *Atractylodes macrocephala* Koidz. (Bai Zhu), *Pericarpium Citri Reticulatae*, *Gentiana macrophylla* Pall., *Lonicerae Japonicae Caulis*, *Rehmannia glutinosa* Libosch, *Anemarrhena asphodeloides* Bunge, *Angelica dahurica* (Fisch. ex Hoffm.) Benth. & Hook. f. ex Franch. & Sav., *Saposhnikovia divaricata* (Turcz.) Schischk., *Glycyrrhiza uralensis* Fisch. The *Li-jie Capsule* alleviates joint symptoms, improves joint function, and modulates immunity in RA patients by increasing CD3+ and CD8+ cells, lowering the CD4+/CD8+ ratio, and reducing erythrocyte sedimentation rate (ESR) and RF levels. This indicates a reduction in humoral immune response and an enhancement of cellular immune response, thereby exerting immunomodulatory effects. It shows better systemic symptom improvement and cellular immune regulation than Tripterygium glycosides Tablets. The comprehensive therapeutic effect of the *Li-jie Capsule* on RA may be attributed to its modulation of T cell immune function (165). *Li-jie Capsule* significantly reduces paw swelling and AI values in CIA mice. Additionally, *Li-jie Capsule* markedly decreased the levels of *Desulfovibrio*, *Streptococcus*, and *Clostridium XIVa*, while increasing the levels of *Barnesiella*, *Bifidobacterium*, *Allobaculum*, and *Erysipelotrichace*. These findings suggest the *Li-jie Capsule* exerts therapeutic effects on RA through immune modulation and GM regulation (166).

4.1.6 New-bi-tong-ling

NBTL, a well-established TCM formula, is widely acknowledged for its efficacy in treating RA (176). It is composed of six herbs, including *Cinnamomi Ramulus*, *Sinomenii Caulis*, *Saposhnikovia divaricata* (Turcz.) Schischk., *Aconiti radix*, *Ephedrae herba*, and *Nidus Vespae*. NBTL reduces joint swelling, bone destruction, and pro-inflammatory cytokines (IL-1 β , IL-6) in CIA rats, while increasing body weight and anti-inflammatory cytokines (IL-10, IL-4). It also inhibits FLS inflammation, induces apoptosis, and hinders proliferation, which was reversed by JAK2/STAT3 activation (167). Another study confirms NBTL alleviates RA by reducing the expression levels of TNF- α , IL-17, IL-6, and apoptosis-associated speck-like protein containing a CARD in synovial tissues. It modulates GM linked to the VEGF pathway, up-regulating *f_Mycoplasmataceae* and *s_Metamycoplasma_sualvi*,

while down-regulating *g_Prevotellaceae_Ga6A1_group*. NBTL suppresses the VEGF signaling pathway and angiogenesis by inhibiting VEGF, its receptors, and HIF-1 α . It also up-regulates microRNA-20-5p (miR-20a-5p) and miR-223-3p, reducing angiogenesis, and lowers the CD4+/CD8+ ratio along with IL-2 and IL-2R levels (168, 177). Morphological observation showed inhibitory effects on synovial cell proliferation (68). These findings suggest NBTL has therapeutic potential in RA by regulating microbiota and the VEGF pathway, supporting its promise as a treatment option requiring further study.

4.1.7 Zhu-bi decoction

ZBD has been utilized for many years in RA treatment. Originating from the classical TCM prescription "Erxian decoction" which is recorded in "the Clinical Manual of Chinese Medical Prescriptions", it has been demonstrated to be effective in treating RA, with minimal side effects (169, 170). This prescription has since been modified to meet modern clinical needs while preserving its therapeutic efficacy. ZBD consists of eight distinct herbs, specifically *Curculigo orchoides* Gaertn., *Epimedium brevicornu* Maxim., *Morinda officinalis* How, *Angelica sinensis* (Oliv.) Diels, *Anemarrhena asphodeloides* Bunge, *Phellodendron chinense* C.K.schneid., *Buthus martensii* Karsch, and *Scolopendra subspinipes mutilans*. ZBD effectively alleviates RA symptoms in CIA rats without significant side effects, showing efficacy comparable to that of MTX. It mitigates inflammation and joint damage by modulating the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB/AKT) (PI3K/AKT) signaling pathway and reducing serum concentrations of cytokines, including TNF- α , IL-1 β , and IL-6. ZBD modulates 170 differential metabolites and partially restores disrupted metabolic profiles. It also mitigates gut dysbiosis and identifies key bacterial genera associated with the treatment effects. Specifically, it increases Firmicutes, Clostridia, and Bacilli abundance while reducing *Prevotella_9*, *Ligilactobacillus*, *Prevotellaceae*, and *Tuzzerella*. In conclusion, ZBD alleviated RA by restoring GM diversity and balancing metabolic and immune pathways, and was a safe and efficacious TCM formula for treating RA (171).

4.1.8 Jing-fang Granule

JFG is a modern formula derived from Jing-fang-Bai-du Powder, a traditional prescription originating from the Ming Dynasty. It retains the same herbal composition and dosage as its predecessor. JFG comprises 11 herbal medicines: *Schizonepeta tenuifolia* (Benth.) Briq., *Notopterygium incisum* K.C. Ting ex H.T. Chang, *Saposhnikovia divaricata* (Turcz.) Schischk., *Heracleum hemsleyanum* Diels, *Bupleurum chinense* DC., *Ligusticum striatum* DC., *Citrus aurantium* L., *Poria cocos* (Schw.) Wolf., *Peucedanum praeruptorum* Dunn, *Platycodon grandiflorus* (Jacq.) A.DC., and *Glycyrrhiza uralensis* Fisch. Over an extended period, JFG has been widely applied in the treatment of inflammatory diseases, including RA (42, 172). JFG protects rats from RA by reducing foot swelling, improving synovial pathology, and lowering TNF- α , IL-1 β , and IL-6 levels via NLRP3 and TLR4/NF- κ B inhibition. It reshapes GM by enhancing Bacteroidota,

Butyricoccus, *Adlercreutzia* and *Enterorhabdus* while decreasing Firmicutes and *Lactobacillus*. This leads to higher levels of acetic, propionic, and butyric acids in the gut and serum. These changes activate AMPK signaling, which regulates fatty acid metabolism and biosynthesis, thereby inhibiting lipid oxidative stress-induced ferroptosis and alleviating tissue damage associated with RA. JFG also strengthens the intestinal barrier by upregulating Claudin 5 and ZO-1 (173). This research provides a new mechanism for JFG's effect on RA through the "Gut-joint" axis.

4.2 Single TCM and its components

4.2.1 *Tripterygium wilfordii* Hook F

TwHF is a traditional medicinal Chinese herb which has been extensively utilized for a long period in the treatment of various autoimmune disorders and inflammatory diseases, including RA (178, 179). Increasing studies have indicated that TwHF might represent a rich source that possesses multiple pharmacological activities, particularly anti-inflammatory, anticancer, antiviral, and antioxidative activities (180). The efficacy and safety of TwHF have been substantiated through multiple multi-center RCTs. A multi-center, open-label RCT demonstrated that TwHF monotherapy was non-inferior to MTX monotherapy, while the combination of MTX and TwHF was superior in controlling disease activity in RA patients (180). A systematic review of data up to 2016 further revealed that TwHF was more effective in improving the American College of Rheumatology (ACR)20 and ACR50 response rates compared to DMARDs. However, TwHF has been associated with adverse menstrual effects (37).

Tripterygium glycosides (TG) are the active components derived from Celastraceae *Tripterygium wilfordii* Hook. F. (TwHF), which encompass a variety of diterpenoids, alkaloids, triterpenoids, and glycosides (181). TG regulates multiple signaling pathways and inflammatory factors in RA patients, including upregulating $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR) expression, inhibiting NF- κ B and STAT3 activation, and reducing IL-17 and high mobility group box protein 1 (HMGB1) levels (182). TG tablets (TGTs) combined with MTX significantly improve RA symptoms and immune function by increasing CD3+ and CD4+/CD8+ T lymphocyte levels in RA patients (41, 178, 183). TGTs reduced joint swelling and lowered IL-6 and TNF- α in CIA rats. TGTs significantly down-regulated the abundances of *Akkermansia*, *Prevotellaceae_NK3B31_group*, and notably, *Prevotella*, which is closely associated with RA in CIA rats. Conversely, TGTs significantly increased the abundances of *Ureibacillus*, *Lactobacillus*, *Butyricoccus*, and *Ruminococcus_UCG-014*. Additionally, after TGTs treatment, the levels of *Blautia*, which is related to inflammation, as well as *Escherichia-Shigella* and *Lachnospirillum*, returned to levels comparable to those observed in normal rats (184). These mechanisms suggest that TG may alleviate RA by enriching butyrate-producing microbiota, reducing *Prevotella*, and suppressing inflammatory pathways (NF- κ B/STAT3) and cytokines (IL-6, TNF- α , IL-17).

4.2.2 *Radix Paeoniae Alba*

Radix Paeoniae Alba is a constituent of JWJG Capsules. Total glucosides of paeony (TGP), an extract from the dried root of *Radix Paeoniae Alba*, contain bioactive compounds such as paeoniflorin, hydroxypaeoniflorin, and paeonin. These compounds exhibit anti-inflammatory, immunomodulatory, antithrombotic, and hepatoprotective properties. TGP can inhibit autoimmune reactions and maintain immune tolerance in the body through multiple pathways. As an adjuvant therapy, TGP has demonstrated efficacy in managing autoimmune diseases, including systemic lupus erythematosus, Sjogren's syndrome, RA, ankylosing spondylitis, and immune-related recurrent abortions. Furthermore, TGP treatment can reduce adverse drug reactions, lower recurrence rates, and enhance patient compliance (185). The results of a systematic review of 1,209 patients with active RA showed that, compared to no additional treatment, the addition of TGP to traditional DMARD (s) may significantly improve ACR 20, ACR 50, and ACR 70 response rates, as well as reduce adverse effects (46). Therefore, TGP could serve as a promising adjuvant therapy for RA.

TGP administration for 12 weeks corrected 78% of taxonomic differences and significantly increased the abundance of beneficial symbiotic bacteria *Ruminococcaceae_UCG-014*, *Oscillibacter*, and *Parabacteroides*. Additionally, it reduced body weight, thymus index, and inflammatory cell infiltration in the ankle joints of CIA rats. TGP down-regulated VEGF, Th1, and Th17 cells while up-regulating Th2 and Treg cells in CIA rats. Furthermore, TGP administration inhibited the levels of intestinal cytokines, secretory immunoglobulin A (SIgA), and IFN- γ . These findings suggest that the therapeutic effects of TGP may be mediated through gut microbiome regulation and modulation of the intestinal mucosal immune response (186).

4.2.3 *Caulis Sinomenii*

Caulis Sinomenii, a pivotal herb in TCM, is a core component of formulas such as QRHDX, JWJG Capsules, and the patented drug Zheng-qing-feng-tong-ning (ZQFTN). Approved by the China Food and Drug Administration two decades ago for RA, ZQFTN was recently added to China's National Health Insurance Directory, reflecting its high clinical efficacy and favorable safety profile in RA management (187). Central to its therapeutic action is sinomenine (SIN), a bioactive alkaloid from *Caulis Sinomenii* and an officially recognized RA treatment.

SIN reduces RA disease activity and DAS28 scores by suppressing pro-inflammatory cytokines (e.g., IL-6, TNF- α , IL-1 β) and modulates immune cells, including synovial macrophages (CD11b+F4/80+CD64+) and splenic/draining lymph node macrophages (CD11b+Ly6C+CD43+), while lowering CD14+CD16+ monocytes in RA patients. These dual mechanisms—cytokine regulation and immune cell subset modulation—position SIN as a cost-effective alternative or adjunct to methotrexate (MTX) (188). It selectively inhibits microsomal prostaglandin E synthase-1 (mPGES-1), reducing prostaglandin E2 (PGE2) without disrupting prostacyclin (PGI2) or thromboxane A2 (TXA2), potentially minimizing cardiovascular risks compared to NSAIDs. This inhibition is mediated by suppressing NF- κ B DNA binding

activity (189). Furthermore, SIN mimics MTX by restoring the balance between MMP and tissue inhibitors of matrix metalloproteinase (TIMP), protecting bone integrity and acting as a natural DMARDs to slow RA (190). SIN enriches anti-CIA *Lactobacillus* species (*L. paracasei* and *L. casei*) and boosts microbial tryptophan metabolites (indole-3-acrylic acid, indole-3-propionic acid, and indole-3-acetic acid), which activate the AhR. AhR activation rebalances Th17/Treg cells, alleviating arthritis severity in preclinical models. Mono-colonization studies confirm that these *Lactobacillus* strains contribute directly to SIN's efficacy, underscoring a "microbiota-metabolite-immunity" axis as a core mechanism (191).

As a multifaceted agent, SIN combines immunosuppressive, anti-inflammatory, and microbiota-modulating properties, offering a holistic approach to RA treatment. Its ability to target both inflammatory pathways and gut dysbiosis highlights its potential as a novel therapeutic strategy.

4.2.4 *Phyllodendron chinense* C.K.Schneid

The utilization of *Phyllodendron chinense* C.K.Schneid. in the aforementioned TCM formula for treating RA has been documented (29). Berberine (BBR), an isoquinoline alkaloid derivative, is one of the primary active components of *Phyllodendron chinense* C.K.Schneid. (192). Research has demonstrated that Berberine exerted an anti-arthritis effect by modulating the GM in CIA rats. Berberine intervention specifically up-regulated butyrate-producing genera positively correlated with anti-inflammatory effects, including *Blautia*, *Butyricoccus*, and *Parabacteroides*, while down-regulating butyrate-suppressing genera linked to pro-inflammatory responses such as *Prevotella*, *Paraprevotella*, and *Coprococcus*. Mechanistically, berberine reduced splenic levels of pro-inflammatory cytokines, particularly Th17-associated IL-17A, IL-17F, IL-21, and IL-22, through suppression of ROR γ t expression and STAT3 phosphorylation. Crucially, antibiotic treatment abolished these immunomodulatory effects, collectively demonstrating berberine's microbiota-dependent therapeutic potential in RA (70).

4.2.5 *Daphne giraldii* Nitsche

The root bark and stem bark of *Daphne giraldii* Nitsche, a plant of the genus *Daphne* in the Thymelaeaceae family, are known as Zushima. The main active components are daphnetin and zushima saponin (193). The Zushima tablet (ZT) has a wide therapeutic basis in Chinese folk medicine and is often used to treat conditions such as pain, injuries from falls, and RA. Clinical observations have shown that the curative effect of ZT in the treatment of RA is better than that of ZQFTN Tablets (194, 195). The study demonstrated that ZT effectively ameliorated CIA. 16S rRNA analysis revealed Firmicutes and Bacteroidetes as the dominant bacterial phyla in the GM of CIA rats. At the family level, 19 bacterial taxa were significantly altered in RA-model rats. Fecal metabolomics further indicated that ZT up-regulated propionate, butyrate, and valerate levels in CIA rats, with the therapeutic mechanism potentially linked to SCFAs enhancing disease mitigation through increased

Treg populations (196). Therefore, the therapeutic mechanism of ZT involves the gut microbiome-driven immunomodulation and solidifies its role as a potent RA treatment.

4.2.6 *Panax ginseng* C. A. Mey. (*P. ginseng*)

P. ginseng first documented in the "Shen Nong Materia Medica", is one of the principal components in DGNTD (174). *P. ginseng* contains a variety of bioactive compounds, including ginsenosides, polysaccharides, amino acids, and others, with ginsenosides being the primary active constituents (197). Research has demonstrated that ginsenoside Rg2, a triol-type saponin, enhances intestinal colonization of *Parabacteroides distasonis*, which directly suppresses Th17 cell differentiation through the production of bioactive metabolites-LCA, DCA, isoLCA, and 3-oxoLCA. Specifically, 3-oxoLCA and isoLCA not only directly suppressed the differentiation of Th17 cells but were also recognized as TGR5 agonists, enhancing the M2 polarization of macrophages. These dual mechanisms-microbiota-dependent immunomodulation and macrophage reprogramming-were validated in both CIA mice and TNF-Tg murine models (129). Therefore, as a prebiotic agent, Rg2 exerts therapeutic effects on arthritic mice by promoting the proliferation of *P. distasonis*.

4.2.7 *Clematis chinensis* Osbeck

Clematis chinensis Osbeck is a key component of Wang-Bi Tablet (WB), which has been patented in China and widely used for the treatment of RA due to its excellent therapeutic efficacy and minimal side effects (43). A study showed that both crude extracts and wine-processed *Clematis chinensis* Osbeck increase Firmicutes and decrease Bacteroidetes, while reducing *Prevotella*, *Bacteroides*, and *Blautia* and increasing *Paraprevotella* in the model group (198). In addition, the extract of *C. chinensis* can inhibit NO produced by peritoneal macrophages, which indicated that *C. chinensis* methanol extract had an obvious immunosuppressive effect (199). This combination of GM restoration and immunomodulation underpins its therapeutic value in RA treatment and supports its use in WB.

4.2.8 *Toddalia asiatica* (L.) Lam.

Toddalia asiatica (L.) Lam. is contained in Ba-wei-long-zuan granule (BLG), a traditional Chinese Zhuang medicine used for treating RA (43). A recent study has indicated that the extract of *Toddalia asiatica* (L.) Lam. (TAE) alleviates joint symptoms in rats with RA by restoring the balance of Th17/Treg cells in the colon and rectifying gut dysbiosis. TAE downregulated the expression levels of IL-17A, IL-1 β , and IL-6 in the colon while up-regulating FOXP3 and IL-10, indicating its regulatory role in the intestinal Th17/Treg balance. Furthermore, TAE improved GM diversity in AIA rats, reducing the abundance of *Ligilactobacillus*, which was elevated in the model group, and increasing the relative abundance of *Muribaculum*, *Subdoligranulum*, *Lachnospira*, and *Marvinbryantia* (200). These findings provide evidence that the efficacy of *Toddalia asiatica* (L.) Lam. and its inclusion in BLG for RA involves a dual mechanism targeting the gut-joint axis: immunomodulation and GM restoration.

4.2.9 *Glycyrrhiza uralensis* Fisch. (*G. uralensis*)

G. uralensis is one component of JWJG Capsules, used for treating RA and showing potent anti-inflammatory activity (43). *G. uralensis* treatment significantly improves joint inflammation, pathological lesions, and inflammation markers in CIA rats. It reverses abnormal GM composition by increasing *Eubacterium*, *Roseburia*, *Desulfovibrio*, *Bacteroides*, *Ruminococcaceae_Clostridium*, and *Peptostreptococcaceae_Clostridium*, while reducing *Helicobacter*, *Prevotella*, *Lachnospiraceae_Clostridium*, and *Barnesiella*. Meanwhile, *G. uralensis* alleviates intestinal damage, enhances intestinal barrier integrity by upregulating TJ proteins (ZO-1, occludin, and claudin-1). It also lowers Th17/Treg cell ratios in blood, colon, and joint fluid. These effects suggest that *G. uralensis* alleviates RA symptoms by modulating GM and immunity (201).

4.2.10 *Notopterygium incisum* K.C. Ting ex H.T. Chang (*N. incisum*)

N. incisum is a key component of DGNTD and JFG (174). Polysaccharides derived from *N. incisum* may represent one of its primary active constituents. A novel polysaccharide, named NIP, was isolated from *N. incisum* with a molecular weight of 2.34×10^6 Da. NIP consists of arabinose, galactose, glucose, and galacturonic acid, linked by methyl esterified 1,4-linked α -galacturonic acid, 1,6-linked β -galactose, 1,5-linked α -arabinose, and 1,4,6-linked β -glucose. NIP suppresses NO production in LPS-stimulated RAW264.7 macrophages. NIP reduces toe inflammation in AIA rats, suppresses inflammatory cytokine release, and inhibits NF- κ B and JAK/STAT3 pathway activation. Furthermore, NIP mitigated oxidative stress by decreasing malondialdehyde (MDA) levels and enhancing superoxide dismutase (SOD) activity in a dose-dependent manner. Additionally, NIP significantly decreases thymus and spleen indices, indicating immunosuppressive effects. NIP also markedly increases GM diversity, restores the Bacteroidetes-to-Firmicutes ratio, a critical index associated with disease susceptibility. Moreover, NIP enhances the abundance of *Eisenbergiella*, a genus known for producing butyrate, an anti-inflammatory metabolite (202, 203). These findings suggest NIP exerts anti-RA effects through anti-inflammatory, antioxidant, and GM-modulating mechanisms (204).

4.3 Herb couple

Angelica sinensis (Oliv.) Diels and *N. incisum* are two main constituents of DGNTD (157). The optimal ratio of AN7:3 herb couple was identified, with the active ingredients combination (AIC) screened as key components. AIC showed similar therapeutic effects as AN7:3 in CIA rats and may alleviate RA by regulating the MAPK signaling pathway, metabolic disorders, and gut microbiome-related autoimmunity. This study provides scientific evidence for using AIC as a prebiotic agent for RA and offers a systematic strategy to optimize medicinal material proportions and screen active ingredients in traditional Chinese herb couples (205).

The *in vivo* and *in vitro* effects of single TCM and its active compounds on the gut-immune axis in RA are summarized in Table 2.

5 Conclusions and future prospective

RA, a chronic autoimmune disorder, is intricately linked to dysregulation of the gut-immune axis, where gut dysbiosis, intestinal barrier dysfunction, and immune hyperactivation converge to drive systemic inflammation and joint destruction. Understanding the interactions between GM and the immune system may provide critical insights for developing novel biomarkers and treatment strategies, as well as for elucidating the pathophysiology of RA (Figures 1, 2).

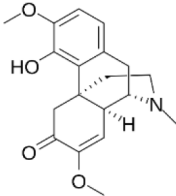
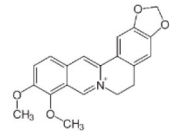
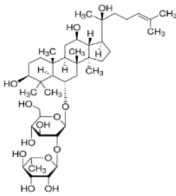
TCM offers a promising therapeutic strategy by targeting this axis through multi-component, multi-pathway mechanisms. TCM can treat RA by improving GM structure, modulating intestinal T lymphocytes, regulating microbiota-derived metabolites, enhancing intestinal barrier function and immunity, and alleviating intestinal dysfunction. TCM not only augments the therapeutic efficacy of conventional RA treatments but also mitigates their side effects. Regulating the gut-immune axis with TCM may become a safer and more effective new method for the treatment of RA, with broad application prospects.

However, there are some current research limitations and model challenges. Interactions between multiple TCM components and the GM are poorly understood. TCM used clinically requires more extensive RCTs to rigorously evaluate efficacy and risks. Due to inherent inconsistencies in TCM formulations, multi-herbal formulas also need greater standardization. This includes addressing variability in plant compounds, batch-to-batch quality, and potential herb-herb interactions, necessitating robust quality control (e.g., HPLC fingerprinting). Widely used AIA/CIA murine models rely on artificial induction, exhibit acute self-limiting inflammation, unlike chronic human RA, and poorly replicate human genetic-environmental interactions (76). Species differences further limit translational relevance.

To overcome these challenges and unlock TCM's potential, future research should focus on the following aspects: advance disease models. Specifically, prioritize TNF-Tg mice due to their human-like autoimmune and metabolic characteristics, such as chronicity and the gut-joint axis (81). Utilize spontaneous or collagen-induced Nonhuman Primate (NHP) models (e.g., macaques) for high-fidelity TCM trials on pharmacokinetics, toxicity, and microbiota interactions, leveraging their closer immune, metabolic, and genetic resemblance to humans (12). Develop quality controls for TCM compounds to ensure consistency and standardize TCM formulations.

As for deciphering mechanisms, establish the causal role of specific bacterial strains (e.g., *Lactobacillus casei*, *Prevotella copri*) and metabolites (e.g., SCFAs, bile acids) using gnotobiotic models and fecal microbiota transplantation (FMT). Combine metagenomics, metabolomics, and proteomics to map TCM-induced microbial shifts

TABLE 2 The effects and mechanisms of single TCM and its active compounds on the gut–immune axis in RA.

Single TCM	Active compounds	GM Modulation (↓↑)	Effects and mechanisms	Compound's structure	References
<i>Tripterygium wilfordii</i> Hook F (TwHF)	Tripterygium glycosides	↓ <i>Akkermansia</i> , <i>Prevotellaceae_NK3B31_group</i> , <i>Prevotella</i> . ↑ <i>Ureibacillus</i> , <i>Lactobacillus</i> , <i>Butyricoccus</i> , <i>Ruminococcus_UCG-014</i>	↓ Joint swelling, IL-6, TNF-α, IL-17, HMGB-1; ↑ α7nAChR expression; ↓ NF-κB and p-STAT3 signaling		(37, 178–182, 184, 206)
<i>Radix Paeoniae Alba</i>	Total glucosides of paeony (TGP)	↑ <i>Oscillibacter</i> , <i>Ruminococcaceae_UCG-014</i> , <i>Parabacteroides</i>	↓Inflammatory infiltration, body weight, thymus index;↓ VEGF, I FN-γ, SIgA; ↑ Th2, Treg, ↓Th1, Th17; Modulate intestinal mucosal immunity		(46, 185, 186)
<i>Caulis Sinomenii</i>	Sinomenine (SIN)	↑ <i>Lactcaseibacillus paracasei</i> <i>Lactcaseibacillus casei</i> ↑ microbial tryptophan metabolites (IA, IPA, IAA)	↓ IL-6, IL-1β, TNF-α, and other cytokines; ↓ mPGEs-1 and PGE ₂ ; ↓ CD11b ⁺ F4/80 ⁺ CD64 ⁺ synovial macrophages, CD11b ⁺ Ly6C ⁺ CD43 ⁺ macrophages (spleen, lymph nodes), CD14 ⁺ CD16 ⁺ monocytes		(187–191);
<i>Phellodendri Chinensis Cortex</i>	Berberine (BBR)	↓ <i>Prevotella</i> , <i>Paraprevotella</i> and <i>Coprococcus</i> ↑ <i>Blautia</i> , <i>Butyricoccus</i> , <i>Parabacteroides</i>	↓ IL-17A, IL-17F, IL-21, IL-22, RORγt expression, STAT3 phosphorylation; Microbiota-dependent immunomodulation		(70, 207)
<i>Daphne giraldii</i> Nitsche	Daphnetin, Zushima saponin	Alters 19 gut taxa at the family level; dominant phyla: Firmicutes and Bacteroidetes	↓ inflammation, ↑Treg cells; ↑ SCFAs (propionate, butyrate, valerate)		(193–196)
<i>Panax ginseng</i> C. A. Mey.	Ginsenoside Rg2	↑ <i>Parabacteroides distasonis</i>	↓ Th17 cell differentiation; ↑ M2 macrophage polarization via TGR5 activation; ↑Bile acid metabolites (LCA, DCA, isoLCA, 3-oxoLCA)		(129, 197)
<i>Clematis chinensis</i> Osbeck	Crude extract; Wine-processed extract; Methanol extract	↓ Bacteroidetes, <i>Prevotella</i> , <i>Bacteroides</i> , <i>Blautia</i> . ↑ Firmicutes, <i>Paraprevotella</i> .	↓ NO production in macrophages; Immunosuppression		(198, 199)
<i>Toddalia asiatica</i> (L.) Lam.	<i>Toddalia asiatica</i> (L.) Lam. (TAE)	↓ <i>Ligilactobacillus</i> . ↑ <i>Muribaculum</i> , <i>Subdoligranulum</i> , <i>Lachnospira</i> , <i>Marvinbryantia</i> .	↓Levels of IL-17A, IL-1β, and IL-6 in the colon, ↑FOXP3 and IL-10; restore Th17/Treg balance		(200)
<i>Glycyrrhiza uralensis</i> Fisch.	<i>G. uralensis</i> extract	↓ <i>Helicobacter</i> , <i>Prevotella</i> , <i>Lachnospiraceae_Clostridium</i> , <i>Barnesiella</i> . ↑ <i>Eubacterium</i> , <i>Roseburia</i> , <i>Desulfovibrio</i> , <i>Bacteroides</i> , <i>Ruminococcaceae_Clostridium</i> , <i>Peptostreptococcaceae_Clostridium</i> .	↓ Th17/Treg ratio in blood, colon, joint fluid; ↑ TJ (ZO-1, occludin, claudin-1), gut barrier		(43, 201)
<i>Notopterygium incisum</i> K.C. Ting ex H.T. Chang	<i>Notopterygium incisum</i> Polysaccharide (NIP)	↑ <i>Eisenbergiella</i> . Restore Bacteroidetes/Firmicutes ratio	↓NF-κB and JAK/STAT3 pathways, NO and cytokines (TNF-α, IL-6). ↓MDA,↑SOD		(202–204)

↑=Increase/Promote/Upregulate, ↓=Decrease/Inhibit/downregulate.

and host pathways, identifying novel biomarkers for personalized therapy. Investigate cross-reactivity between microbial antigens (e.g., *Prevotella*-derived peptides) and host proteins to unravel RA's autoimmune origins and design targeted interventions. Develop TCM-derived prebiotics and probiotics to reinforce intestinal barrier function and prevent microbial translocation to mitigate RA. Implement stringent quality controls and standardize TCM formulations.

In conclusion, TCM's ability to harmonize the gut-immune axis offers a transformative, holistic approach to RA treatment. Realizing TCM's full potential requires resolving mechanistic complexities, advancing clinical validation through rigorous RCTs, and ensuring standardization. Prioritized interdisciplinary collaboration is essential to advance this microbiota-centric approach and improve global RA outcomes.

Author contributions

JZ: Writing – review & editing, Writing – original draft, Investigation, Data curation. YF: Investigation, Writing – original draft, Data curation. ZL: Conceptualization, Data curation, Writing – original draft. SZ: Conceptualization, Data curation, Formal Analysis, Writing – original draft. CW: Project administration, Data curation, Conceptualization, Writing – review & editing, Formal Analysis.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

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Acknowledgments

Figures were created with BioRender software, biorender.com (accessed on May 22, 2025).

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Glossary

3-oxoLCA	3-oxolithocholic acid	MMP	Matrix metalloproteinase
ACPAs	anti-citrullinated protein antibodies	mPGES-1	microsomal prostaglandin E synthase 1
ACR	American College of Rheumatology	MTX	Methotrexate
AhR	aryl hydrocarbon receptor	NETs	neutrophil extracellular traps
AI	the arthritis index	NF- κ B	Nuclear factor-kappaB
APCs	antigen-presenting cells	NO	nitric oxide
CIA	collagen-induced arthritis	Nrf2	the NF-E2-related factor 2
DAS	joint disease activity score	NSAID	Non-steroidal anti-inflammatory drug
DAS28	28-joint disease activity score	Ocln	encoding occludin
DCA	deoxycholic acid	PADs	peptidyl arginine deiminases
DCs	dendritic cells	PGE2	Prostaglandin E2
DMARDs	disease-modifying anti-rheumatic drugs	PI3K/AKT	phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB/AKT)
ESR	erythrocyte sedimentation rate	PPAR γ	peroxisome proliferator-activated receptor gamma
FDA	Food and Drug Administration	PSA	polysaccharide A
FLNA	filamin A	PTMs	Post-translational modifications
FLS	fibroblast-like synoviocytes	RA	Rheumatoid arthritis
FMT	Fecal microbiota transplantation	RCT	Randomized controlled trial
Foxp3	Forkhead box P3	RF	rheumatoid factor
GCs	glucocorticoids	ROS	reactive oxygen species
GF	germ-free	SCFAs	short-chain fatty acids
GM	gut microbiota	SFB	Segmented filamentous bacteria
GNS	N-Acetyl-glucosamine-6-sulfatase	SIgA	secretory immunoglobulin A
HCs	healthy controls	SLECs	short-lived effector T cells
HDACs	histone deacetylases	SOD	superoxide dismutase
HLA	human leukocyte antigen	STAT3	signal transducer and activator of transcription 3
HLA-DRB1	human leukocyte antigen-DR beta chain 1	TCM	Traditional Chinese Medicine
IAA	indole-3-acetic acid	TCR	T-cell receptor
IAld	indole-3-aldehyde	Tfh	follicular helper T cells
IFN	interferon	TGF- β	Transforming growth factor β
IL	Interleukin	TGP	Total glucosides of paeony
IPA	indole-3-propionic acid	TGTs	Tripterygium glycosides tablets
isoLCA	isolithocholic acid	Th1	T helper-1 cells
JAK	Janus kinase	TJ	Tight junction
JNK	C-Jun N-terminal kinase	TLR	Toll-like receptor
LCA	lithocholic acid	TNF	Tumor necrosis factor
LPD	live <i>P. distasonis</i>	Tph	peripheral helper T cells
MAPK	Mitogen-activated protein kinase	Tregs	regulatory T cells
MCP-1	monocyte chemoattractant protein-1	TwHF	Tripterygium wilfordii Hook F
MDA	malondialdehyde	TXA2	thromboxane A2
MHC	major histocompatibility complex	ZO	Zonula Occludens
miR-20a-5p	microRNA-20-5p	α 7nAChR	alpha7 nicotinic acetylcholine receptor
MLs	macrophage-like synoviocytes		