Review

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The Efficacy and Immune Mechanism of Thymosin Alpha 1 as a Valuable Adjunctive Therapy for Tuberculosis

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Tuberculosis remains the leading cause of death among global infectious diseases with increasing challenges of antimicrobial resistance. Conventional anti-tuberculosis chemotherapy is aggravated by a limited success rate, a long course of treatment, and numerous side effects. Once again, we highlighted the significance of immuno-therapy. In this review, we focus on assessing the efficacy and safety of thymosin alpha 1 (Tα1) as a valuable adjunctive therapy for tuberculosis. We aim to examine the potential mechanism through which Tα1 influences the immune system of tuberculosis patients, intending to provide a theoretical foundation for its clinical applications. After reviewing the articles published in PubMed, Web of Science, Embase, BIOSIS Library, and China-national-knowledge-internet, we identified 21 clinical cohort studies investigating Tα1 as an auxiliary treatment for tuberculosis. These studies included 11 articles on pulmonary tuberculosis, 2 articles on tuberculous pleurisy, and 8 articles on intestinal tuberculosis. These studies have demonstrated the safety and effectiveness of Tα1, an immunomodulator, in the treatment of tuberculosis. The probable immune mechanism of Tα1 might involve the up-regulation of T lymphocyte ($CD3^+$, $CD4^+$), helper T 17 (Th17), natural killer (NK), interferon-γ (IFN-γ), and interleukin-2 (IL-2) levels. Consequently, Tα1 may be suggested as an effective and safe auxiliary treatment for mycobacterium tuberculosis infection in clinical settings. However, several key aspects regarding Tα1 remain unclear, including the molecular mechanism involved in Tα1's upregulation of immune cell differentiation and cytokine secretion, the synergistic association between Tα1 and anti-tuberculosis drugs, and its therapeutic dose and treatment duration for tuberculosis. Therefore, there is an urgent need to investigate these aspects and explore more scientific and effective treatment strategies to provide a reference for the treatment of tuberculosis.

Keywords: thymosin alpha 1; efficacy; adjunctive therapy

Introduction

In 2022, tuberculosis ranked as the second most deadly infectious disease worldwide, just after Corona Virus Disease 2019 (COVID-19) [1]. It has been recognized as the leading cause of deaths among individuals with antimicrobial resistance and those infected with human immunodeficiency virus (HIV) [2,3]. As per the WHO Global Tuberculosis Report 2023, there were approximately 10.6 million diagnosed tuberculosis cases and 1.3 million deaths in 2022 [1]. Among tuberculosis patients, the highest global tuberculosis burden was in Southeast Asia, accounting for 46% of cases, with India contributing 27%, followed by Indonesia at 10%, China at 7.1%, and Philippines at 7% [1]. Despite this, new anti-tuberculosis drugs were introduced, such as bedaquilin, delamanid and retomanid [2]. Due to several adverse reactions (including gastrointestinal symptoms, liver function impairment, and renal insufficiency), as well as challenges like poor adherence, lengthy treatment time, and substantial antimicrobial resistance [3,4], conventional anti-tuberculosis chemotherapy yields unsatisfactory outcomes [3,4]. In 2022, approximately 410,000 new tuberculosis patients (3.9%) were diagnosed with multidrug-resistant tuberculosis (MDR-TB) or rifampicin-resistant tuberculosis (RR-TB) [1]. Furthermore, a higher antimicrobial resistance rate of 54.5% has been observed in retreatment tuberculosis patients [5]. Therefore, conventional anti-tuberculosis chemotherapy is far away from the phased goal of global tuberculosis prevention and cure. Hence, there is an urgent need for new, effective, and comprehensive anti-tuberculosis treatment options.

To solve this dilemma, researchers are committed to developing new drugs and exploring effective adjuvant therapy [6], such as traditional Chinese medicine [5], rosuvastatin [4], and metformin, to improve tuberculosis treatment outcomes. Thymosin alpha 1 (Tα1), identified as a fa-

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vorable immunomodulator, is widely used for treating various infections and tumors, such as COVID-19, hepatitis C, hepatitis B, malignant melanoma, hepatocellular carcinoma, and DiGeorge's syndrome [7–12].

Thymosin Alpha 1 (Tα1) may be a Valid Auxiliary Treatment for Tuberculosis

The standard treatment regimen for drug-susceptible tuberculosis, which includes a combination of isoniazid, rifampicin, ethambutol, and pyrazinamide for 2 months followed by isoniazid and rifampicin for 4 months, is commonly used to inhibit or eradicate *Mycobacterium tuberculosis* (*MTB*) [13]. Despite being a curable disease, the success rate of anti-tuberculosis treatment is only 82% for drug-susceptible tuberculosis and 55% for multidrug-resistant tuberculosis (MDR-TB) [1]. The longer the course of tuberculosis treatment, the higher the occurrence of side effects. However, numerous studies have reported that patients died of liver failure or allergy reactions due to the limitations of these drugs [14–16].

Previously, research has indicated that the combination of Tα1 with multi-modality chemotherapy yields a significant curative effect on tuberculosis patients. This combination therapy effectively regulates immune function and reduces the levels of inflammatory cytokines, indicating its potential as a safe therapeutic option for further use in clinical practice [12]. We performed a comprehensive search across various databases such as PubMed, Web of Science, Embase, BIOSIS Library, and China-national-knowledge-internet for original case reports and cohort studies on Tα1 treatment in tuberculosis patients published between January 1, 1979, and December 31, 2023. After reviewing the abstracts of these manuscripts, we found 21 clinical cohort studies exploring the efficacy of Tα1 as an auxiliary treatment for tuberculosis, including 11 articles on pulmonary tuberculosis, 2 articles on tuberculous pleurisy, and 8 articles on intestinal tuberculosis (Table 1) [12,17–36].

A total of 1100 tuberculosis cases received combined treatment with Tα1 and anti-tuberculosis medications, including 588 pulmonary tuberculosis, 408 intestinal tuberculosis, and 104 tuberculosis pleurisy patients [12,17–36]. The outcomes of these studies suggest that the ultimate negative conversion rate of sputum smear among the Tα1 combined with anti-tuberculosis treatment ranged from 73.3% to 100%, exceeding the rate observed in those only undergoing anti-tuberculosis treatment, which ranged from 44.3% to 86.0%. The ultimate rate of lesion absorption among the patients undergoing Tα1 combined with anti-tuberculosis treatment ranged from 66.0% to 100%, exceeding those patients only receiving anti-tuberculosis treatment, which ranged from 50.0% to 90.5%. In addition, the ultimate rate of cavity closure among those receiving Tα1 combined with anti-tuberculosis treatment ranged from 47.7% to 95.0%, surpassing those only receiving anti-tuberculosis treatment, ranging from 50.0% to 95.0% [12,17–36]. In specific populations, including elderly people, individuals with diabetes, and patients with multidrug-resistant tuberculosis, we found the effectiveness of Tα1 in improving the sputum negative conversion rates, lesion absorption rates, and cavity closure rates. Furthermore, Tα1 does not increase the adverse reactions in these patients. In summary, combining Tα1 with anti-tuberculosis drugs can improve clinical symptoms, promote cavity reduction and closure, increase the negative conversion rates of sputum smears, and exhibit no visible side effects [12]. Thus, due to its efficacy, safety, and economic benefits, Tα1 may play a vital role in the treatment of tuberculosis, offering a new valuable adjunctive therapy. However, there is a lack of clinical understanding regarding this issue.

However, the optimal therapeutic dose and dose cycle of Tα1 for tuberculosis remain unclear. Among these 21 studies, the therapeutic dose cycle of Tα1 varied from 1.5 months to 24 months, with a significant emphasis on a 6-month treatment regimen [12,17–36]. Among them, eight studies specifically evaluated the impact of different therapeutic cycle doses of Tα1. They found a significant correlation between the effectiveness of Tα1 and the duration of treatment [22,28]. Long-term regular treatment may help improve the prognosis of tuberculosis patients. Among the analyzed manuscripts, the subcutaneous injection was the most used form of treatment (17/21 articles), followed by intravenous injection (3/21 articles) and oral administration (11/21 articles). The most common therapeutic dosage of Tα1 for tuberculosis was subcutaneous injections of 1.6 mg Tα1 twice a week. The therapeutic dose of Tα1 for intravenous injection ranged from 40 to 80 mg. However, there is a lack of research focusing on the relationship between the therapeutic dose and efficacy of Tα1 for tuberculosis. In addition, except for intestinal tuberculosis and tuberculosis pleurisy, there has been limited research on the treatment of other forms of extra-pulmonary tuberculosis utilizing Tα1. Therefore, there is an urgent need to investigate this aspect and explore more scientific and effective treatment strategies to provide a reference for the management of *Mycobacterium tuberculosis* infection.

The Immune System Plays an Important Role in the Progress of Tuberculosis

MTB remains one of the most challenging pathogenic bacteria, with prognosis decided by the balance between the host immune system and the bacteria. The mucosal barriers within the respiratory tract constitute the first line of defense against MTB, utilizing various mucosal immune responses [37]. After reaching the alveoli, surviving mycobacteria encounter a set of innate immune cells from the host, which exert multiple cellular bactericidal functions. Adaptive immunity, predominantly mediated by a range of different T cell and B cell subsets, is subsequently activated, and

Table 1. The effective of clinical studies of thymosin alpha 1 as an effective adjuvant therapy for tuberculosis (TB).

Studies	Treatment	Patients enrolled		Primary outcome (AT vs AT+T)		
		Number	Type of tuberculosis	Negative conversion ratio of sputum smear	Lesion absorption rate	Cavity closure rate
Li XW [17]	AT/AT+T	50/50	New PTB patients	62.0% (31/50) vs 80.0% (40/50)*	62.0% (31/50) vs 66.0%(33/50)	-
Wu BH [18]	AT/AT+T	44/44	Retreatment PTB	65.9% (29/44) vs 90.9% (40/44)*	68.2% (30/44) vs 88.6% (39/44)*	
Ma QQ [19]	AT/AT+T	88/68	New and retreatment PTB	64.8% (57/88) vs 100.0% (68/68)*	73.3% (72/88) vs 81.8% (66/68)*	70.8% (17/24) vs 91.3% (21/23)*
Tan JM [20]	AT/AT+T	32/32	Multidrug-resistant PTB	63.3% (19/30) vs 86.7% (26/30)*	-	-
Deng B [21]	AT/AT+T	41/46	Multidrug-resistant PTB	73.2% (31/41) vs 91.3% (42/46)*	68.3% (28/41) vs 89.1% (41/46)*	63.2% (24/41) vs 84.1% (37/46)*
Wang GH [22]	AT/AT+T	50/50	PTB in older patients	76.0% (28/50) vs 90.0% (45/50)*	-	-
Li X [23]	AT/AT+T	105/105	PTB in older patients	86.0% (90/105) vs 98.0% (102/105)*	90.5% (95/105) vs 99.7% (104/105)*	77.5% (31/40) vs 95.0% (38/40)*
Liu C [24]	AT/AT+T	38/38	PTB with diabetes	78.9% (30/38) vs 92.1% (35/38)*	86.8% (33/38) vs 100.0%(38/38)*	26.3% (10/38) vs 47.7% (18/38)*
Wu L [12]	AT/AT+T	60/60	PTB with diabetes	43.3% (26/60) vs 73.3% (44/60)*	50.0% (30/60) vs 80.0% (48/60)*	46.7% (28/60) vs 76.7% (46/60)*
Yao HJ [25]	AT/AT+T	32/32	PTB with diabetes	53.1% (17/32) vs 78.1% (25/32)*	62.5% (20/32) vs 87.5% (28/32)*	
Cao Y [26]	AT/AT+T	43/43	PTB with diabetes	74.4% (32/43) vs 93.0% (40/43)*	-	-
Jiao X [27]	AT/AT+T	54/54	TB pleurisy	-	83.3% (45/54) vs 96.3% (52/54)*	-
Xu QF [28]	AT/AT+T	50/50	TB pleurisy	60.0% (30/50) vs 82.0% (41/50)*	-	-
Li H [29]	AT/AT+T	51/51	Intestinal TB	-	72.6% (37/51) vs 94.1% (48/51)*	-
Wang T [30]	AT/AT+T	60/60	Intestinal TB	-	78.3% (47/60) vs 91.7% (55/60)*	-
Liu C [31]	AT/AT+T	17/20	Intestinal TB	-	76.5% (13/17) vs 95.0% (19/20)*	-
Liang XF [32]	AT/AT+T	62/66	Intestinal TB	-	72.6% (45/62) vs 90.9% (60/66)*	-
Han Y [33]	AT/AT+T	55/55	Intestinal TB	-	69.1% (38/55) vs 94.6% (52/55)*	-
Li X [34]	AT/AT+T	48/48	Intestinal TB	-	75.0% (36/48) vs 91.7% (44/48)*	-
Zhu N [35]	AT/AT+T	60/60	Intestinal TB	-	76.7% (46/60) vs 96.7% (58/60)*	-
Shi S [36]	AT/AT+T	48/48	Intestinal TB	-	77.1% (37/48) vs 91.7% (44/48)*	-

*$p < 0.05$; AT, anti-tuberculosis chemotherapy; PTB, pulmonary tuberculosis; AT+T, anti-tuberculosis chemotherapy combine with thymosin alpha 1.

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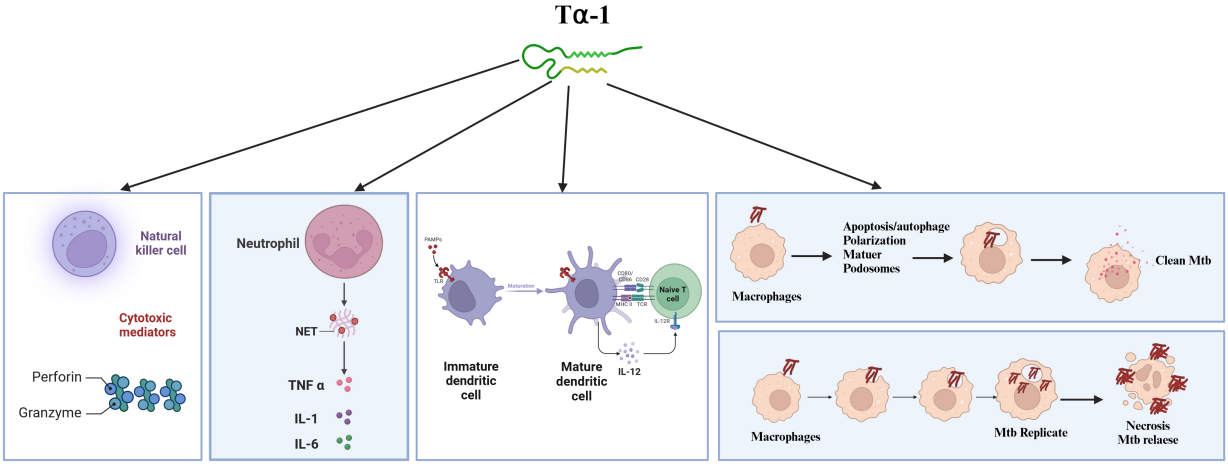

Fig. 1. The possible mechanisms through which Tα1 works on immune cells during *M. tuberculosis* infection. *M. tuberculosis* primarily targets innate immune cells, including macrophages, dendritic cells, neutrophils, and natural killer (NK) cells. Tα1 affects various aspects of macrophage such as polarization, maturation and podosome structure formation, which determines the fate of *M. tuberculosis*. In addition, the impact of Tα1 on the manner of death in infected macrophages remains unclear. Neutrophils can release neutrophil extracellular traps (NETs), facilitating the transfer of human heat shock protein 72 (HSP-72) to adjacent macrophages, thereby inducing a pro-inflammatory response. Additionally, NK cells can kill *M. tuberculosis* through perforin, granzyme, and factor-related apoptosi (FasL). However, the impact of Tα1 on the function of infected neutrophils NK cells is not quite clear (illustration can be accessed online at https://app.biorender.com/illustrations). TNF-α, tumor necrosis factor α; Tα1, thymosin alpha 1; IL, interleukin.

participates in the host's anti-mycobacterial defense mechanisms [38]. During *MTB* infection, the host's bactericidal immune responses are exquisitely adjusted and balanced through multifaceted mechanisms, including genetic and epigenetic regulation, metabolic regulation, and neuroendocrine modulation. These mechanisms are indispensable for maintaining the efficiency of the host immune system and avoiding excessive tissue injury [38–40]. The innate immune cell types involved in tuberculosis include macrophages (Mac), neutrophils, dendritic cells (DCs), and natural killer (NK) cells [41–43]. Macrophages are activated to secrete nitric oxide and reactive oxygen species, effectively eliminating mycobacterium tuberculosis after phagocytosis. It is facilitated by the abundant expression of pattern recognition receptors (PRR) and complement receptors [40]. Moreover, Mac autophagy plays a significant role in protecting the host against tuberculosis. Certain proteins such as ATG7 and ATG14 restrict cytosolic and phagosomal Mycobacterium tuberculosis replication in human macrophages [44,45]. However, *MTB* can suppress host DNA repair mechanisms to boost its intracellular survival and hijack host processes such as tripartite motif containing 21 (TRIM21)-dependent and nuclear receptor coactivator 4 (NCOA4)-dependent ferritinophagy, thus enhancing intracellular growth and leading to the spread of tuberculosis while inducing immune tolerance [39,46]. Notably, the interaction between Mac and T cells plays a core role in anti-tuberculous immunity. Research has indicated that apoptosis of Mac caused by Alox5 deficiency leads to a greater $CD4^+$ and $CD8^+$ T-cell response compared to wild-type Mac [42]. Additionally, another study has demonstrated that the interaction between macrophages and CD8 T cells in bronchoalveolar lavage fluid is associated with latent tuberculosis infection [47,48].

DCs are specialized antigen-presenting cells that facilitate the innate and adaptive immunity by decomposing pathogens into essential components and presenting them on the cell surface for recognition by T cells [49,50]. However, *MTB* blocks the migration of DCs to reach the lymph gland and inhibits the initiation of the adaptive immune response by reducing the expression of integrin on the surface of infected DCs [50,51]. Furthermore, *MTB* is supposed to impair DC maturation by inducing the production of IL-10 [52]. In brief, targeting DC maturation may benefit for decreasing the inhibition of T-cell activation by *MTB*.

Additionally, neutrophils participate in innate immune-mediated resistance against *MTB* infection. It has been reported that healthy people in contact with patients with pulmonary tuberculosis are less susceptible to *MTB* if they have higher neutrophil counts in their peripheral blood [53]. Neutrophils contribute to clear *MTB* infection through various mechanisms, including phagocytosis, degranulation, and the formation of neutrophil extracellular traps (NETs) [54,55]. These cells are supposed to induce a pro-inflammatory response to kill *MTB* through cooperation with resident macrophages, while also secreting cytokines (IFN-γ) which serve as an immunomodulator to promote the pro-inflammatory function of neutrophils [56,57]. Additionally, NK cells are non-specific immune cells that possess cytolytic capabilities [53], and directly

Table 2. The Immune change of clinical studies of Thymosin alpha 1 as an effective adjuvant therapy for tuberculosis.

Studies	Immune change (AT VS AT+T)		
	T lymphocyte	NK cell	cytokines
Li XW [17]	the number of $CD3^+$ and $CD4^+$ increased, $CD8^+$ decreased, the ratio of $CD4^+/CD8^+$ increased	NK cells decreased	-
Ma QQ [19]	the number of $CD3^+$ and $CD4^+$ increased, $CD8^+$ decreased, the ratio of $CD4^+/CD8^+$ increased	-	-
Tan JM [20]	Th17, Treg and Th17/Treg increased	-	-
Deng B [21]	the number of $CD3^+$ and $CD4^+$ increased, $CD8^+$ decreased, the ratio of $CD4^+/CD8^+$ increased	-	-
Liu C [24]	the number of $CD4^+$ increased, $CD8^+$ decreased, the ratio of $CD4^+/CD8^+$ increased		
Yao HJ [25]	the number of $CD3^+$ and $CD4^+$ increased, $CD8^+$ decreased, the ratio of $CD4^+/CD8^+$ increased	NK cells increased	IFN-γ, IL-2 increased, IL-4, IL-5 decreased
Cao Y [26]	the number of $CD3^+$ and $CD4^+$ increased, $CD8^+$ decreased, the ratio of $CD4^+/CD8^+$ increased	-	IFN-γ increased, PCT, sTREM-1 and IL-10 decreased
Xu QF [28]	-	-	IL-6, TNF-α, IL-23 decreased
Li H [29]	the number of $CD3^+$ and $CD4^+$ increased, $CD8^+$ decreased, the ratio of $CD4^+/CD8^+$ increased	-	-
Wang T [30]	the number of $CD3^+$ and $CD4^+$ increased, $CD8^+$ decreased, the ratio of $CD4^+/CD8^+$ increased	NK cells increased	-
Liang XF [32]	the number of $CD3^+$, $CD4^+$ and $CD8^+$ increased, the ratio of $CD4^+/CD8^+$ increased	NK cells increased	-
Han Y [33]	the number of $CD3^+$, $CD4^+$ and $CD8^+$ increased, the ratio of $CD4^+/CD8^+$ increased	NK cells increased	-
Li X [34]	the number of $CD3^+$, $CD4^+$ and $CD8^+$ increased, the ratio of $CD4^+/CD8^+$ increased	NK cells increased	-
Zhu N [35]	the number of $CD3^+$, $CD4^+$ and $CD8^+$ increased, the ratio of $CD4^+/CD8^+$ increased	NK cells increased	-
Shi S [36]	the number of $CD3^+$, $CD4^+$ and $CD8^+$ increased, the ratio of $CD4^+/CD8^+$ increased	NK cells increased	TNF-α, and IL-10 decreased

IL, interleukin; Th17, helper T 17; IFN-γ, interferon-γ; PCT, procalcitonin; sTREM-1, souble triggering receptor expressed on myeloid cells-1.

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resist *MTB* growth through cytotoxic mechanisms, including the release of perforin, granzyme and expression of FasL, as well as indirectly through immune activation of macrophage. In addition, NK cells are capable of producing interferon-γ (IFN-γ), and interleukin-12 (IL-12) to enhance phagolysosomal fusion, ultimately inhibiting intracellular *MTB* growth [52,58,59]. Furthermore, NK-derived exosome miR-1249-3p has been found to inhibit Mycobacterium tuberculosis survival in macrophages by targeting *SKI* family transcriptional corepressor 1 (SKOR1) [60].

The Potential Mechanism of Tα1 in Tuberculosis

Tα1, widely distributed in various tissues and cells, is a short peptide consisting of 28 amino acids and can exist either naturally or in a synthetic form [61,62]. This peptide possesses positive immunomodulatory properties and plays important roles in the activation and regulation of various immune cells, particularly Mac and DCs (Fig. 1) [10,58,63]. The recognition and phagocytosis of microorganisms by Mac represents the first step in the destruction of pathogens through lysosomal enzymes [40]. Macrophages express different kinds of antigen receptors on their surface, such as Toll-like receptors (TLR), C-type lectin receptors, and others, helping them to recognize *MTB* through the TLR pathway [63–65]. A previous study showed that Tα1 increased the phagocytic activity of monocyte–derived macrophages against non-microbic foreign particles as well as fungi in a dose-dependent manner [63]. Another study verified that Tα1 acts as a TLR agonist (especially in TLR-2 and TLR-9), thereby elevating the host's phagocytic response [64]. Therefore, the TLR pathway may be a key aspect in elucidating the mechanism of how Tα1 synergistically fights against tuberculosis. In addition, Tα1 stimulation could affect the structure and function of Mac protostomes, a highly dynamic actin-rich adhesion structure involved in Mac adhesion and chemotaxis [66]. Chemotactic migration of macrophages is critical in the host's response to infection. Previously, it has been shown that Tα1 can significantly upregulate DC biomarkers [67]. Furthermore, Tα1 treated DCs can promote $CD3^+$ T-cell proliferation and induce the release of a wide range of cytokines, including IFN-γ, IL-5, IL-10, IL-13, and TNF-α [68]. Thus, Tα1 exerts an important role in Mac and DCs differentiation as well as antigen-presenting function to fight against bacterial infections. Through the literature review, we found only 15 articles that explored the effect of Tα1 on the human adaptive immunity system. The results of these studies suggest that the levels of $CD3^+$, $CD4^+$, the ratio of $CD4^+/CD8^+$, helper T 17 (Th17), Treg, NK, IFN-γ, IL-2 were increased. However, the levels of IL-4, IL-5, souble triggering receptor expressed on myeloid cells-1 (sTREM-1), IL-10 IL-6, and IL-23 were decreased (Table 2, Ref. [17,19–21,24–26,28–30,32–36]). However, few studies provide insights into how Tα1 exerts its regulatory activity on Mac, DCs, and T lymphocytes in conditions of *MTB* infection, further research is needed to fully uncover the mechanisms involved in Tα1-Mac/DCs/T lymphocyte interactions.

Conclusion

Tα1 plays a synergistic role when used in combination with conventional anti-tuberculosis drugs in clinical settings. When combined with conventional anti-tuberculosis drugs, Tα1 effectively increases the rate of the negative conversion and foci absorption during the treatment of various forms of *MTB* infection, such as primary tuberculosis, secondary tuberculosis, and senile tuberculosis. The interactions between Tα1 and innate immune cells, particularly macrophages and DCs, may exert a crucial role in the adjuvant treatment of tuberculosis. Therefore, it needs further investigations to elucidate the involved immune mechanism of Tα1 in tuberculosis.

Availability of Data and Materials

Not applicable.

Author Contributions

WY, SZ and FW designed the research study. WY, YH, YZ and SZ performed the research. WY and FW analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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