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Incomplete Immune Reconstitution and Traditional Chinese Medicine in Patients with HIV/AIDS: Challenges and Perspectives

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Abstract: Antiretroviral therapy can reduce human immunodeficiency virus (HIV) load to undetectable levels and restore CD4+ T cells to rebuild immune function in patients with HIV. However, some patients fail to achieve immune reconstitution despite treatment. Traditional Chinese medicine is an important branch of complementary and alternative medicine for the treatment of HIV infection, and a growing number of studies has demonstrated that traditional Chinese medicine can increase CD4+ T cell counts in patients, thereby promoting immune reconstitution, ameliorating symptoms and signs, and improving quality of life. Here, we review pathogenesis in immunological non-responders and research into their treatment with traditional Chinese medicine. Furthermore, we summarize potential future research directions, including elucidation of how traditional Chinese medicine can regulate CD4+ T cells to reduce opportunistic infections and improve quality of life in immunological non-responders.

Keywords: immunological non-responders, drug mechanism, traditional Chinese medicine, future research directions

Introduction

Despite the introduction of effective antiretroviral therapy (ART), which successfully controls human immunodeficiency virus (HIV) replication, 10–40% of people living with HIV (PLWH) fail to recover their CD4+ T lymphocyte counts. Those who experience this incomplete immune reconstitution are termed "immunological non-responders" or "immune non-responders" (INR).[1,2] Low levels of CD4+ T cell recovery after ART are significantly associated with the occurrence of non-AIDS-related events.[3] INR have an elevated risk of non-AIDS-related morbidity and mortality compared with PLWH who achieve complete immune reconstitution.[4]

Traditional Chinese medicine (TCM), which typically utilizes plants with complex components in specific proportions and dosages, is often used to treat infectious diseases. Tu Youyou isolated artemisinin from *Artemisia annua* L., which effectively suppressed the spread of malaria. The ability of TCM to effectively improve CD4+ T cell counts with surprisingly long-term effects when used as a means to treat AIDS—known as "Yi Du" in TCM—is garnering increasing attention.

Numerous single herbs and TCM formulae capable of enhancing CD4+ T cell numbers and immunological function have been listed in medical texts.[5] Multi-target treatment with TCM can effectively improve the effect of ART. A body of clinical data supports the increasing use of TCM in the treatment of INR.[6] However, the main challenges to expanding its use are the needs to further improve the efficacy of TCM for the treatment of INR and to understand the mechanisms of action. We will discuss the advantages of integrating TCM and ART to gain in-depth understanding of the mechanisms of TCM in immune restoration and the prevention of acquired immunodeficiency syndrome (AIDS)-related events.

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Potential Mechanism Underlying Incomplete Immune Reconstitution

The underlying mechanisms for incomplete immune recovery in INR are complex and may be multifactorial—changes in the bone marrow (BM) microenvironment, decreased thymic output, disturbed cytokine secretion, aberrant immune activation, residual viral replication, gut damage and associated microbial translocation, and specific genetic or metabolic characteristics can all lead to abnormal CD4+ T cell numbers and function in patients with AIDS.[7–10] The low CD4+ T cell counts in INR appear to be mainly caused by an imbalance in the production and destruction of CD4+ T cells, such that damaged CD4+ T cells cannot be effectively replenished.[11]

BM Microenvironment

CD4+ T cells are derived from hematopoietic cells in the BM, and both multilineage and lineage-restricted hematopoietic progenitors are decreased in the BM after HIV infection, leading to a decrease in the number of CD4+ T cells.[12–14] HIV-infected BM cannot provide the optimal milieu for the growth of hematopoietic colonies. Moreover, infected BM secretes TNF-α, which induces apoptosis through the Fas ligand–FAS receptor pathway in the BM and inhibits hematopoiesis.[15] BM cells in INR secrete high levels of TNF-α and show significant upregulation of Fas ligand and the receptor Fas. In addition, the interstitial layer of the BM of INR shows abnormal morphological features similar to those observed in BM obtained from PLWH without ART.[16,17] INR widely lack colony formation by BM cells and display altered early lymphoid progenitors at the level of BM CD34+ precursors; these mechanisms may explain the cause of CD4+ T cell lymphopenia in INR.[17]

Thymic Output

The thymus is responsible for T cell development, including the production of CD4+ T cells, and thymic development is a primary mechanism of CD4+ T cell reconstitution.[18] Evaluation of the ability of the thymus to export mature T lymphocytes often involves the quantification of T cell receptor excision circles in cells referred to as recent thymic emigrants (RTE).[19] The thymus is most active in early life, and its function and thymogenic activity are limited in adulthood.[20] However, when an individual is infected with HIV-1, the thymus is reactivated and releases RTEs to replenish CD4+ T cell counts.[21] Previous studies have shown that INR exhibit lower levels of RTEs than immunological responders, and a lower proportion of RTEs among CD4+ T cells, which indicates that thymic output is significantly lower in INR.[22] This decrease in thymic activity is critical for maintaining the immunosuppressed state.[23]

Cytokine Disorders

Cytokines—especially the common gamma chain cytokines, including interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, and IL-21—are important players in immune reconstruction. In particular, IL-2 and IL-7 contribute to T cell recovery owing to their abilities to reverse HIV-1-specific CD4+ T cell anergy and activate resting CD4+ T cells; their loss is associated with the progressive depletion of CD4+ T cells.[24,25] Most IL-2 is produced by activated T cells, specifically CD4+ cells, and it acts on these cells in an autocrine or paracrine manner.[26] A central component of T cell homeostasis is signaling through the IL-7 receptor a chain (IL-7Rα, CD127).[27] Loss of expression of the IL-7Rα chain on CD4+ T cells has been associated with a decrease in CD4+ T cell count.[28] T helper 17 (Th17) cells secrete IL-17; they are preferentially targeted by HIV-1 infection, and Th17 cell depletion is associated with disease progression.[29] Therefore, cytokine disorders are not conducive to the recovery of immune function in INR.

Pyroptosis

Pyroptotic cells secrete their intracellular contents and pro-inflammatory cytokines, including IL-1β and IL-18.[30] During HIV infection, pyroptosis enhances the host's ability to rapidly eradicate infection and inhibit HIV replication through the production of pro-inflammatory cytokines and endogenous danger signals. However, programmed cell death caused by HIV-induced inflammatory responses leads to the massive loss of CD4+ T cells, which may promote and sustain immunological non-responsiveness.[31] The gp120 receptor, the only viral protein exposed on the surface of HIV, binds to CD4 on the surface of host cells, promotes the expression

of Fas by CD4+ cells, and increases intracellular Ca^{2+}, leading to cell apoptosis.[32,33] Thus, pyroptosis may play a key role in the inability of the immune systems of INR to mount a protective response to HIV and associated therapies.

Immune Activation

During HIV-1 infection, persistent immune activation commonly occurs in INR, stimulated by the virus and non-AIDS-related events, which causes CD4+ T cell depletion.[34] Driving factors for HIV-related immune activation include the persistence of HIV reservoirs, intestinal microbial translocation, depletion of regulatory T (Treg) cells, and coinfection with other viruses.[34] Conversely, immune overactivation can maintain virus reservoirs, accelerate the depletion of Treg cells, aggravate mucosal barrier damage, and decrease CD4+ T cell numbers.[35] Overactivation of T cells, which is associated with decreases in CD4+ T cell counts, is an important mechanism of action in INR.

Intestinal Barrier and Microbiota

The intestinal lamina propria is the main site of HIV infection and replication. HIV replication through the intestinal barrier leads to intestinal flora disturbance and induces intestinal mucosal CD4+ T cell apoptosis.[36,37] Depletion of CD4+ T cells decreases the numbers of important Treg cells in the intestinal mucosa, resulting in mucosal immune and functional deficits, thereby accelerating the progression of HIV.[38] INR exhibit lower CD4+ T cell counts, and more severe intestinal epithelial cell damage and tight junction protein changes, than immunological responders, indicating more severe intestinal damage and mucosal immune deficiency.[39] The gut microbiota is critical for maintaining immune homeostasis, and HIV infection can cause significant changes in the gut microbiota.[40,41] Studies have demonstrated significant differences in the gut microbiota of INR and responders, with the families Succinivibrionaceae and Erysipelotrichaceae (known for their protective effects against intestinal inflammation) significantly enriched in responders, but not detected in INR.[42] Therefore, it is particularly important to study the association between intestinal immune barrier function and microbial imbalance in INR.

Th17 and Treg Cells

T lymphocytes can differentiate into various lineages, including Treg and Th17 cells, which mediate inflammation and immune tolerance. Treg cell numbers in INR negatively correlate with Naive CD4+T cells compared with those in responders.[43] A balance between Th17 and Treg cells is necessary to facilitate protection against pathogens while maintaining immune stability.[44] An obvious imbalance between Th17 and Treg cells is observed in the peripheral blood and intestinal mucosa during HIV infection, which is related to the progression of AIDS.[45] Studies have reported that the Th17:Treg ratio is significantly lower in patients with low CD4+ T lymphocyte counts and lower still in INR.[46] Therefore, maintaining or reinstating the Th17:Treg ratio may be an important strategy for successful immune reconstruction.

TCM and INR

Since INR is unneglected group associated with increased morbidity and mortality due to immunodeficiency and immune activation. TCM has the effect of multi-target and bidirectional regulation, which can promote the immune reconstitution of INR.

Mechanism of TCM in INR

The pathogenesis of INR is complex, and individual patients have different pathogenesis, so the therapy should be individualized according to different pathogenesis. We explain the various mechanisms of Chinese herbal medicines in treating INR and provide a reference for the advancement of TCM in treating INR (Figure 1).

Reduced the T Cell Activation, Pyroptosis and Promote Immune Reconstruction

INR is unable to achieve adequate immunologic recovery, in which immune activation plays a crucial role. Continuous immune activation affects the proliferation of CD4+T cells and accelerates cell proptosis. The current study results confirmed that TCM can reduce the T cell activation and proptosis, promote the recovery of CD4 + T cells and immune function in INR

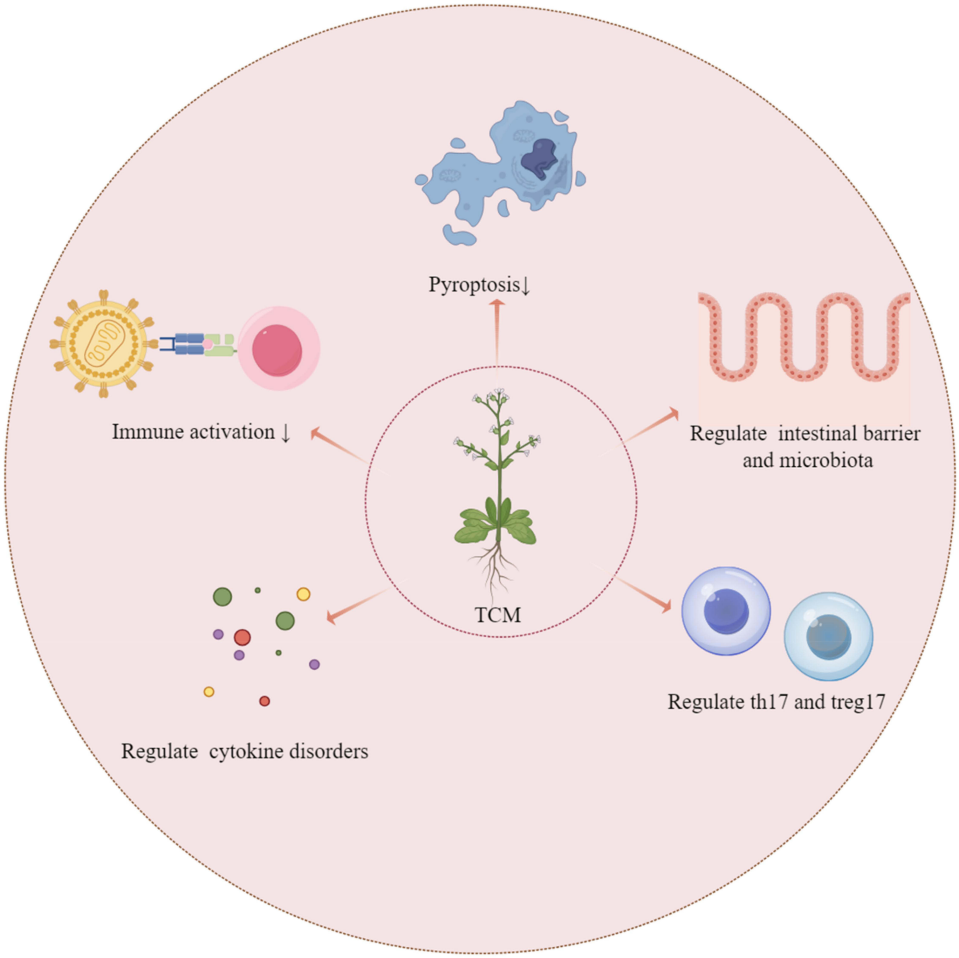

Figure 1 Summary of the potential mechanism underlying incomplete immune reconstitution and the role of traditional Chinese medicine in immunological non-responders.

patients. Several studies on TCM in the treatment of INR have been completed, demonstrating the potential advantages of treating INR. Tripterygium wilfordii Hook F (TwHF) is a Chinese herbal medicine, its main bioactive component triptolide (TPL) has been extracted, and modified into a novel compound (5R)-5-hydroxytriptolide (LLDT-8) with immunosuppressive activity and reduced toxicity. The application of TwHF pill and LLDT-8 has been clinically proved efficacy drugs in reduced the T cell activation, promoted the circulating CD4+ T cell counts and alleviated inflammation among INR.[47,48] Combined transcriptional, proteomic and network pharmacology approach reveals that TPL could inhibit the interferon (IFN) response and the phosphorylation of signal transducer and activator of transcription 1 (STAT1).[49] Artesunate, as a semi-synthetic artemisinin derivative of sesquiterpene lactone, is widely used in clinical immune-related diseases treatment due to its immunomodulatory activity and reduced toxicity. Considering its immunomodulatory properties, researchers applied Artesunate in treating INR. The application of Artesunate in 50mg once daily or 50mg twice a day for 48 weeks successfully improved the initial T cell count level, promoted the circulating CD4+ T cell counts and immune reconstitution among INR.[50] They also launched a multi-centered, double-blinded clinical trial to validate these findings clinical effects of Artesunate among 269 INR.[51] Subsequent studies demonstrated that Artesunate could reduce the early apoptosis of CD4 + T lymphocytes and increase the abundance of *Verrucomicrobiota*.[52]

Regulate Intestinal Barrier, Microbes and the Treg/Th17 Balance

Ectopic intestinal flora and intestinal mucosa damage lead to the persistence of abnormal immune activation, which affects the immune reconstruction in INR. The diversity of intestinal flora in patients with poor immune reconstruction is low. Explore the immune reconstruction by regulating intestinal barrier and microbes is of great significance for

improving immune function. Yiaikang capsule is composed of Ginseng, Astragalus membranaceus, Atractylodes rhizoma, et al, which has definite curative effect in the treatment of AIDS. Yiaikang Capsule can increase the CD4+T cell count, regulate Treg/Th17 balance, and enhance the abundance of probiotics in the intestinal flora among 18 INR.[53] Yiaikang Capsule inhibited the expression of tight junction protein ZO-1, maintained the normal tight junction, reduced the permeability of intestinal mucosal barrier induced by IFN-γ, and maintained the integrity of intestinal mucosal barrier.[54] Shenling Guben granule is composed of Ganoderma lucidum, American ginseng, Knotweed, etc. which can enhance the immune function of INR, increase the CD4+T lymphocyte count, and promote the growth of Sarteria.

Regulate Cytokines Disorders

Abnormal immune activation leads to a high inflammatory response and releases interleukin (IL), including IL-1, IL-6, IL-8, IL-10, tumor necrosis factor (TNF) and other cytokines and chemokines, which increases the difficulty of immune reconstitution. Toll-like receptors can promote the maturation of immune cells by promoting the synthesis and release of cytokines. Yiqi Jianpi granules are composed of Astragalus, Poria cocosa, Wolfberry fructus, etc., which can increase CD4+ cell count by affecting the activation of Toll-like receptors and up-regulating the expression of IL-2 in INR.[55,56] Therefore, TCM can regulate the balance of pro-inflammatory factors and anti-inflammatory factors, alleviate inflammatory response, and promote immune reconstruction.

Increased CD4+ T Cell Counts

The number of CD4+CD45RA+T cells produced by the thymus is considered to be an effective predictor of INR, with the number of CD45RA+T cells in immune responders significantly higher than that in non-responders.[57] CD4+CD45RA+ and CD4+CD45RO+T cells express two important subtypes of CD45 that are closely related to the regeneration of thymic function and immune responsiveness; their expression and abundance can reflect changes in cellular immunity.[58,59] Clinical research supports the ability of TCM to improve CD4+T lymphocyte counts and CD4+CD45RA+T cell numbers in INR and promote immune reconstitution and improve patient quality of life[60] (Table 1).

Table 1 The Link Between Chinese Herbal Medicine and Immunological NonResponders

Chinese Herb Medicine	Sample	Research Design	Effect on Immune Reconstitution	Ref.
Invigorating spleen and tonifying kidney method	32	Randomized, double-blind, controlled	The proportion of CD4+CD45RA+T cells and the ratio value of CD4+CD45RA+T/CD4+CD45RO+T cells↑ the proportion of CD4+CD45RO+T↓	[61,62]
Artesunate	269	Multicenter, prospective clinical trial	CD4+ T lymphocytes count, CD45RA+ T subsets count, The ratio of CD4+ Ki67+ /CD4+↑, IR ↑	[63–65]
Aikeqing Granule	70	Randomized, controlled	CD4+T lymphocyte count↑, effective rate of immune reconstitution ↑,QoL↑	[66,67]
Fuzheng Kangdu Wan	180	Pretherapy and post-treatment	CD4+T lymphocyte count↑, immune reconstitution ↑, clinical symptoms and immune function↑	[68–70]
Wenshen Jianpi Granule	60	Randomized, double-blind, controlled	CD4+ T lymphocytes count, CD45RA+ T cells ↑, immune reconstitution ↑	[71,72]
Bushenfang	41	Randomized, controlled	CD4+T lymphocyte counts↑, CD4+/CD8+↑, IR ↑, clinical symptoms ↑	[73]
Yiaikang Capsules	83	Pretherapy and post-treatment	CD4+T lymphocyte counts↑, CD4+/CD8+↑, IR ↑, clinical symptoms ↑, quality of life↑	[74,75]

(*Continued*)

Table 1 (Continued).

Chinese Herb Medicine	Sample	Research Design	Effect on Immune Reconstitution	Ref.
Jianpi Yiqi Formula	62	Randomized, controlled	CD4+T lymphocyte counts↑, IR ↑	[76]
Diwu Yanggan Capsule	57	Randomized, double-blind, controlled	CD45RA+↑, CD4+T↑, IR ↑	[77]
Astragalus membranaceus	30	Randomized, controlled	CD4+T lymphocyte counts↑	[78,79]
Yiqi Jianpi Granules	22	Pretherapy and post-treatment	CD4+T lymphocyte counts↑	[80]
Ganoderma lucidum	92	Retrospective study	CD4+T lymphocyte counts↑, Th/Ts ↑	[81]
Mianyi NO.2	264	Randomized, double-blind, controlled	CD4+ T lymphocyte counts, CD4CD45RA+, CD4CD45RO +↑, clinical symptoms ↑	[82]
Tripterygium Wilfordii Hook F	33	Pretherapy and post-treatment	CD4 + T cell counts and recovery↑, T cell activation↓	[47,49]

TCM Interventions Against Opportunistic Infections

The incidence is immunological non-responsiveness is 10%–40%, and affected patients are at significantly higher risk for opportunistic infections (OIs).[83] The prevention and treatment of OIs is important to improve the quality of life of PLWH. Clinical studies on OIs show that TCM is efficacious for reducing OIs—such as AIDS-associated lung infections, AIDS-related diarrhea, AIDS-associated fevers, AIDS-associated skin injuries, and AIDS-associated oral lesions—and improving quality of life[84] (Table 2). TCM has preventative and curative effects for OIs, but some OIs, such as tuberculosis, lymphoma, and Kaposi's sarcoma, still require effective treatments.

Potential Future Directions

Elucidate the Potential Mechanisms Through Which TCM Regulates the CD4+ T Cells of INR

Changes in the number and function of CD4+ T cells are critical to the progression of AIDS. Although TCM therapy can effectively increase CD4+ T cell counts, and represents a promising approach to treating INR, its mechanisms of

Table 2 Chinese Herbal Medicine and Opportunistic Infections

Opportunistic infections	Chinese Herb Medicine	Sample	Research Design	Consequence	Potential Mechanisms	Ref.
AIDS-associated lung infections	Qingfei Peiyuan Granules	141	Randomized, double-blind, controlled	Cough, wheezing, chest tightness, phlegm↓, QoL↑	Regulates T lymphocyte subsets, Th1/Th2, TLR/MyD88,and IL-6, PCT↓,	[85–88]
	Fuzheng Qingfei Decoction	106	Randomized, controlled	Cough↓, phlegm↓, fever↓	CD 4+T↑	[89]
	Tanreqing injection	100	Randomized, controlled	Temperature↓, hemameba↓, neutrophile granulocyte↓	CD 4+T↑, CD8+↑, natural killer cell↑	[90]

(*Continued*)

Table 2 (Continued).

Opportunistic infections	Chinese Herb Medicine	Sample	Research Design	Consequence	Potential Mechanisms	Ref.
AIDS-related diarrhea	Xieli Kang Capsule	130	Randomized, controlled	Diarrhea, abdominal distension and pain↓	Regulate TNF-α, secreted Ig A↑, IL-17↑, CD40L↓,	[91–93]
	Jianpi Wenyang Jiedu granule	40	Randomized, controlled	Diarrhea↓, Stomachache↓, Bloating↓, anorexia↓	Acidaminococcus↓, Oscillospira↓, Dorea↑, Coprococcus_3↑, NF-κB↓, IL-1β↓, TNF-α↓, IL-6↓	[94]
	Guchang Zhixie Pills	86	Randomized, controlled	Diarrhea↓, Stomachache↓,	NR	[95]
AIDS-associated fevers	Jiebiao Qingli granules, Shenqi Jiere capsules and Chaihopedayuan mixture	270	Randomized, controlled	Fever↓	IL-1↓, IL-6↓, TNF-α↓, hemameba↓, C-reactive protein↓,	[96]
	Modified minor radix bupleuri decoction	90	Randomized, controlled	Fever↓	NR	[97]
	Buzhong Yiqi decoction	40	Randomized, controlled	Fever↓	NR	[98]
	Lianhua Qingwen Decoction	120	Randomized, controlled	Fever↓ Fatigue↓	NR	[99]
AIDS-associated skin injuries	Modified Longdan Xiegan Decoction	149	Randomized, double-blind, controlled	Pruritus and skin lesions↓, QoL↑	The eosinophil count and serum IgE↓	[100]
	Kangai Baosheng Pills, Fuzheng Kangdu Pills	34	Randomized, controlledrash	Rash↓ Ulceration↓	NR	[101]
	Luhui Pikang Liquid	58	Pretherapy and post-treatment	Pruritus↓, rash↓, ulceration↓	NR	[102]
AIDS-associated oral lesions	Licorice heart-draining decoction, Xiaolu Granules	78	Randomized, controlled	Ulcer pain and area↓, QoL↑	Regulation of oral flora	[103,104]
	Chinese herbal gargle	80	Randomized, controlled	Leukoplakia↓, Ulceration↓, QoL↑	Regulating oral candida	[105]

Abbreviations: AIDS, acquired immunodeficiency syndrome; QoL, quality of life, NR, not reported.

action in immune recovery remain to be elucidated. A synergistic approach utilizing single-cell sequencing, transcriptomics, proteomics, and metabolomics can effectively analyze the biological processes and molecular interactions involved in the development of disease. We believe a similar synergistic approach applied to the analysis of blood, gut, and stool samples in the context of TCM may reveal key information. Priority should be given to the gut microbiota because some studies have shown that the gut microbiota is closely related to CD4+ T cell numbers and immune reconstitution during the resolution of poor immune reconstitution upon treatment with TCM.[74,106–108] Chen et al best illustrated this approach when they explored the mechanism of Yiaikang capsules in the treatment of INR using serum metabolomics. They compared the metabolomics results of 58 patients treated with Yiaikang capsules before and after treatment, and concluded that Yiaikang capsules increased CD4+ T cell counts and the CD4+:CD8+ T cell ratio in INR. Metabolites such as 1-phosphatidylyl-D-mercaptoinositol, PC(18:3 (9Z,12Z,15Z)/20:1 (11Z)), PE(14:0/P-18:0),

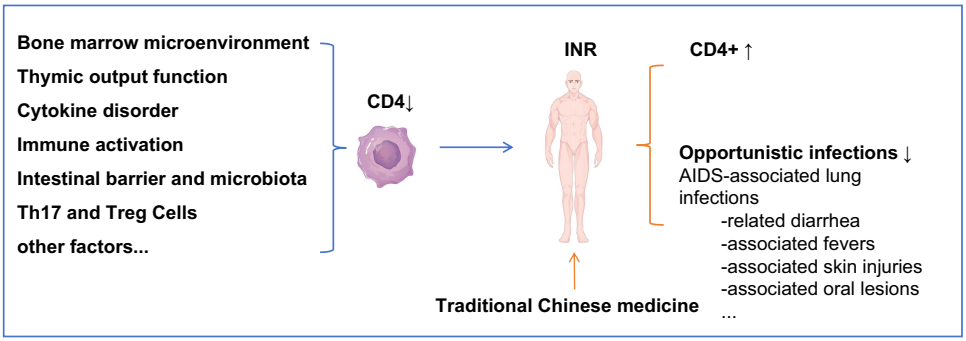

Figure 2 Mechanism outline of traditional Chinese medicine on treating infectious diseases incomplete immune reconstitution.
Abbreviation: TCM, traditional Chinese medicine.

quinolinic acid, deoxycorticosterone, and selenocysteine are closely related to the therapeutic effects of Yiaikang capsules. This metabolic pathway may be a potential therapeutic target of Yiaikang capsules in the treatment of INR.[109] Researchers who study TCM to prevent and treat immunological non-responsiveness are gaining insight into potential research targets. Moreover, in-depth analysis of gene upregulation and/or other changes in genes during TCM treatment of INR may provide a clearer understanding of the role of TCM in the recovery of CD4+ T cells and immune responses in INR.

Reduce OIs and Improve Quality of Life

Declines in CD4+ T lymphocyte counts can increase the risk of OIs, and infected hosts are more susceptible to a variety of OIs, usually caused by fungi, bacteria, viruses, and parasites that are typically controlled by the immune system. OIs are the leading cause of death in PLWH, and the key to AIDS treatment is to accurately evaluate the changes in a patient's condition and reduce the incidence of poor prognosis. Therefore, it is essential to find effective treatments for HIV OIs. TCM treatment is holistic and individual; it has obvious advantages for the clinical treatment of low immunity accompanied by OIs, and has achieved clinical efficacy.[110] We believe that early intervention with integrated TCM and Western medicine for the prevention and treatment of OIs will improve clinical efficacy and reduce the recurrence rate and mortality (Figure 2).

Conclusion

INR is an unneglected group, we explored the pathogenesis of INR, but it is also associated with older age, male, low level of pre-ART CD4T lymphocytes, ethnic factors, etc. There is no method to fully restore the CD4*T lymphocyte count. TCM therapy has potential advantages in INR, and its mechanism is related to the reduction of immune activation, pyroptosis and the regulation of cytokine disorders, intestinal barrier and microbiota, Th17 and treg17. TCM can regulate intestinal microecology, and intestinal flora is closely related to the number of CD4+ T cells and immune reconstitution, so it should be given priority. Comprehensive analysis of single-cell RNA sequencing, transcriptomics, genomics and proteomics can provide an in-depth understanding of INR. Analyzing the role of TCM therapy in INR using the multi-omics method can accelerate the research of TCM promoting immune reconstitution. In the TCM therapy of INR, it is of great significance to elucidate the possible mechanism of TCM regulating INR CD4+ T cells and reducing OIs and improving quality of life. There are limitations in the TCM therapy of INR. First, it will be necessary to screen and analyze the active ingredients of TCM products and their therapeutic targets. Second, combined with serum pharmacology, systems biology and bioinformatics technology must be applied to verify the research results. As this area of research continues to evolve, we hope that TCM will use these technologies to overcome its own limitations to achieve a more comprehensive treatment of complex diseases. We recommend that researchers use a synergistic omics approach to study the key problems restricting clinical efficacy in INR and to develop Chinese herbs with clear mechanisms and precise efficacy.

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Disclosure

The authors report no conflicts of interest in this work.

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