Chinese Journal of Natural Medicines

Gut microbiota: a novel target for traditional Chinese medicine in the treatment of HIV/AIDS immunological non-responders

Shousheng Chen, Pengyu Li, Huijun Guo

Citation: Shousheng Chen, Pengyu Li, Huijun Guo, Gut microbiota: a novel target for traditional Chinese medicine in the treatment of HIV/AIDS immunological non-responders, Chinese Journal of Natural Medicines, 2026, 24(2), 180-188. doi: 10.1016/S1875-5364(26)61089-8.

View online: https://doi.org/10.1016/S1875-5364(26)61089-8

Chinese Journal of Natural Medicines 24 (2026) 180-188

Contents lists available at ScienceDirect

Chinese Journal of Natural Medicines

journal homepage: www.cjnmcpu.com/

Review

Gut microbiota: a novel target for traditional Chinese medicine in the treatment of HIV/AIDS immunological non-responders

Shousheng Chen, Pengyu Li, Huijun Guo*

AIDS Research Center of the First Affiliated Hospital of Henan University of Traditional Chinese Medicine, Zhengzhou 450000, China

ARTICLE INFO

Article history:
Received 27 January 2025
Revised 11 April 2025
Accepted 28 July 2025
Available online 20 February 2026

Keywords:
Human immunodeficiency virus (HIV)
Acquired immune deficiency syndrome (AIDS)
Immunological non-response (INRs)
Gut microbiota
Traditional Chinese medicine

ABSTRACT

Despite effective antiretroviral therapy (ART), many individuals with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) achieve viral suppression but fail to fully restore cluster of differentiation 4 $(CD4)^+$ T lymphocyte (CD4 cell) counts—a condition known as immunological non-response (INRs). INRs are associated with elevated health risks, including increased susceptibility to AIDS-related and non-AIDS-related complications. The pathogenesis of INRs remains incompletely understood, and no established therapeutic interventions exist, posing a major challenge in contemporary HIV/AIDS management. Emerging evidence indicates that INRs exhibit significant alterations in gut microbiota composition. Dysbiosis of the gut microbiota may contribute to persistent immune activation, cytokine imbalance, and cellular pyroptosis, all of which could impair immune reconstitution in people living with HIV/AIDS. Traditional Chinese medicine (TCM) has demonstrated potential immunomodulatory effects and is increasingly utilized in the management of INRs. Targeting the gut microbiota and elucidating the mechanisms by which TCM modulates this microbial ecosystem may offer new avenues for preventing and treating INRs. This review explores the interplay between gut microbiota and TCM, examines the association between gut dysbiosis and INRs, discusses the mechanistic pathways through which microbiota imbalance contributes to INRs development, and highlights how TCM interventions regulate gut microbiota to promote immune recovery. By focusing on the gut microbiota as a therapeutic interface, this article provides novel insights into TCM-based strategies for improving outcomes in INRs and supports the development of innovative treatment approaches.

1. Introduction

Immunological non-responders (INRs) are defined as individuals with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), who, despite sustained viral suppression through antiretroviral therapy (ART), fail to achieve adequate recovery of cluster of differentiation 4 $(CD4)^+$ T cell counts [1]. It is estimated that 10% to 40% of patients on ART develop this condition, which is linked to accelerated disease progression and heightened risks of both AIDS-defining and non-AIDS-defining illnesses. Traditional Chinese medicine (TCM) has been widely integrated into clinical practice due to its capacity to enhance the efficacy of ART while reducing drug-associated toxicities [2]. Characterized by multi-targeted actions and holistic regulation, TCM offers distinct advantages in promoting immune reconstitution. Pharmacological studies have identified immune-enhancing properties in several herbal formulations, such as Huang qi (*Astragalus membranaceus*) and Si-Jun-Zi Tang [3, 4]. Clinical utilization of TCM for INRs has grown rapidly; however, the prevalence of INRs has not substantially decreased, underscoring the need for more effective therapeutic strategies. Previous research suggests that TCM influences immune recovery through mechanisms involving thymic output, inhibition of pyroptosis, and modulation of chronic immune activation [5]. Recently, accumulating evidence has highlighted gut microbiota dysbiosis as a key factor in the pathophysiology of INRs, with microbial restoration shown to support immune function recovery. This paper focuses on the gut microbiota as a central axis to examine the relationships among TCM, gut microbial ecology, and INRs. We analyze how TCM modulates gut microbiota to prevent or treat INRs and explore the underlying biological mechanisms. This synthesis aims to provide new perspectives on TCM-based interventions for INRs and inform the development of targeted therapies.

2. Current status of TCM in the treatment of INRs

In the framework of TCM, INRs are categorized under the pattern of "deficiency labor", consistent with TCM's emphasis on systemic balance and dynamic homeostasis [6]. The integration of TCM with ART has gained increasing recognition for its synergistic benefits in enhancing therapeutic outcomes and minimizing adverse effects. A meta-analysis encompassing 1691 INRs patients across 12 randomized controlled trials (RCTs) and 7 non-randomized controlled trials (nRCTs) confirmed that TCM contributes to immune reconstitution in this population [7]. One randomized, double-blind, placebo-controlled trial evaluated Diwu-Yanggan Capsule combined with ART in 57 INRs, assessing TCM syn-

* Corresponding author.
E-mail address: guo.6268505@163.com (H. Guo)

https://doi.org/10.1016/S1875-5364(26)61089-8

drome scores, quality of life, CD4 cell counts, and the proportion of CD45RA$^+$ cells. Results showed that the combination therapy significantly increased CD4 cell counts and CD45RA$^+$ cell percentages, improved TCM syndrome scores, and attenuated quality-of-life decline, with no reported adverse events [8]. A prospective single-center RCT demonstrated that adding Shenling-Baizhu San to ART led to increased CD4 cell levels and improved clinical symptoms in INRs, without safety concerns [9]. In another study of 177 INRs treated with Tangcao Tablets plus ART, the combination group exhibited a greater rise in CD4 cell counts after six months compared to those receiving ART alone [10]. Notably, the effect was more pronounced in patients with lower baseline CD4 counts, and the intervention did not interfere with ART's antiviral activity, with no adverse effects observed. Additionally, Buzhong-Yiqi Tang combined with ART was shown to improve immune function in patients exhibiting Qi deficiency, reduce TCM symptom scores, lower inflammatory markers, and maintain a favorable safety profile [11].

3. Clinical study of TCM regulating gut microbiota in the treatment of INRs

A growing body of clinical evidence supports the efficacy of TCM in managing INRs. Alterations in gut microbiota are closely linked to HIV disease progression, and ART itself can significantly alter intestinal microecology [12]. While modern medicine excels in viral suppression—as reflected in updated guidelines such as those in the *AIDS Diagnosis and Treatment Guide*—persistent challenges remain, including the presence of viral reservoirs and ART-induced disruptions to gut integrity. These factors can exacerbate gut microbiota dysbiosis and compromise mucosal barrier function. The gut microbiota plays a pivotal role in systemic immunity, influencing immune cell differentiation, inflammation regulation, and host defense. TCM exerts broad regulatory effects, not only enhancing immune function but also alleviating gastrointestinal side effects commonly associated with ART [13]. The strengths of TCM lie in immune modulation and symptom management, whereas conventional medicine is superior in direct antiviral action and control of opportunistic infections. Modulation of the gut microbiota serves as a critical interface, enabling the integration of these complementary therapeutic systems in the management of INRs. This section systematically reviews clinical evidence on how TCM regulates gut microbiota to improve immune outcomes in INRs. Various TCM prescriptions, patented herbal products, and non-pharmacological interventions have demonstrated immune-enhancing effects and contribute to immune restoration, primarily through mechanisms involving gut microbiota regulation and the reestablishment of microbial equilibrium (see Table S1 for details) [14-22].

4. INRs associated with significant gut microbiota dysbiosis

The gut is recognized as the largest immune organ in the human body. It harbors diverse immune cells, including T cells and macrophages, which collectively form the gut mucosal immune system. These mucosal immune cells constitute approximately 80% of the body's total immune cells and serve as a critical defense line against pathogens [23]. The gut microbiota is intricately linked to the human immune system, contributing to immune system maturation and playing a pivotal role in regulating both innate and adaptive immune responses [24]. Dysbiosis of the gut microbiota can lead to immune dysfunction. Disruption of the intestinal mucosal barrier facilitates translocation of pathogenic bacteria into the bloodstream, while the proliferation of harmful microbes increases endotoxin production, triggering inflammatory damage and systemic immune activation [25, 26]. Thus, the gut microbiota and immune system engage in bidirectional interaction and co-evolution to maintain immune homeostasis.

The gut is a primary target for HIV and a key site for viral replication and reservoir formation [27]. Previous studies have demonstrated that HIV/AIDS patients exhibit marked gut microbiota dysbiosis. Although ART effectively suppresses viral replica-

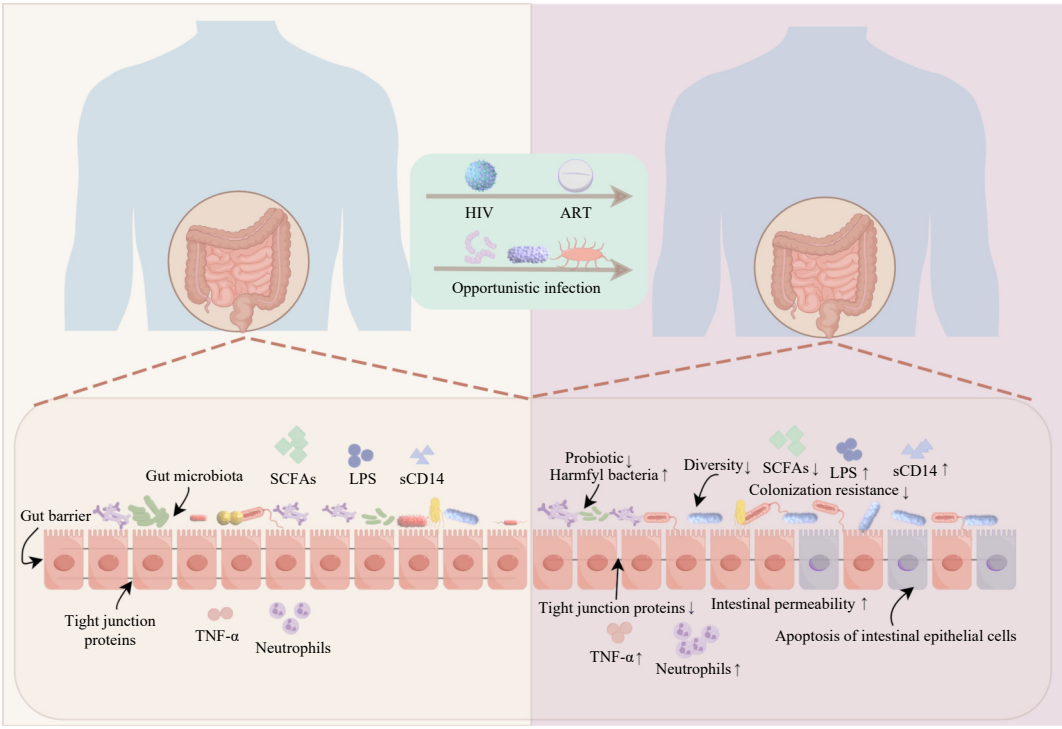

Fig. 1 INRs associated with significant gut microbiota dysbiosis. In healthy individuals, the gut microbiota maintains normal intestinal mucosal barrier function and exists in a state of dynamic equilibrium. HIV infection and opportunistic pathogens disrupt this balance in INRs, leading to gut microbiota dysbiosis and intestinal mucosal dysfunction. Key features include reduced microbial diversity, depletion of beneficial bacteria, expansion of pathogenic species, increased intestinal permeability, impaired colonization resistance, enhanced intestinal epithelial apoptosis, elevated levels of lipopolysaccharides (LPS) and soluble CD14 (sCD14), reduced short-chain fatty acid (SCFA) production , increased pro-inflammatory cytokines (e.g., TNF-α), and heightened neutrophil infiltration, as illustrated by Figdraw.

tion, it fails to fully restore microbial balance [28] (Fig. 1). Significant disturbances in gut microbiota persist after ART initiation, particularly in individuals with low CD4$^+$ T cell counts [29, 30], suggesting that ART may exacerbate dysbiosis in INRs. Compared to healthy individuals, INRs display reduced gut microbial diversity and a lower *Firmicutes*-to-*Bacteroidetes* ratio [20]. One study reported decreased levels of beneficial bacteria such as *Ruminococcus* and *E. faecalis*, alongside increased abundance of pathogenic taxa including *Aspergillus*, *Enterobacteriaceae*, and *Escherichia coli–Shigella* [31]. This study further emphasized that both the structure and diversity of the gut microbiota in INRs differ significantly from those in immunological responders (IRs). Beyond compositional changes, INRs also exhibit diminished gut colonization resistance, impairing their ability to resist enteric infections [32]. Microscopic analysis revealed fewer intestinal glands and markedly reduced expression of the tight junction protein claudin-1 in INRs, indicating compromised epithelial integrity and increased intestinal permeability [33, 34]. Additionally, darker caspase-3 staining and elevated tumor necrosis factor α (TNF-α) mRNA levels were observed in the intestines of INRs, accompanied by increased neutrophil infiltration—findings consistent with enhanced epithelial apoptosis and heightened inflammatory responses [33, 35]. SCFAs are essential for maintaining intestinal homeostasis and mucosal barrier integrity. A reduction in gut phyla *Firmicutes* and *Bacteroidetes* among HIV/AIDS patients has been linked to decreased production of butyric and valeric acids, two major SCFAs [36]. Another study showed that elevated levels of lipopolysaccharide (LPS) and soluble CD14 (sCD14) correlate closely with AIDS progression and systemic inflammation [37]. Future research should prioritize investigating intestinal structural injury and gut microbiota dysbiosis in the pathogenesis of poor immune reconstitution.

5. Mechanisms of the occurrence of INRs due to gut microbiota dysbiosis

The underlying mechanisms of INRs remain incompletely understood. Gut microbiota dysbiosis likely contributes to INRs development through multiple interconnected pathways (Fig. 2).

5.1. Abnormal immune activation

HIV/AIDS patients with compromised immunity are highly susceptible to opportunistic infections, which drive persistent immune activation—characterized by heightened T cell activation, accelerated turnover, and increased T cell apoptosis [38]. For every 5% increase in activated CD4$^+$ T cells, a corresponding decline of 45 cells/μL in total CD4$^+$ cell count has been observed [39]. Plasma concentrations of inflammatory cytokines such as IP-10 and IL-6 are positively correlated with T cell depletion and senescence in INRs [40]. Moreover, INRs with lower CD4$^+$ cell counts exhibit higher degrees of immune activation [41]. Persistent T cell activation during ART reduces *de novo* CD4$^+$ T cell production and may be a major impediment to immune reconstitution [42]. Gut microbiota disturbances in HIV-infected individuals contribute significantly to aberrant immune activation [43]. *Aspergillus*, a common opportunistic pathogen, reduces gut colonization resistance and damages the intestinal mucosal barrier. Studies report in-

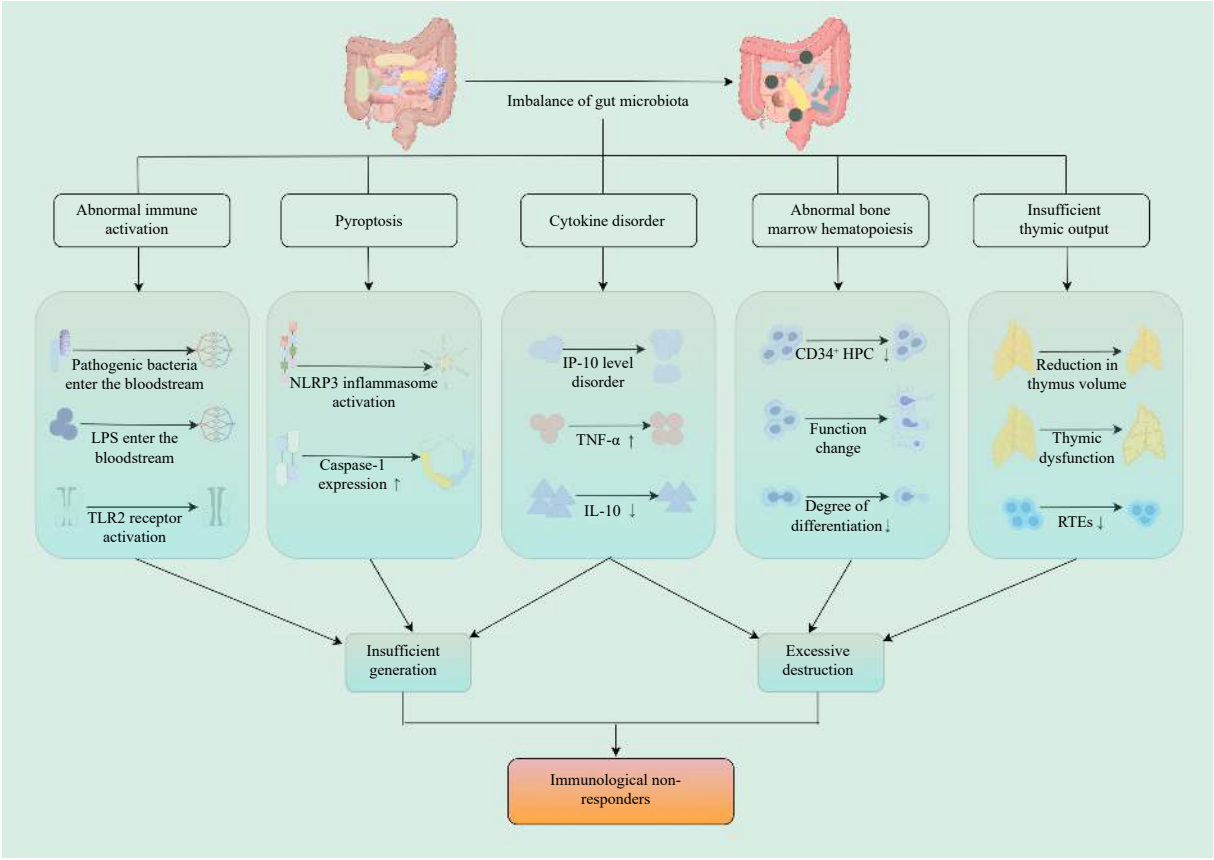

Fig. 2 Mechanisms by which gut microbiota dysbiosis induces INRs. Dysbiosis compromises the intestinal mucosal barrier, enabling translocation of pathogenic bacteria and LPS into systemic circulation. This activates Toll-like receptor 2 (TLR2), triggering abnormal immune activation and CD4$^+$ T cell depletion. Pathogenic gut microbes stimulate the NOD-like receptor protein 3 (NLRP3) inflammasome and upregulate caspase-1, inducing pyroptosis of CD4$^+$ T cells. Dysbiosis also disrupts cytokine profiles, including IP-10, TNF-α, and interleukin-10 (IL-10), impairing CD4$^+$ T cell differentiation and function. Furthermore, microbial imbalance impairs bone marrow hematopoiesis, characterized by reduced numbers and altered function of CD34$^+$ hematopoietic progenitor cells (HPCs), along with diminished differentiation capacity. Dysbiosis additionally affects thymic output, manifesting as thymic atrophy, dysfunction, and reduced recent thymic emigrants (RTEs). Collectively, these factors contribute to inadequate generation or excessive loss of CD4$^+$ T cells, culminating in INRs, as depicted by Figdraw.

creased intestinal abundance of *Aspergillus* in INRs, promoting bacterial and microbial metabolite translocation into circulation, thereby amplifying systemic inflammation and immune activation [31, 44, 45]. LPS, an endotoxin produced by Gram-negative bacteria, exhibits strong immunostimulatory activity [46]. In HIV/AIDS patients, disruption of the intestinal barrier allows LPS to enter the bloodstream, where it binds Toll-like receptor 4 (TLR4), initiating systemic immune activation [47, 48]. Prevotella activates TLR2 and promotes Th17 cell polarization, a process implicated in chronic inflammation [49]. Recent evidence shows elevated relative abundance of *Prevotella* in the gut microbiota of HIV/AIDS patients, contributing to widespread immune dysregulation [28, 50]. These findings indicate that gut microbiota-driven immune activation plays a critical role in impaired immune recovery.

5.2. Cytokine disorders

Cytokines, serving as the third messengers of the immune system, regulate immune cell differentiation and function. Recent studies indicate that in HIV-infected individuals receiving ART, the diversity of rumen-associated bacteria and *Vibrio* species increases, while *Escherichia coli* abundance decreases. Concurrently, serum levels of interferon-γ (IFN-γ)-induced protein 10 (IP-10) decrease, whereas interleukin-8 (IL-8) levels rise [51]. However, another study found that lower $CD4^+$ cell counts in INRs are strongly associated with elevated serum IP-10, potentially due to IP-10 overexpression and sustained T cell activation [52]. One investigation revealed that INRs exhibit significantly lower abundance of *Ruminococcaceae* compared to IRs, along with differences in gut microbiota alpha diversity [29]. Elevated serum levels of pro-inflammatory cytokines, including TNF-α, IP-10, and IL-1α, were also detected in IL-10, a key anti-inflammatory cytokine, which regulates gut microbiota composition, maintains intestinal epithelial homeostasis, and supports mucosal barrier integrity [53]. Research indicates that plasma IL-10 levels, crucial for regulatory T (Treg) cell-mediated immunosuppression, are significantly lower in INRs than in responders [54]. Both experimental and clinical studies show that probiotics such as *Bifidobacterium bifidum* can substantially elevate IL-10 levels, improving immune function [55, 56]. An intervention study demonstrated that oral enteral nutrition supplementation significantly increased $CD4^+$ cell counts in INRs and reduced levels of the pro-inflammatory cytokine IL-1β [57].

5.3. Pyroptosis

Emerging evidence suggests that HIV infection, combined with ART-induced pyroptosis of infected $CD4^+$ T cells and bystander cell death, contributes significantly to INRs [58]. Activation of the NOD-like receptor protein 3 (NLRP3) inflammasome and upregulation of caspase-1 expression in AIDS patients may induce $CD4^+$ T cell pyroptosis, potentially driving immune failure [59]. A cross-sectional study identified excessive caspase-1-mediated pyroptosis as a primary mechanism of $CD4^+$ T cell loss in advanced AIDS [60]. The main contributors to immune reconstitution failure in ART-treated patients are diminished thymic function and pyroptosis of recent thymic emigrant (RTE) $CD4^+$ T cells [61]. Gilad et al. reported that over 95% of resting lymphoid $CD4^+$ T cells undergo caspase-1-dependent pyroptosis, releasing inflammatory signals before death, perpetuating a destructive cycle [62]. The gut microbiota and its metabolites influence pyroptosis; sodium butyrate (NaB), a microbial metabolite, inhibits TGFβ1-induced NLRP3/caspase-1 activation and pyroptosis [63]. In HIV-infected individuals, a damaged intestinal barrier permits pathogenic bacteria to trigger inflammasome assembly (e.g., NLRP3), directly inducing pyroptosis [64]. Dysbiosis increases pathogen-associated molecular patterns (PAMPs) such as LPS and peptidoglycan, which activate cellular pyroptosis *via* the NLRP3/caspase-1 pathway. Pyroptosis also aids in eliminating intracellular pathogens like *Shigella* and *Salmonella* by promoting epithelial shedding [65]. Ginsenoside Rg3 has been shown to inhibit NLRP3 inflammasome activation, partially reverse gut dysbiosis, and reduce pyroptosis [66]. These findings underscore the critical interplay between gut microbiota and pyroptosis in INRs pathogenesis.

5.4. Decreased hematopoiesis in bone marrow

Human $CD4^+$ T cells originate from $CD34^+$ hematopoietic stem cells (HSCs) and hematopoietic progenitor cells (HPCs) in the bone marrow and mature in the thymus. As AIDS progresses, the number of $CD34^+$ HPCs in peripheral blood declines, accompanied by functional alterations and preferential loss of lymphoid precursors among remaining $CD34^+$ cells [67]. HIV infects multiple bone marrow HPC subpopulations, affecting $CD34^+$ cell differentiation and survival [68, 69]. Another study found reduced differentiation of $CD34^+$ HPCs into T cells in INRs compared to IRs and healthy controls, possibly due to upregulation of the ATP receptor P2X7 on $CD34^+$ HPCs [70]. In rat models, a reduced proportion of $CD45^+CD3^+$ T cells in the bone marrow was associated with increased abundance of *Proteobacteria*, *Actinobacteria*, *Escherichia–Shigella*, and *Staphylococcus*, and decreased levels of *Firmicutes* and *Lactobacillus* [71]. In patients undergoing hematopoietic stem cell transplantation (HSCT), gut microbiota diversity declined, with reduced proportions of *Pseudomonas*, *Rumen cocci*, and butyrate-producing bacteria, and increased *Proteus* [72, 73]. These observations support a strong association between gut microbiota dysbiosis and impaired bone marrow hematopoiesis, implicating this axis in INRs development.

5.5. Insufficient thymic output

Thymic output is closely tied to $CD4^+$ T cell recovery and can be assessed *via* thymus size, T cell receptor excision circles (TREC), RTEs, and naive $CD4^+$ T cells [74]. Positive correlations between thymus volume and $CD4^+$ cell counts have been documented in HIV-infected patients [75, 76]. Patients with thymic failure (TREC ratio < 10) exhibit lower $CD4^+$ cell counts, whereas those with higher $CD4^+$ cell levels and slower disease progression demonstrate better thymic function [77]. Rb-Silva et al. proposed that TREC levels could predict immune recovery in chronically infected individuals [78]. One study found lower absolute numbers of RTEs in INRs compared to responders [79], a finding confirmed by subsequent research [70]. Animal studies show that rats with reduced thymic $CD3^+$ T lymphocytes exhibit significant gut microbiota disruption [71]. Probiotics such as *Bifidobacterium bifidum* enhance immune organ recovery and increase thymic index in immunocompromised mice [80]. Growing evidence indicates that gut microbiota and their metabolites play essential roles in thymic T cell development and function [81, 82]. These results suggest that gut microbiota-mediated impairment of thymic output may significantly contribute to INRs.

5.6. Other potential causes

Beyond the aforementioned mechanisms, additional factors may underlie INRs. Under physiological conditions, immune homeostasis depends on the balance between Th17 and Treg cells; disruption of this equilibrium is strongly linked to AIDS progression [83]. Individuals with low $CD4^+$ cell counts, especially INRs, exhibit more pronounced Th17/Treg imbalance [84]. Certain microbes—including *Bacteroides fragilis*, *Clostridia*, and segmented filamentous bacteria—modulate the Th17/Treg ratio. Yiaikang Capsules have been reported to improve this ratio in INRs and al-

leviate gut dysbiosis [14, 85]. Studies also reveal suppressed immune response pathways in peripheral blood T cell subsets of INRs, impaired memory $CD4^+$ T cell expansion, and defective differentiation of $CD34^+$ HPCs into T cells [70, 86]. Additionally, abnormal natural killer (NK) cell activation in INRs mediates cytotoxic effects against both infected and uninfected $CD4^+$ T cells [87]. Strong correlations exist between gut microbiota dysbiosis and serum T cell subset levels [88, 89]. Probiotic supplementation increases $CD4^+$ and $CD8^+$ T cell populations and modulates NK cell activity [80]. TCMs such as Shaoyao Tang and Sishen Wan have been shown to restore gut microbiota balance and correct T cell subset imbalances [90, 91]. INRs exhibit higher viral reservoirs and lower baseline $CD4^+$ cell counts than responders, factors that may hinder immune recovery [92]. Intestinal lymphoid tissue serves as a major HIV reservoir, and TCMs like Fuzheng Yiqi Tang and Aikeqing Capsules enhance ART efficacy and reduce drug resistance [93, 94]. A recent review highlights that age, timing of ART initiation, platelet-T cell complexes, co-infections, adipokines, and host metabolism may also influence INRs development [95].

6. Modulation of gut microbiota by TCM for the treatment of INRs

6.1. Modulation of gut microbiota and metabolites

Accumulating evidence indicates that modulation of gut microbiota and their metabolites underlies the therapeutic effects of TCM, whether administered as compound formulas, single herbs, or active ingredients. The 2023 Top 10 Academic Advances in TCM featured a study on Pien-Tze-Huang, which modulates gut microbiota in mice with colorectal cancer, suppressing carcinogenesis and pro-inflammatory signaling [96]. Given the close interplay between gut microbiota and immunity, TCM-based regulation of microbial communities offers promise for enhancing immune reconstruction in AIDS patients [97]. One study linked post-ART immune status in HIV/AIDS patients to structural shifts in gut microbiota [31]. Gu et al. reported that multiple traditional Chinese medicines can regulate the populations of intestinal *Lactobacillus*, *Bifidobacterium*, and *Escherichia coli*, thereby improving immune function [98]. Shenling-Guben Granules and artesunate tablets have been shown to modulate gut microbiota structure and dominant species while increasing probiotic abundance [20]. Both formulations increase $CD4^+$ cell counts in INRs and promote immune reconstitution [99, 100]. Buzhong-Yiqi Tang modulates gut microbiota composition in mice with spleen deficiency and improves immune function and TCM symptom scores in INRs [11, 101]. Yi-Aikang Capsule, used clinically for nearly two decades, has demonstrated efficacy in immune reconstruction through both animal and human studies [102, 103]. It regulates beta diversity of gut microbiota in INRs, reverses abundance changes in *Trichomonas* and *Prevotella*, and enhances immune homeostasis [14]. Jian-Aikang Concentrated Pill increases beneficial bacterial proportions, elevates intestinal SCFAs such as acetic acid, and reduces LPS levels in HIV/AIDS patients [16]. A combination of Chinese and Western medicine has been shown to lower LPS and repair intestinal mucosal damage [104]. A comprehensive literature review suggests that gut microbiota modulation may reduce immune activation and inflammation in INRs, supporting immune reconstitution, with particular emphasis on TCM interventions such as moxibustion, artesunate, and *Tripterygium wilfordii* [95].

6.2. Suppression of immune activation and inflammatory response

Abnormal immune activation and chronic inflammation persist throughout HIV infection and ART [105]. Microbial translocation, driven by gut dysbiosis and mucosal barrier disruption, is a major contributor to sustained immune activation. Probiotics enhance immunity and mitigate inflammation in HIV/AIDS patients. Buzhong-Yiqi Tang not only modulates gut microbiota and boosts immunity in INRs but also reduces inflammatory markers [11]. Xie-Likang Capsules regulate TNF-α secretion, restore gut microbiota structure, repair the intestinal barrier, and reduce ongoing $CD4^+$ T cell loss [106]. Yi-Aikang Capsule has demonstrated significant modulatory effects on gut microbiota in patients with HIV/AIDS. Experimental evidence indicates that it attenuates interferon (IFN)-γ-induced increases in intestinal permeability by preventing downregulation of tight junction proteins—ZO-1, Claudin-1, and Claudin-5. By preserving the integrity of the intestinal epithelial barrier, Yi-Aikang reduces microbial translocation, thereby mitigating systemic immune activation and inflammation [107, 108]. Another study demonstrated that Yi-Aikang Capsule downregulates the expression of SAMHD1 in peripheral blood mononuclear cells (PBMCs) and lowers plasma levels of IFN-α and IFN-γ, thereby alleviating abnormal immune cell activation. Modern pharmacological studies confirm the immunomodulatory effects of key TCM herbs such as Huangqi (Astragalus) and Renshen (Ginseng), commonly used in INRs treatment [109, 110]. These herbs also modulate gut microbiota in mice, reduce LPS levels, and suppress release of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α [111, 112].

6.3. Increase of bone marrow hematopoiesis and thymus output

Impaired bone marrow hematopoiesis and reduced thymic output are potential pathogenic mechanisms in INRs and are closely linked to gut microbiota disturbances. A herbal extract known for clearing heat, dampness, and detoxification increased TREC content and enhanced thymic output in simian immunodeficiency virus (SIV)-infected rhesus monkeys [113]. The extract also promoted migration of precursor cells from bone marrow to thymus, increased precursor cell proportions, and supported thymocyte differentiation [114]. Si-Jun-Zi Tang, a representative formula for tonifying spleen and Qi, enhances immunity and regulates gut microbiota [115]. Clinical application in HIV/AIDS patients has yielded positive outcomes [116]. In mice, Si-Jun-Zi Tang increases intestinal *Bifidobacterium* and *Lactobacillus*, improves immunity, and elevates spleen and thymus indices [4]. Danggui Buxue Decoction modulates gut microbiota balance and increases peripheral NK cell and bone marrow HSC ratios [117]. Sheng-Mai-San regulates gut microbiota, enhances immunity, increases thymus and spleen indices, promotes bone marrow mesenchymal stem cell proliferation, and improves the hematopoietic microenvironment [118]. Yi-Aikang Capsule increases thymus weight and thymic index in murine leukemia virus-induced immunodeficient mice [119]. Tangcao Tablets elevate bone marrow nucleated cell counts and organ indices in zidovudine-induced myelosuppressed mice [120]. These findings suggest that TCM can regulate gut microbiota, enhance bone marrow hematopoiesis and thymic output, and improve immune function. However, studies specifically targeting AIDS remain limited, and underlying mechanisms require further elucidation. Fig. 3 illustrates how TCM prevents and treats INRs through gut microbiota regulation.

7. Discussion

In the post-ART era, INRs represent a major challenge in AIDS management, with gut microbiota alterations playing a central role in their pathogenesis. Investigating the contribution of gut dysbiosis to INRs not only clarifies underlying mechanisms but also identifies novel therapeutic targets. Strategies such as probiotics, prebiotics, fecal microbiota transplantation, and microbiota-informed drug selection may promote immune reconstitution. TCM, characterized by multi-target actions and holistic

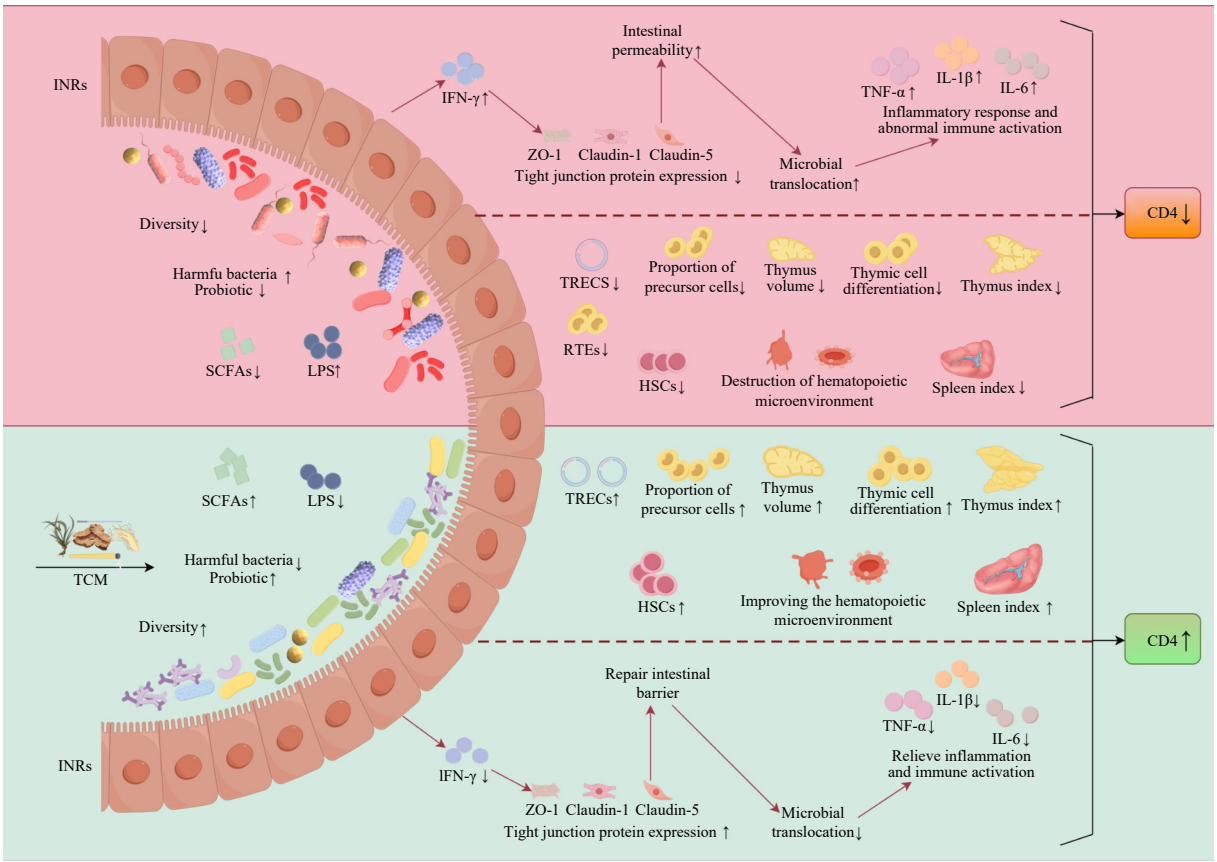

Fig. 3 Mechanisms by which TCM regulates gut microbiota to prevent and treat INRs. TCM increases the proportion of beneficial intestinal bacteria in INRs, reduces harmful species , enhances microbial diversity, elevates SCFA levels, and decreases LPS content. TCM lowers interferon (IFN)-γ levels, inhibits downregulation of tight junction proteins ZO-1, Claudin-1, and Claudin-5, thereby repairing intestinal mucosal barrier damage, reducing microbial translocation, and suppressing abnormal immune activation and inflammation. Additionally, TCM not only modulates gut microbiota structure but also increases T cell receptor excision circle (TREC) levels in immunocompromised individuals, enhances thymic mass, improves thymic differentiation, and raises thymic index. TCM also increases hematopoietic stem cell (HSC) proportions and improves splenic index, thereby enhancing the hematopoietic microenvironment. Through these mechanisms, TCM increases $CD4^+$ T cell counts, preventing and treating INRs, as illustrated by Figdraw.

regulation, offers unique advantages in enhancing immunity and alleviating clinical symptoms. According to TCM theory, immune function corresponds to "righteous Qi", and INRs reflect insufficiency of righteous Qi. HIV is viewed as a toxic exogenous pathogen, so TCM treatments often involve herbs that regulate Qi, clear heat, and detoxify. Increasing evidence confirms that TCM treats INRs by modulating gut microbiota. However, INRs symptoms are complex, and numerous confounding factors affect gut microbiota, resulting in most studies focusing on isolated microbial changes rather than mechanistic insights. Additionally, the chemical complexity and low bioavailability of TCM compounds complicate efforts to define precise mechanisms of action through single-target approaches.

Future research should employ systems biotechnology to characterize typical INRs symptoms and uncover their molecular links to gut microbiota. Establishing the efficacy of TCM interventions will enable monitoring of relevant biomarker dynamics. Advanced tools—including 16S rDNA sequencing, metagenomics, flow cytometry, and TCM extraction techniques—can identify specific microbial targets associated with TCM treatments. A report indicates that 47.17% of clinical studies in this field include fewer than 50 participants, and a meta-analysis found only 5 of 19 studies exceeded this threshold [7, 121]. Although $CD4^+$ cell count is the primary outcome in TCM trials for HIV, reported increases vary widely, secondary endpoints are inconsistently defined, and long-term prognostic indicators are underutilized [122]. Some clinical studies on TCM for INRs lack standardized randomization, blinding, or proper allocation concealment [7]. Overall, high-quality research remains scarce, plagued by small sample sizes, inconsistent evaluation criteria, and incomplete protocol design. Diagnostic and therapeutic strategies should be optimized based on current evidence, with priority given to large-scale, rigorous clinical trials. The only existing guideline—the *Expert Consensus on Integrated Traditional Chinese and Western Medicine Treatment of AIDS Immune Deficiency*—was issued in 2020 by the AIDS Prevention Branch of the Chinese Society of TCM. Future efforts should develop high-quality guidelines or expert consensus using evidence from literature, expert opinion, and clinical data. Progress is hindered by social stigma around HIV/AIDS, disparities in TCM research capacity, and insufficient clinical data sharing. To accelerate innovation, national platforms—including the National Clinical Research Base for TCM in AIDS, the TCM Inheritance and Innovation Center, and P3 Laboratories—should be leveraged to develop potent, low-toxicity TCM formulations [123].

The adverse effects of ART are well-documented, and evidence suggests ART may worsen gut microbiota imbalances in HIV/AIDS patients. Effective ART options are limited, and modifying regimens to reduce toxicity remains challenging. Current studies show that combining TCM with Western medicine does not introduce new adverse effects and may even alleviate some ART-related side effects [124]. However, TCM itself carries potential risks. Commonly used herbs such as *Tripterygium wilfordii* and *Artemisia annua* have been associated with hepatotoxicity, nephrotoxicity, neurotoxicity, and gastrointestinal discomfort [125-128]. Whether combining these herbs with ART exacerbates toxicity or introduces new adverse reactions requires further investigation. In 2003, a multicenter phase III trial of Tangcao Tablets was conducted at Beijing You'an Hospital, Ditan Hospital, and PLA 302 Hospital. The drug remains in use for INRs and has shown promising results [10, 129]. Given the slow pace of new AIDS drug develop-

ment, rigorous phase III trials are essential to ensure safety and efficacy before market approval, with careful risk-benefit assessment. Regulatory coordination and pharmaceutical accountability must be strengthened. Adverse reactions related to TCM should be recorded in the *International Dictionary of Medical Terms* (MedDRA) to support post-marketing surveillance. Rational herb compatibility can minimize toxicity; for example, licorice reduces the hepatotoxicity of *Tripterygium wilfordii* [130]. In clinical practice, physicians can use synergistic TCM combinations to mitigate side effects.

In summary, gut microbiota plays a pivotal role in INRs development, and TCM-based modulation of gut microbiota represents a promising strategy for prevention and treatment. Integrating TCM theory with modern mechanistic insights may provide scientific validation for these interventions. However, challenges remain—including unclear biological bases for TCM syndromes, inadequate diagnostic protocols, slow drug development, and safety concerns. Future progress depends on prioritizing both basic and clinical research, supported by national policies and funding initiatives, to improve outcomes for INRs.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82274474).

Supporting information

Supporting information for this work can be obtained by contacting the corresponding authors *via* E-mail.

Declaration of competing interest

These authors have no conflict of interest to declare.

References

1 Liu J, Ding C, Shi Y, et al. Advances in mechanism of HIV-1 immune reconstitution failure: understanding lymphocyte subpopulations and interventions for immunological nonresponders. *J Immunol*. 2024;212(11):1609-1620. https://doi.org/10.4049/JIMMUNOL.2300777.
2 Qian ZZ, Zhang YJ, Xie XL, et al. Efficacy and safety of traditional Chinese herbal medicine combined with HAART in the treatment of HIV/AIDS: a protocol for systematic review and meta-analysis. *Medicine*. 2021;100(52):e28287. https://doi.org/10.1097/MD.0000000000028287.
3 Zhao S, Li X, Wang Y, et al. Comparison of the immune enhancing activity and chemical constituents between imitation wild and cultivated Astragali Radix. *Molecules*. 2025;30(4):923. https://doi.org/10.3390/MOLECULES30040923.
4 Wu Z , Zhang W, Miao W, et al. The efficacy of Sijunzi on immune function in patients with gastrointestinal cancers after surgery: integrating systematic review and network pharmacology. *Medicine*. 2025;104(6):e41419. https://doi.org/10.1097/MD.0000000000041419.
5 Li XH, Li HY, Li CY, et al. Traditional Chinese medicine can improve the immune reconstruction of HIV/AIDS patients. *AIDS Res Human Retroviruses*. 2020;36(4):258-259. https://doi.org/10.1089/AID.2019.0274.
6 Li HM, Liu JZ. "Marrow" as the central therapeutic target. *J Chin Med Mater Res*. 2022;40(1):1-6. https://doi.org/10.13193/j.issn.1673-7717.2022.01.001.
7 Yang CL, Jin YT, Wu ZH, et al. Systematic review and meta-analysis of the clinical efficacy of traditional Chinese medicine in immune reconstitution failure in AIDS. *Chin J Integr Tradit West Med*. 2022;42(9):1072-1079. https://doi.org/10.7661/j.cjim.20211123.255.
8 Ke WJ, Chen Y, Lei ZE, et al. Investigation on improving immunologic reconstitution insufficiency using Diwu-Yanggan Capsules in AIDS patients. *Front Pharmacol*. 2024;15:1485719. https://doi.org/10.3389/FPHAR.2024.1485719.
9 Zhou SJ, Wang YL, Yuan HZ, et al. Efficacy of Shenling Baizhu Powder combined with antiretroviral therapy in the intervention of immune reconstitution failure with lung-spleen Qi deficiency syndrome in HIV/AIDS patients. *J Med Forum*. 2024;45(8):811-815. https://doi.org/10.20159/j.cnki.jmf.2024.08.006.
10 Song YB, Long H, Fu YH, et al. Observation on the efficacy of Tangcao Tablet in patients with immune reconstitution failure in AIDS. *Chin J Dermatovenerol*. 2024;38(3):298-302. https://doi.org/10.13735/j.cjdv.1001-7089.202304102.
11 Huang ZY, Zhu XH, Zou MY, et al. Application of Buzhong Yiqi Jiedu Decoction as an adjuvant to highly active antiretroviral therapy in AIDS patients with incomplete immune reconstitution. *J Harbin Med Univ*. 2022;56(4):373-377. https://doi.org/10.20010/j.issn.1000-1905.2022.04.0373.
12 Shi Y, Hu M, Wu J, et al. Association between gut microbiota in HIV-infected patients and immune reconstitution following antiretroviral therapy (ART). *BMC Infect Dis*. 2025;25(1):666. https://doi.org/10.1186/S12879-025-10995-3.
13 Liu ZB. Treating older patients with AIDS using traditional Chinese medicine combined with conventional Western medicine in China. *Aging Dis*. 2021;12(8):1872-1878. https://doi.org/10.14336/AD.2021.0925.
14 Liu YN, Liu ZB, Sang F, et al. Effects of Yi Aikang Capsule on intestinal flora and immune function in HIV/AIDS patients with immune reconstitution failure and lung-spleen Qi deficiency syndrome. *Chin J Tradit Chin Med*. 2022;37(5):2729-2733.
15 Lan YL, Zhang Y, Yang XY, et al. Observation and correlation analysis of the efficacy of traditional Chinese medicine in asymptomatic HIV-infected patients with deficiency constitution. *Chin J Pharmacol Clin Chin Mater Med*. 2024;40(4):15-21. https://doi.org/10.13412/j.cnki.zyyl.2024.04.006.
16 Yang Q, Yang XY, Peng X, et al. Effects of Jian Aikang Concentrated Pill combined with cART on gut and intestinal flora in HIV-infected patients. *Chin J AIDS STD*. 2024;30(4):354-360. https://doi.org/10.13419/j.cnki.aids.2024.04.04.
17 Xu QH, Wu X, Zheng HP, et al. Effects of artesunate on immune function and intestinal flora in HIV/AIDS patients with immune reconstitution failure after HAART. *Acta Chin Med Pharmacol*. 2022;50(12):54-59. https://doi.org/10.19664/j.cnki.1002-2392.220274.
18 Wu X. Clinical observation on the effect of traditional Chinese medicine in regulating intestinal flora to improve incomplete immune reconstitution in AIDS. *Chin Acad Tradit Chin Med*. 2021. https://doi.org/10.27658/d.cnki.gzzyy.2021.000109.
19 Gao GJ, Li X, Dong JP, et al. Effects of artesunate tablets on the intestinal bacterial community structure of male HIV/AIDS patients based on high-throughput sequencing analysis. *Chin J AIDS STD*. 2021;27(8):799-804. https://doi.org/10.13419/j.cnki.aids.2021.08.02.
20 Xu QH, Chen SY, Li YP, et al. Preliminary exploration of the effects of traditional Chinese medicine on intestinal flora in HIV/AIDS patients with immune reconstitution failure based on 16S rDNA. *Chin J AIDS STD*. 2020;26(11):1150-1153. https://doi.org/10.13419/j.cnki.aids.2020.11.02.
21 Yang Q, Su C, Qing Y, et al. Study on the effects of traditional Chinese medicine on gut microbiota structure and immunity in HIV patients. *Sichuan J Tradit Chin Med*. 2023;41(12):82-89. https://doi.org/10.3969/j.issn.1000-3649.2023.12.sczy202312023.
22 Gao GJ. Effects of moxibustion on immune function and intestinal flora diversity in 200 AIDS patients with incomplete immune reconstitution. *Chin Acad Tradit Chin Med*. 2022. https://doi.org/10.27658/d.cnki.gzzyy.2022.000111.
23 Ahluwalia B, Magnusson MK, Öhman L. Mucosal immune system of the gastrointestinal tract: maintaining balance between the good and the bad. *Scand J Gastroenterol*. 2017;52(11):1185-1193. https://doi.org/10.1080/00365521.2017.1349173.
24 Mao K, Baptista AP, Tamoutounour S, et al. Innate and adaptive lymphocytes sequentially shape the gut microbiota and lipid metabolism. *Nature*. 2018;554(7691):255-259. https://doi.org/10.1038/nature25437.
25 Chen J, Xu C, He Q, et al. *Tupistra chinensis* polysaccharides remitted intestinal inflammation induced by LPS *via* regulating gut microbiota. *3 Biotech*. 2025;15(11):378. https://doi.org/10.1007/S13205-025-04554-5.
26 Salami TA, Akpamu U, Echendu PN, et al. Crohn's colitis-induced alterations in colonic morphology, immunology, and microbiota are modulated by potassium bromate in experimental rats. *Adv Gut Microbi Res*. 2025;2025(1):3195642. https://doi.org/10.1155/AGM3/3195642.
27 Cavarelli M, Scarlatti G. HIV-1 infection: the role of the gastrointestinal tract. *Am J Reprod Immunol*. 2014;71(6):537-542. https://doi.org/10.1111/aji.12245.
28 Armstrong AJS, Shaffer M, Nusbacher NM, et al. An exploration of *Prevotella*-rich microbiomes in HIV and men who have sex with men. *Microbiome*. 2018;6(1):198. https://doi.org/10.1186/s40168-018-0580-7.
29 Lu D, Zhang JB, Wang YX, et al. Association between $CD4^{(+)}$ T cell counts and gut microbiota and serum cytokines levels in HIV-infected immunological non-responders. *BMC Infect Dis*. 2021;21(1):742. https://doi.org/10.1186/s12879-021-06491-z.
30 Dolo O, Coulibaly F, Somboro AM, et al. The human gut microbiome and its metabolic pathway dynamics before and during HIV antiretroviral therapy. *Microbiol Spectr*. 2025;13(8):e0220524. https://doi.org/10.1128/SPECTRUM.02205-24.
31 Liu YN, Li PY, Sang F, et al. Analysis of immune function and gut microbiota changes in HIV/AIDS patients with different immune levels after ART. *Chin J Dermatovenerol*. 2025;39(2):194-201. https://doi.org/10.13735/j.cjdv.1001-7089.202208207.
32 Supram SH, Indira B, Niranjan N, et al. Low rate of gut colonization by extended-spectrum *β*-lactamase producing *Enterobacteriaceae* in HIV infected persons as compared to healthy individuals in Nepal. *PLoS One*. 2019;14(2):e0212042. https://doi.org/10.1371/journal.pone.0212042.
33 Guo XY, Guo YT, Wang ZR, et al. Severe intestinal barrier damage in HIV-infected immunological non-responders. *Heliyon*. 2023;9(10):e20790. https://doi.org/10.1016/j.heliyon.2023.e20790.
34 Tincati C, Merlini E, Braidotti P, et al. Impaired gut junctional complexes feature late-treated individuals with suboptimal $CD4^{+}$ T-cell recovery upon virologically suppressive combination antiretroviral therapy. *AIDS*. 2016;30(7):991-1003. https://doi.org/10.1097/QAD.0000000000001015.
35 Somsouk M, Estes JD, Deleage C, et al. Gut epithelial barrier and systemic inflammation during chronic HIV infection. *AIDS*. 2015;29(1):43-51. https://doi.org/10.1097/QAD.0000000000000511.
36 Qing Y, Xie H, Su C, et al. Gut microbiome, short-chain fatty acids, and

mucosa injury in young adults with human immunodeficiency virus infection. *Dig Dis Sci*. 2019;64(7):1830-1843. https://doi.org/10.1007/s10620-018-5428-2.
37 Negi N, Singh R, Sharma A, et al. Comparative evaluation of microbial translocation products (LPS, sCD14, lgM Endocab) in HIV-1 infected Indian individuals. *Microb Pathog*. 2017;111:331-337. https://doi.org/10.1016/j.micpath.2017.08.004.
38 Tavenier J, Margolick JB, Leng SX. T-cell immunity against cytomegalovirus in HIV infection and aging: relationships with inflammation, immune activation, and frailty. *Med Microbiol Immunol*. 2019;208(3-4):289-294. https://doi.org/10.1007/s00430-019-00591-z.
39 Hunt PW, Martin JN, Sinclair E, et al. T cell activation is associated with lower CD4$^+$ T cell gains in human immunodeficiency virus-infected patients with sustained viral suppression during antiretroviral therapy. *J Infect Dis*. 2003;187(10):1534-1543. https://doi.org/10.1086/374786.
40 Shive CL, Freeman ML, Younes SA, et al. Markers of T cell exhaustion and senescence and their relationship to plasma TGF-β levels in treated HIV$^+$ immune non-responders. *Front Immunol*. 2021;12:638010. https://doi.org/10.3389/fimmu.2021.638010.
41 Massanella M, Negredo E, Pérez-Alvarez N, et al. CD4 T-cell hyperactivation and susceptibility to cell death determine poor CD4 T-cell recovery during suppressive HAART. *AIDS*. 2010;24(7):959-968. https://doi.org/10.1097/QAD.0b013e328337b957.
42 Zhen L, Ping Y, Rui W, et al. Persistent T cell proliferation and MDSCs expansion precede incomplete CD4$^+$ T cell recovery in people with acute HIV-1 infection with early ART. *Heliyon*. 2023;9(5):e15590. https://doi.org/10.1016/J.HELIYON.2023.E15590.
43 Dinh DM, Volpe GE, Duffalo C, et al. Intestinal microbiota, microbial translocation, and systemic inflammation in chronic HIV infection. *J Infect Dis*. 2015;211(1):19-27. https://doi.org/10.1093/infdis/jiu409.
44 Xu H, Ou Z, Zhou Y, et al. Intestinal mucosal microbiota composition of patients with acquired immune deficiency syndrome in Guangzhou, China. *Exp Ther Med*. 2021;21(4):391. https://doi.org/10.3892/etm.2021.9822.
45 Rocafort M, Noguera-Julian M, Rivera J, et al. Evolution of the gut microbiome following acute HIV-1 infection. *Microbiome*. 2019;7(1):73. https://doi.org/10.1186/s40168-019-0687-5.
46 Pither MD, Silipo A, Molinaro A, et al. Extraction, purification, and chemical degradation of LPS from gut microbiota strains. *Methods Mol Biol*. 2023;2613:153-179. https://doi.org/10.1007/978-1-0716-2910-9_13.
47 Tincati C, Douek DC, Marchetti G. Gut barrier structure, mucosal immunity and intestinal microbiota in the pathogenesis and treatment of HIV infection. *AIDS Res Ther*. 2016;13:19. https://doi.org/10.1186/s12981-016-0103-1.
48 Ciesielska A, Matyjek M, Kwiatkowska K. TLR4 and CD14 trafficking and its influence on LPS-induced pro-inflammatory signaling. *Cell Mol Life Sci*. 2021;78(4):1233-1261. https://doi.org/10.1007/s00018-020-03656-y.
49 Larsen JM. The immune response to *Prevotella* bacteria in chronic inflammatory disease. *Immunology*. 2017;151(4):363-374. https://doi.org/10.1111/imm.12760.
50 Colorado BSA, Lazzaro A, Neff PC, et al. Differential effects of antiretroviral treatment on immunity and gut microbiome composition in people living with HIV in rural versus urban Zimbabwe. *Microbiome*. 2024;12(1):18. https://doi.org/10.1186/S40168-023-01718-4.
51 Russo E, Nannini G, Sterrantino G, et al. Effects of viremia and CD4 recovery on gut "microbiome-immunity" axis in treatment-naïve HIV-1-infected patients undergoing antiretroviral therapy. *World J Gastroenterol*. 2022;28(6):635-652. https://doi.org/10.3748/wjg.v28.i6.635.
52 Stiksrud B, Lorvik KB, Kvale D, et al. Plasma IP-10 is increased in immunological non-responders and associated with activated regulatory T cells and persisting low CD4 counts. *J Acquir Immune Defic Syndr*. 2016;73(2):138-148. https://doi.org/10.1097/QAI.0000000000001080.
53 Quiros M, Nishio H, Neumann PA, et al. Macrophage-derived IL-10 mediates mucosal repair by epithelial WISP-1 signaling. *J Clin Invest*. 2017;127(9):3510-3520. https://doi.org/10.1172/JCI90229.
54 Georgia AN, Claudine NE, Carole SN, et al. Regulatory T cells modulate monocyte functions in immunocompetent antiretroviral therapy-naïve HIV-1 infected people. *BMC Immunol*. 2024;25(1):68. https://doi.org/10.1186/s12865-024-00654-8.
55 Agraib LM, Yamani MI, Rayyan YM, et al. The probiotic supplementation role in improving the immune system among people with ulcerative colitis: a narrative review. *Drug Metab Pers Ther*. 2021;37(1):7-19. https://doi.org/10.1515/DMDI-2021-0150.
56 Supriya R, Suneela D. Role of prebiotics, probiotics, and synbiotics in management of inflammatory bowel disease: current perspectives. *World J Gastroenterol*. 2023;29(14):2078-2100. https://doi.org/10.3748/WJG.V29.I14.2078.
57 Geng ST, Zhang JB, Wang YX, et al. Pre-digested protein enteral nutritional supplementation enhances recovery of CD4$^{(+)}$ T cells and repair of intestinal barrier in HIV-infected immunological non-responders. *Front Immunol*. 2021;12:757935. https://doi.org/10.3389/fimmu.2021.757935.
58 Xia C, Zhang X, Harypursat V, et al. The role of pyroptosis in incomplete immune reconstitution among people living with HIV: potential therapeutic targets. *Pharmacol Res*. 2023;197:106969. https://doi.org/10.1016/j.phrs.2023.106969.
59 Bandera A, Masetti M, Fabbiani M, et al. The NLRP3 inflammasome is upregulated in HIV-infected antiretroviral therapy-treated individuals with defective immune recovery. *Front Immunol*. 2018;9:214. https://doi.org/10.3389/fimmu.2018.00214.
60 Lao X, Mei X, Zou J, et al. Pyroptosis associated with immune reconstruction failure in HIV-1-infected patients receiving antiretroviral therapy: a cross-sectional study. *BMC Infect Dis*. 2022;22(1):867. https://doi.org/10.1186/s12879-022-07818-0.
61 Carvalho-Silva WHV, Andrade-Santos JL, Souto FO, et al. Immunological recovery failure in cART-treated HIV-positive patients is associated with reduced thymic output and RTE CD4$^+$ T cell death by pyroptosis. *J Leukoc Biol*. 2020;107(1):85-94. https://doi.org/10.1002/JLB.4A0919-235R.
62 Doitsh G, Galloway NL, Geng X, et al. Cell death by pyroptosis drives CD4 T-cell depletion in HIV-1 infection. *Nature*. 2014;505(7484):509-514. https://doi.org/10.1038/nature12940.
63 Dong T, Huang D, Jin Z. Mechanism of sodium butyrate, a metabolite of gut microbiota, regulating cardiac fibroblast transdifferentiation *via* the NLRP3/Caspase-1 pyroptosis pathway. *J Cardiothorac Surg*. 2024;19(1):208. https://doi.org/10.1186/s13019-024-02692-0.
64 Sharma D, Kanneganti TD. The cell biology of inflammasomes: mechanisms of inflammasome activation and regulation. *J Cell Biol*. 2016;213(6):617-629. https://doi.org/10.1083/jcb.201602089.
65 Zhou CB, Fang JY. The role of pyroptosis in gastrointestinal cancer and immune responses to intestinal microbial infection. *Biochim Biophys Acta Rev Cancer*. 2019;1872(1):1-10. https://doi.org/10.1016/j.bbcan.2019.05.001.
66 Liu D, Tian Q, Liu K, et al. Ginsenoside Rg3 ameliorates DSS-induced colitis by inhibiting NLRP3 inflammasome activation and regulating microbial homeostasis. *J Agric Food Chem*. 2023 Online ahead of print. https://doi.org/10.1021/acs.jafc.2c07766.
67 Sauce D, Larsen M, Fastenackels S, et al. HIV disease progression despite suppression of viral replication is associated with exhaustion of lymphopoiesis. *Blood*. 2011;117(19):5142-5151. https://doi.org/10.1182/blood-2011-01-331306.
68 Nixon CC, Vatakis DN, Reichelderfer SN, et al. HIV-1 infection of hematopoietic progenitor cells *in vivo* in humanized mice. *Blood*. 2013;122(13):2195-2204. https://doi.org/10.1182/blood-2013-04-496950.
69 Tsukamoto T. HIV impacts CD34$^{(+)}$ progenitors involved in T-cell differentiation during coculture with mouse stromal OP9-DL1 cells. *Front Immunol*. 2019;10:81. https://doi.org/10.3389/fimmu.2019.00081.
70 Menkova-Garnier I, Hocini H, Foucat E, et al. P2X7 receptor inhibition improves CD34 T-cell differentiation in HIV-infected immunological nonresponders on c-ART. *PLoS Pathog*. 2016;12(4):e1005571. https://doi.org/10.1371/journal.ppat.1005571.
71 Wang SS, Cai JY, Shi AW, et al. Effects of intestinal microbial homeostasis on the hematopoietic system in a neonatal rat model of necrotizing enterocolitis. *Chin J Contemp Pediatr*. 2023;25(8):855-863. https://doi.org/10.7499/j.issn.1008-8830.2301082.
72 Elgarten CW, Tanes C, Lee JJ, et al. Early stool microbiome and metabolome signatures in pediatric patients undergoing allogeneic hematopoietic cell transplantation. *Pediatr Blood Cancer*. 2022;69(1):e29384. https://doi.org/10.1002/pbc.29384.
73 Bansal R, Park H, Taborda CC, et al. Antibiotic exposure, not alloreactivity, is the major driver of microbiome changes in hematopoietic cell transplantation. *Transpl Cell Ther*. 2022;28(3):135-143. https://doi.org/10.1016/j.jtct.2021.12.015.
74 Chen C, Wang J, Xun J, et al. Role of thymosin α1 in restoring immune response in immunological nonresponders living with HIV. *BMC infectious diseases*. 2024;24(1):97. https://doi.org/10.1186/S12879-024-08985-Y.
75 Rosado-Sánchez I, Herrero-Fernández I, Genebat M, et al. Thymic function impacts the peripheral CD4/CD8 ratio of HIV-infected subjects. *Clin Infect Dis*. 2017;64(2):152-158. https://doi.org/10.1093/cid/ciw711.
76 Guedes SCM, Silva CVHW, Santos ALJ, et al. HIV-induced thymic insufficiency and aging-related immunosenescence on immune reconstitution in ART-treated patients. *Vaccines*. 2024;12(6):612. https://doi.org/10.3390/VACCINES12060612.
77 Ferrando-Martinez S, De Pablo-Bernal RS, De Luna-Romero M, et al. Thymic function failure is associated with human immunodeficiency virus disease progression. *Clin Infect Dis*. 2017;64(9):1191-1197. https://doi.org/10.1093/cid/cix095.
78 RB-Silva R, Nobrega C, Azevedo C, et al. Thymic function as a predictor of immune recovery in chronically HIV-infected patients initiating antiretroviral therapy. *Front Immunol*. 2019;10:25. https://doi.org/10.3389/fimmu.2019.00025.
79 Briceño O, Chávez-Torres M, Peralta-Prado A, et al. Associations between recent thymic emigrants and CD4$^+$ T-cell recovery after short-term antiretroviral therapy initiation. *AIDS*. 2020;34(4):501-511. https://doi.org/10.1097/QAD.0000000000002458.
80 Menglin C, Hong Y, Huizi T, et al. Impact of *Bifidobacterium longum* NSP001 on DSS-induced colitis in conventional and humanised mice. *Food Sci Hum Wellness*. 2023;12(4):1109-1118. https://doi.org/10.1016/J.FSHW.2022.10.028.
81 Hebbandi NR, Sokke UC, Geuking MB. The impact of the gut microbiota on T cell ontogeny in the thymus. *Cell Mol Life Sci*. 2022;79(4):221. https://doi.org/10.1007/s00018-022-04252-y.
82 Zegarra-Ruiz DF, Kim DV, Norwood K, et al. Thymic development of gut-microbiota-specific T cells. *Nature*. 2021;594(7863):413-417. https://doi.org/10.1038/s41586-021-03531-1.
83 Alexis Y, Mboumba RB, Petronela A, et al. Immuno-metabolic control of the balance between Th17-polarized and regulatory T-cells during HIV infection. *Cytokine Growth Factor Rev*. 2023;69:1-13. https://doi.org/10.1016/J.CYTOGFR.2023.01.001.
84 Guo YT, Guo XY, Fan LN, et al. The imbalance between intestinal Th17 and Treg cells is associated with an incomplete immune reconstitution during long-term antiretroviral therapy in patients with HIV. *Viral Immunol*. 2023;36(5):331-342. https://doi.org/10.1089/VIM.2023.0017.
85 Li D, Tao H, Tan X, et al. Gut microbiota and their metabolites ameliorate acute and chronic colitis in mice *via* modulating Th17/Treg balance. *Front Microbiol*. 2025;16:1643209. https://doi.org/10.3389/FMICB.2025.1643209.

86 Azzam S, Schlatzer D, Maxwell S, et al. Proteome and protein network analyses of memory T cells find altered translation and cell stress signaling in treated human immunodeficiency virus patients exhibiting poor CD4 recovery. *Open Forum Infect Dis*. 2016;3(2):ofw037. https://doi.org/10.1093/ofid/ofw037.

87 Zhenwu L, Zhen L, Lisa M, et al. Increased natural killer cell activation in HIV-infected immunologic non-responders correlates with $CD4^+$ T cell recovery after antiretroviral therapy and viral suppression. *PLoS One*. 2017;12(1):e0167640. https://doi.org/10.1371/journal.pone.0167640.

88 Ha B, Cao X. Gut microbiota-specific T cell subset drives CNS inflammation. *Trends Immunol*. 2025;S1471-4906(25):200-205. https://doi.org/10.1016/J.IT.2025.08.002.

89 Ma Z, Wang Z, Cao J, et al. Regulatory roles of intestinal $CD4^+$ T cells in inflammation and their modulation by the intestinal microbiota. *Gut Microbes*. 2025;17(1):2560019. https://doi.org/10.1080/19490976.2025.2560019.

90 Zhen JH, Li YN, Zhang YN, et al. Shaoyao Decoction reduced T lymphocyte activation by regulating of intestinal flora and 5-hydroxytryptamine metabolism in ulcerative colitis. *Chin Med*. 2024;19(1):87. https://doi.org/10.1186/S13020-024-00958-2.

91 Chen F, Yin YT, Zhan HM, et al. Sishen Pill treatment of DSS-induced colitis *via* regulating interaction with inflammatory dendritic cells and gut microbiota. *Front Physiol*. 2020;11:801. https://doi.org/10.3389/fphys.2020.00801.

92 Zhang LX, Song JW, Zhang C, et al. Dynamics of HIV reservoir decay and naïve CD4 T-cell recovery between immune non-responders and complete responders on long-term antiretroviral treatment. *Clin Immunol*. 2021;229:108773. https://doi.org/10.1016/j.clim.2021.108773.

93 Zhang GH, Han JB, Zhu L, et al. Aikeqing decreases viral loads in SHIV89.6-infected Chinese rhesus macaques. *Chin Med*. 2016;11:31. https://doi.org/10.1186/s13020-016-0105-x.

94 Wei QL, Huang ZX, Wei L, et al. Observation of the efficacy of early combination of traditional Chinese medicine intervention with antiretroviral therapy in AIDS patients. *Chin J AIDS STD*. 2016;22(3):207-208. https://doi.org/10.13419/j.cnki.aids.2016.03.18.

95 Sun XB, Xie ZP, Wu Z, et al. Mechanisms of HIV-immunologic non-responses and research trends based on gut microbiota. *Front Immunol*. 2024;15:1378431. https://doi.org/10.3389/fimmu.2024.1378431.

96 Gou H, Su H, Liu D, et al. Traditional medicine Pien Tze Huang suppresses colorectal tumorigenesis through restoring gut microbiota and metabolites. *Gastroenterology*. 2023;165(6):1404-1419. https://doi.org/10.1053/j.gastro.2023.08.052.

97 Zhou M, Liu Z, Shang Y. Study on the effect of traditional Chinese medicine regulating intestinal microecology on AIDS prevention and treatment. *J Contemp Med Pract*. 2025;7(4):33-37. https://doi.org/10.53469/JCMP.2025.07(04).08.

98 Gu W, Sun MJ, Wang LR, et al. Effects of four common Chinese medicinal herbs on immune function and intestinal flora in immunosuppressed mice. *Chin Anim Husb Vet Med*. 2019;46(1):147-156. https://doi.org/10.16431/j.cnki.1671-7236.2019.01.017.

99 Ma C. Exploration of prescription rules in traditional Chinese medicine for treating HIV/AIDS immunological non-responders based on data mining and clinical research on Shenling Guben Formula. *Chin Acad Tradit Chin Med*. 2023. https://doi.org/10.27658/d.cnki.gzzyy.2023.000026.

100 Tao Z, Dong JP, Guo HJ, et al. Effects of artesunate tablets on immune reconstruction failure in HIV/AIDS patients after ART. *Chin J AIDS STD*. 2021;27(9):921-925. https://doi.org/10.13419/j.cnki.aids.2021.09.03.

101 Yu HC, Meng YY, Wang EK, et al. Mechanism of Buzhong Yiqi Decoction in improving spleen deficiency syndrome through gut microbiota regulation. *Chin J Chin Mater Med*. 2024;49(4):1028-1043. https://doi.org/10.19540/j.cnki.cjcmm.20231013.701.

102 Ding X, Fan L, Xu L, et al. Clinical applications and therapeutic mechanisms of Chinese herbal medicine Yi Aikang Capsules in treating acquired immune deficiency syndrome. *Infect Drug Resist*. 2025;18:3317-3327. https://doi.org/10.2147/IDR.S526449.

103 Zhao ML, Wang Q, Liu BB, et al. Experimental study on Yi Aikang combined with antiretroviral therapy in the treatment of SIV-infected rhesus macaque AIDS models. *Liaoning J Tradit Chin Med*. 2023;50(3):193-199. https://doi.org/10.13192/j.issn.1000-1719.2023.03.054.

104 Yang YQ, Fang L, He ZZ, et al. Preliminary study on the effect of traditional Chinese medicine intervention on serum diamine oxidase and lipopolysaccharide in HIV-infected individuals. *Yunnan J Tradit Chin Med Mater Med*. 2014;35(4):10-11. https://doi.org/10.16254/j.cnki.53-1120/r.2014.04.040.

105 Mohamed A, Zungu Y, Shalekoff S, et al. Innate immune dysfunction and persistent activation in South African HIV elite controllers. *Front Immunol*. 2025;16:1603436. https://doi.org/10.3389/FIMMU.2025.1603436.

106 Meng P, Zhang G, Ma X, et al. Traditional Chinese medicine (Xielikang) reduces diarrhea symptoms in acquired immune deficiency syndrome (AIDS) patients by regulating the intestinal microbiota. *Front Microbiol*. 2024;15:1346955. https://doi.org/10.3389/FMICB.2024.1346955.

107 Sang F, Li Q, Qian JY, et al. Protective effects of Yi Aikang Capsule on intestinal mucosal barrier injury in HIV/AIDS by affecting permeability and tight junctions. *Chin J Emerg Tradit Chin Med*. 2018;27(5):769-772. https://doi.org/10.3969/j.issn.1004-745X.2018.05.005.

108 Yao JY, Deng BW, Li CC, et al. Effects of Yi Aikang Capsule on tight junctions and related proteins Claudin-1 and Claudin-5 in intestinal mucosal barrier injury induced by IFN-γ. *Chin J Hosp Pharm*. 2020;40(8):897-901. https://doi.org/10.13286/j.1001-5213.2020.08.12.

109 Jia M, Yuan M, Zhu X, et al. Evidence of honey-processed Astragalus polysaccharides improving intestinal immune function in spleen Qi deficiency mice integrated with microbiomics and metabolomics analysis. *J Sci Food Agric*. 2024;105(4):2158-2168. https://doi.org/10.1002/JSFA.13986.

110 Sung H, Kang MS, Lee SM, et al. Korean red ginseng slows depletion of CD4 T cells in human immunodeficiency virus type 1-infected patients. *Clin Diagn Lab Immunol*. 2005;12(4):497-501. https://doi.org/10.1128/CDLI.12.4.497-501.2005.

111 Zhang YX, Saeid K, Han SY, et al. Ginseng extracts improve circadian clock gene expression and reduce inflammation directly and indirectly through gut microbiota and PI3K signaling pathway. *NPJ Biofilms Microbiomes*. 2024;10(1):24. https://doi.org/10.1038/S41522-024-00498-5.

112 Yuan H, Xu G, Liu J, et al. *Astragalus mongholicus* polysaccharides alleviate insulin resistance through modulation of PI3K/AKT, TLR4/NF-κB signaling pathway and microbiota in rats with Type 2 diabetes mellitus. *J Tradit Complement Med*. 2024;15(3):274-285. https://doi.org/10.1016/J.JTCME.2024.05.007.

113 Zhu HB, Chen S, Chen YY, et al. Effects of the traditional Chinese medicine compound extract HNA-1 on thymic output function in chronically SIV-infected Chinese rhesus monkeys. *Chin J Integr Tradit West Med*. 2016;36(3):351-358. https://doi.org/10.7661/CJIM.2016.03.0351.

114 Wang XM, Chen S, Chen YY, et al. Effects of the traditional Chinese medicine compound extract HNA-1 on thymic output and thymocyte development in chronically SIV-infected rhesus monkeys. *J Hunan Univ Tradit Chin Med*. 2016;36(4):6-10. https://doi.org/10.3969/j.issn.1674-070X.2016.04.002.

115 Yang L, Fang Z, Zhu J, et al. The potential of Sijunzi Decoction in the fight against gastrointestinal disorders: a review. *Front Pharmacol*. 2025;16:1464498. https://doi.org/10.3389/FPHAR.2025.1464498.

116 Zhang QQ, Meng JL, Guo HJ. Clinical observation on treating 67 cases of HIV /AIDS from the spleen perspective. *J Henan Univ Tradit Chin Med*. 2007;3:1-2. https://doi.org/10.16368/j.issn.1674-8999.2007.03.002.

117 Chen W, Xu XK, Lyu YH, et al. Research advances in chemical constituents of Danggui Buxue Decoction and its hematopoietic function. *J Navy Med Univ*. 2023;44(5):609-615. https://doi.org/10.16781/j.cn31-2187/r.20220003.

118 Cao ZH, Pan JH, Li N, et al. Research progress on the modern pharmacological effects and mechanisms of Shengmai Powder. *Chin J Exp Tradit Med Formulae*. 2019;25(22):212-218. https://doi.org/10.13422/j.cnki.syfjx.20192208.

119 Wei Z, Xu LR. Effects of Yi Aikang Capsule on immune function in immunodeficient mice induced by murine leukemia virus. *Chin J Gerontol*. 2015;35(10):2615-2617. https://doi.org/10.3969/j.issn.1005-9202.2015.10.008.

120 Yang QQ. Effects of Tangcao Tablet on zidovudine-induced bone marrow suppression in mice. *Zhengzhou Univ*. 2020. https://doi.org/10.27466/d.cnki.gzzdu.2020.003935.

121 Lou YF, Cai SX, Hu XN, et al. Analysis of clinical research evidence on traditional Chinese medicine for immune reconstruction failure in AIDS. *Chin J AIDS STD*. 2024;30(3):253-258. https://doi.org/10.13419/j.cnki.aids.2024.03.06.

122 Zhang XX, Hu XN, Luo LL, et al. Analysis of outcome indicators in randomized controlled trials of traditional Chinese medicine for the treatment of HIV/AIDS. *Chin J AIDS STD*. 2024;30(6):584-590. https://doi.org/10.13419/j.cnki.aids.2024.06.05.

123 Gong YF, Liu ZB. Focusing on clinical intervention studies of traditional Chinese medicine in AIDS. *Chin J Dermatovenerol*. 2022;36(8):865-871. https://doi.org/10.13735/j.cjdv.1001-7089.202111080.

124 Wang J, Zou W. Practices, challenges, and opportunities: HIV/AIDS treatment with traditional Chinese medicine in China. *Front Med*. 2011;5(2):123-126. https://doi.org/10.1007/s11684-011-0124-z.

125 Xie LJ, Zhao YW, Duan JY, et al. Integrated proteomics and metabolomics reveal the mechanism of nephrotoxicity induced by triptolide. *Chem Res Toxicol*. 2020;33(7):1897-1906. https://doi.org/10.1021/acs.chemrestox.0c00091.

126 Zhang Q, Li Y, Liu M, et al. Compatibility with *Panax notoginseng* and *Rehmannia glutinosa* alleviates the hepatotoxicity and nephrotoxicity of *Tripterygium wilfordii via* modulating the pharmacokinetics of triptolide. *Int J Mol Sci*. 2018;19(1):305. https://doi.org/10.3390/ijms19010305.

127 Kong LL, Zhuang XM, Yang HY, et al. Inhibition of P-glycoprotein gene expression and function enhances triptolide-induced hepatotoxicity in mice. *Sci Rep*. 2015;5:11747. https://doi.org/10.1038/srep11747.

128 Thio J, Haig A, Swe PPE, et al. Artemisinin-induced cholestatic liver injury and intrahepatic ductopenia. *Oxf Med Case Rep*. 2024;2024(7):omae070. https://doi.org/10.1093/OMCR/OMAE070.

129 Shao BP, Yang LY, Li Q, et al. A decade of application review for Tangcao Tablet, an adjuvant therapy drug for AIDS. *Chin J AIDS STD*. 2017;23(10):978-979. https://doi.org/10.13419/j.cnki.aids.2017.10.31.

130 Yang YF, Fu XT, Xia B, et al. Glycyrrhizic acid glycosides reduces extensive tripterygium glycosides-induced lipid deposition in hepatocytes. *Heliyon*. 2023;9(7):e17891. https://doi.org/10.1016/J.HELIYON.2023.E17891.