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Narrative Review

Potential of immunomodulatory biomolecules from Indonesia's volcanic soil microbiome for tuberculosis immunotherapy: A conceptual perspective

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Abstract

Tuberculosis (TB) remains a major global health problem, with substantial incidence and mortality worldwide, including in Indonesia. The prolonged duration of standard antibiotic-based therapy and the growing risk of drug resistance have highlighted the need for complementary therapeutic approaches, including immunotherapy. Indonesia possesses volcanic soil ecosystems enriched with extremophilic microbiomes that may represent a potential source of immunomodulatory biomolecules. However, their possible relevance to TB immunotherapy remains underexplored. This review aimed to discuss the potential of volcanic soil microbiomes as a source of immunomodulatory biomolecules for TB immunotherapy and to introduce GeoImmunology Nusantara as a conceptual framework linking geological environments, microbial ecology, and host immune modulation. It outlines the immunological basis of host-directed therapeutic approaches, examines the potential role of microbial-derived biomolecules in modulating host immune responses, and highlights the significance of Indonesia's volcanic environments as a source of biological diversity. In addition, this review presents GeoImmunology Nusantara as an integrative framework to support the development of locally grounded strategies for TB immunotherapy.

Keywords: Tuberculosis, immunotherapy, immunomodulatory biomolecule, GeoImmunology Nusantara, volcanic soil microbiome

Introduction

Tuberculosis (TB) remains a major global public health challenge. It is estimated that approximately one-third of the world's population has been infected with *Mycobacterium tuberculosis*, the causative agent of TB [1]. Each year, the disease causes approximately 9 million new cases and 1.5 million deaths worldwide [1]. In Indonesia, an estimated 1 million TB cases and 125,000 TB-related deaths occur annually, equivalent to approximately 14 deaths per hour [2]. According to the World Health Organization (WHO) Global TB Report 2024, Indonesia has the second-highest TB burden globally after India, highlighting TB as a persistent national health priority and a key component of the global agenda for TB elimination by 2030 [2].

The Indonesian Ministry of Health has established national guidelines for TB management, in which combination antibiotic therapy is considered one of the most effective strategies to prevent disease transmission [3]. However, this approach requires prolonged treatment of at least six months. The lengthy treatment duration, often accompanied by adverse effects of anti-TB

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drugs, may reduce treatment adherence and contribute to the emergence of drug-resistant TB. This complicates disease management and increases the cost of TB control, particularly in high-burden settings [1]. These challenges have prompted increasing interest in alternative therapeutic strategies, including approaches that exploit soil-derived microbiomes and their bioactive products [4].

Studies have begun to explore the potential of soil bacteria and organic compounds present in terrestrial environments to target and inhibit drug-resistant mycobacteria. Several species of *Streptomyces*, a major group of soil-dwelling bacteria, have been reported to produce bioactive compounds capable of inhibiting the growth of *M. tuberculosis*, including drug-resistant strains [4]. These findings highlight new opportunities for the development of innovative therapeutic strategies against TB.

Indonesia possesses abundant natural resources, extending from Aceh to Papua, including one of the highest concentrations of active volcanoes in the world. These conditions give rise to volcanic soil ecosystems with extreme characteristics that support distinctive communities of extremophilic microorganisms, which may serve as sources of biomolecules with unique immunological activities [5]. The richness of soil ecosystems and their microbiomes represents a strategic opportunity for the development of immunology-based theurapeutic approach [6,7]. However, current research has not specifically examined the potential of Indonesian volcanic soils as a source of microbiomes for the development of TB immunotherapy. Therefore, this review aims to introduce the concept of GeoImmunology Nusantara as a novel framework for the development of TB immunotherapy based on Indonesian volcanic soil microbiomes.

Methods

This study was conducted as a narrative literature review to identify and synthesize published evidence on the potential use of volcanic soil microbiomes as an immunotherapeutic approach for TB. A literature search was performed on December 14, 2025, using four electronic databases: PubMed, Scopus, ScienceDirect, and Google Scholar. The search strategy combined terms related to volcanic soil microbiomes, immunotherapy, and TB, using the following keywords and their synonyms: ("Volcanic-based microbiome" OR "Extremophiles") AND ("Immunotherapy" OR "Immunomodulator") AND ("Tuberculosis" OR "TB" OR "*Mycobacterium tuberculosis*").

The search was restricted to articles published within the last 10 years, covering the period from 2015 to 2025, to ensure the inclusion of recent evidence. Studies were considered eligible if they investigated the use of volcanic soil microbiomes as an immunotherapy-related approach for TB or identified microbial biomolecules with immunomodulatory, immunostimulatory, or immunoregulatory activities relevant to TB. Only articles published in English or those with an available English translation were included.

Studies were excluded if they focused solely on the geological characterization of soil without microbiological analysis or immunological relevance. Articles were also excluded if they discussed microbiomes with immunological activity that were not derived from soil. The initial screening and selection of the literature were conducted independently by the first and second authors (SK, FN), while the third author (SS) provided additional review, input, and suggestions when needed.

Potential of volcanic soil microbiomes as a source of immunomodulatory biomolecules

Volcanic soils constitute unique microbial ecosystems because they originate from mineral-rich but organic-poor eruptive materials. Microbial communities in fresh volcanic ash can establish rapidly and exhibit complex metabolic functions even during the earliest stages of soil succession [11]. The physicochemical properties of volcanic soils, including pH and metal content, are major determinants of microbial community structure [12]. Moreover, extreme environments such as volcanic soils provide promising settings for the bioprospecting of microorganisms capable of producing novel secondary metabolites [13].

The microbiomes of volcanic soils are generally dominated by Actinobacteria, Proteobacteria, and Firmicutes, together with pioneer soil fungi [12]. Among these, Actinobacteria, particularly the genus *Streptomyces*, are well recognized as major producers of

naturally derived bioactive compounds from soil environments [14]. Soil microbiomes also harbor a wide diversity of biosynthetic gene clusters, including those encoding polyketides and nonribosomal peptides [15]. The abundance of these biosynthetic gene clusters in volcanic soil microorganisms indicates substantial potential for the discovery of immunomodulatory biomolecules [12].

Various biomolecules produced by soil microorganisms have demonstrated immunomodulatory activity. Exposure to soil microbiota may enhance immune regulation and support a health-associated microbial balance [16]. Dermal exposure to microbially rich soil has also been shown to modulate cellular immune responses to pneumococcal vaccination [17]. More broadly, human interactions with environmental microbes, including soil microorganisms, are increasingly recognized as important for the development of a balanced and tolerant immune system [18].

Mechanistically, microbial biomolecules such as polysaccharides and β-glucans interact with pattern recognition receptors (PRRs) expressed on host immune cells. Fungal β-glucans activate the Dectin-1 receptor and initiate innate immune responses [19]. Some microbial molecules also function as immunoregulatory agents, suppressing excessive inflammation and supporting immune homeostasis [18]. In addition, microbial signals may exert systemic effects on both innate and adaptive immune pathways [20].

Contemporary approaches for exploring immunomodulatory biomolecules from volcanic soils combine conventional microbial culture with omics-based technologies. Genome mining has emerged as an effective strategy for identifying biosynthetic gene clusters responsible for secondary metabolite production in soil microorganisms [21]. Integration of metagenomics and metabolomics can further uncover the biosynthetic potential of uncultured microbes that may not be detected through conventional methods, underscoring the importance of multidisciplinary strategies for accelerating the discovery of bioactive biomolecules from extreme environments [13].

Types of immunomodulatory biomolecules from volcanic microbes

One of the main classes of immunomodulatory biomolecules produced by volcanic soil microbes comprises microbial polysaccharides, including exopolysaccharides and β-glucans. β-glucans derived from fungi and bacteria can activate the Dectin-1 receptor on macrophages and dendritic cells, thereby initiating innate immune responses [19]. Exposure to environmental microbial polysaccharides has also been associated with enhanced immune regulation and tolerance. Extreme-soil microbes, including those from volcanic environments, therefore represent a potentially important but underexplored source of immunomodulatory polysaccharides [16].

Another important class of immunomodulatory biomolecules is polyketides, which are synthesized primarily by Actinobacteria such as *Streptomyces*, commonly found in volcanic soils. Microbial polyketides exhibit broad biological activities, including anti-inflammatory and immunoregulatory effects [14]. Polyketide-producing biosynthetic gene clusters are highly abundant in soil microbiomes, particularly in environments exposed to strong selective pressures [15]. Consequently, volcanic soil bacteria may serve as a valuable source of novel immunomodulatory polyketides [12].

In addition to polyketides, nonribosomal peptides (NRPs) represent another important class of biomolecules produced by volcanic soil microbes. NRPs possess complex chemical structures and frequently demonstrate immunomodulatory or immunostimulatory properties [21]. Actinobacterial metabolites, including NRPs, may influence cytokine production and immune cell activity [14]. Since NRP biosynthetic gene clusters are frequently identified in microbes from extreme soils, they constitute attractive targets for immunomodulatory bioprospecting [15].

Lipopeptides produced by bacteria such as *Bacillus* and *Pseudomonas* are also relevant immunomodulatory biomolecules. These molecules could modulate innate immunity through activation of Toll-like receptors [20]. Microorganisms inhabiting geothermal and volcanic environments may produce lipopeptides with high stability and distinctive biological activities

[13]. Accordingly, lipopeptides derived from soil microbes are promising candidates for the development of immunomodulatory agents and vaccine adjuvants [21].

Another important class of immunomodulatory biomolecules includes microbial cell wall components, such as lipopolysaccharide, peptidoglycan, and lipoteichoic acid. Exposure to environmental microbial cell wall molecules contributes to the development of a balanced and tolerant immune system [18]. Soil-derived microbial components can modulate human cellular immune responses without necessarily provoking excessive inflammation [17]. These structural molecules therefore represent important mediators of communication between environmental microbes and the host immune system [20].

Immunomodulation mechanisms: Activation of innate and adaptive immunity

Immunomodulatory biomolecules produced by volcanic soil microbes are thought to act initially on innate immunity through interactions with pattern recognition receptors on macrophages, dendritic cells, and other immune cells. Microbial components, including polysaccharides and lipopeptides, are recognized by Toll-like receptors and can trigger signaling pathways such as nuclear factor kappa B [20]. A study demonstrated that microbial β-glucans bind to Dectin-1, thereby enhancing phagocytosis and cytokine production [19]. Activation of innate immunity by environmental microbial signals is critical for maintaining balanced inflammatory responses [18].

Activation of innate immune pathways by microbial biomolecules also directly affects dendritic cell function, thereby linking innate and adaptive immunity. Dendritic cell maturation is promoted, together with increased expression of costimulatory molecules required for T-cell activation [22]. Microbial signals can therefore influence the direction of T-cell differentiation through regulation of early cytokine responses [20]. Exposure to soil microbiota may modulate adaptive cellular responses without inducing excessive inflammation [17].

Microbial biomolecules may also regulate the balance among T-cell subsets, including T helper type 1, T helper type 2, T helper type 17, and regulatory T cells [18]. Exposure to environmental microbes has been reported to support the induction of regulatory T cells, which contribute to immune tolerance and prevention of inflammatory disease [18]. Signals derived from β-glucans may direct protective immune responses without causing excessive immune activation [19]. This mechanism is important for maintaining a stable and balanced adaptive immune system [18].

In addition to their effects on T cells, microbial immunomodulatory biomolecules may influence B-cell activation and antibody production. Toll-like receptor activation on B cells can enhance proliferation and differentiation into plasma cells [22]. Exposure to soil microbes has also been shown to alter vaccine-related immune responses, suggesting involvement of the humoral immune system [17]. More broadly, systemic interactions between environmental microbes and the host contribute to maturation of adaptive immunity [20].

Overall, the immunomodulatory mechanisms of biomolecules derived from volcanic soil microbes involve complex interactions between innate and adaptive immunity. Activation of innate immune pathways serves as an early signal that shapes the differentiation and function of adaptive immune cells. Such coordinated responses are essential for maintaining immune homeostasis and preventing inflammatory dysregulation [18].

Immunomodulation as a basis for TB immunotherapy

TB is a chronic infectious disease in which clinical outcomes are strongly influenced by the quality of the host cellular immune response, particularly T helper type 1 responses that produce interferon-gamma (IFN-γ) and activate macrophages to kill *M. tuberculosis*. The ability of *M. tuberculosis* to survive within macrophages by inhibiting phagolysosome maturation and manipulating inflammatory pathways indicates that failure of TB control is not determined solely by pathogen virulence, but also by dysregulated host immunity. This underscores the rationale for strategies aimed at strengthening and reprogramming host immune responses to improve TB control [21].

Host-directed therapy has emerged as a complementary immunotherapeutic strategy that targets host immune pathways without imposing direct selective pressure on the pathogen. This approach aims to enhance the bactericidal capacity of macrophages, improve coordination of adaptive immune responses, and reduce lung tissue damage caused by chronic inflammation [21]. Immunomodulators capable of optimizing both innate and adaptive immunity are particularly relevant for the development of host-based TB therapies [22].

Activation of PRRs such as Toll-like receptors plays a central role in the recognition of *M. tuberculosis* and the initiation of protective immune responses [23]. Stimulation of these receptors promotes dendritic cell maturation, enhances antigen presentation, and directs T-cell differentiation toward a T helper type 1 phenotype that is effective against intracellular pathogens [24]. Therefore, immunomodulatory biomolecules capable of activating these pathways may serve as immunological adjuvants or supportive immunotherapeutic agents in TB [23,24]. To facilitate conceptual understanding of the host immune mechanisms involved in TB control, a schematic representation of the major immunological pathways is presented in **Figure 1**.

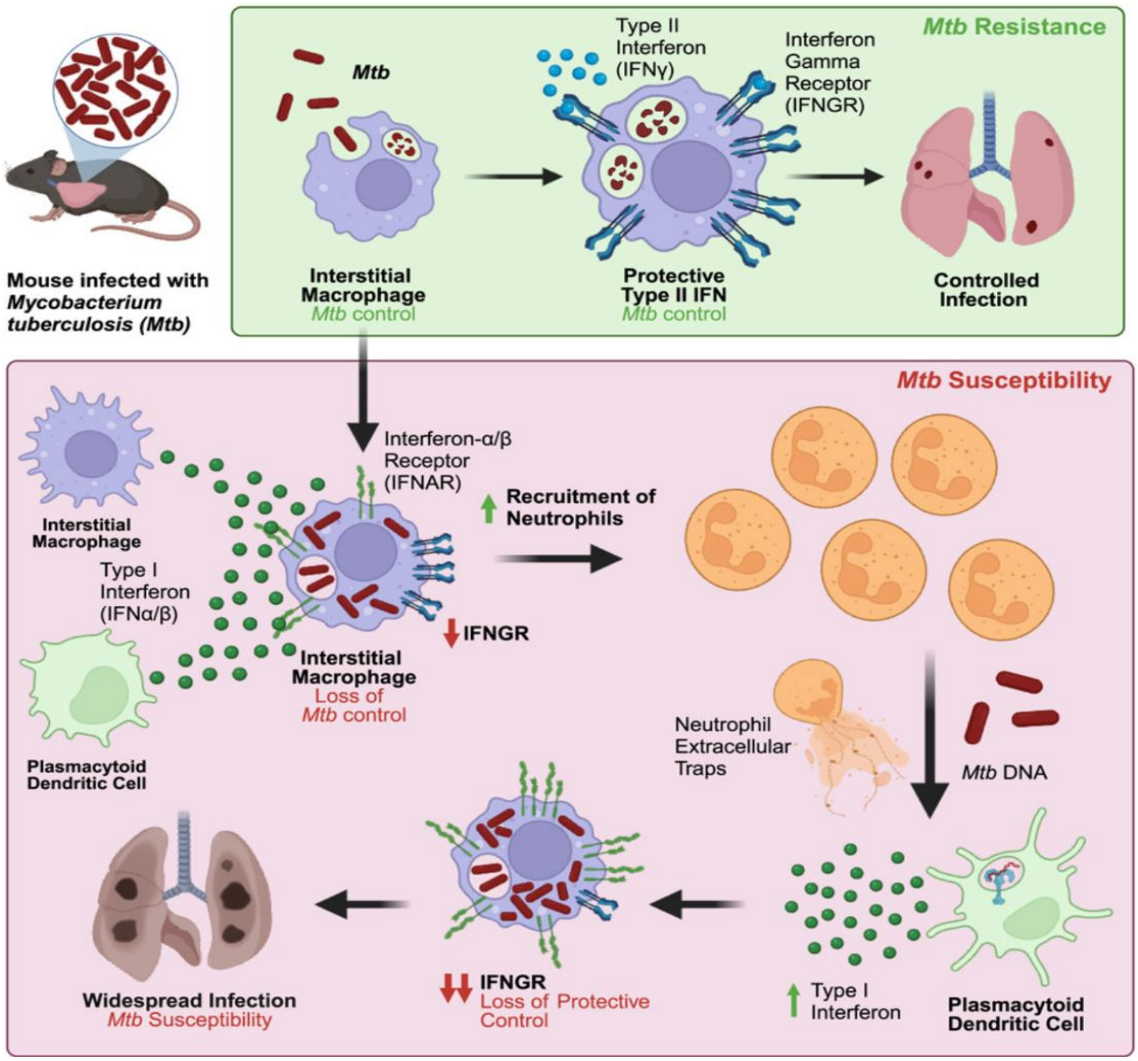

Figure 1. Schematic representation of host immune responses in tuberculosis (TB), highlighting protective type II interferon-driven macrophage activation and type I interferon-associated pathways linked to susceptibility to *Mycobacterium tuberculosis*. Type II interferon responses support macrophage-mediated bacterial control and localized infection. By contrast, heightened type I interferon responses are associated with impaired protective signaling, neutrophil-dominant inflammation, and disseminated disease.

Furthermore, the concept of trained immunity suggests that specific stimulation of innate immune cells can induce epigenetic and metabolic reprogramming that enhances antibacterial responses over the medium to long term. This concept highlights the potential utility of natural

immunomodulators for sustainably strengthening innate immunity against TB without relying on narrow antigen specificity [22]. In the context of chronic diseases such as TB, such an approach may be relevant for improving host resilience against recurrent infection [21].

Various biomolecules derived from extremophilic microorganisms, including archaeal membrane lipids and archaeosome vesicles, have demonstrated immunostimulatory properties through activation of antigen-presenting cells and enhancement of T-cell responses. Experimental studies have suggested that these molecules can promote T helper type 1-skewed immune responses and increase production of protective cytokines, both of which are critical for TB control [25]. These characteristics support their potential value as candidates for host-directed TB immunotherapy [26].

Although most available evidence remains at the preclinical stage, the literature consistently suggests a mechanistic pathway involving innate immune activation through PRRs, followed by enhanced antigen presentation and strengthening of the IFN-γ axis, ultimately increasing the capacity of macrophages to eliminate *M. tuberculosis* [21,22,25]. Therefore, immunomodulation provides a strong conceptual foundation for TB immunotherapy, including exploration of biomolecules derived from the Indonesian volcanic soil microbiome within the GeoImmunology Nusantara framework [26].

GeoImmunology Nusantara as a conceptual framework for TB immunotherapy

GeoImmunology Nusantara is a conceptual framework that integrates geological factors, microbial ecology, and host immune responses in the development of TB immunotherapy based on Indonesia's local natural resources (**Figure 2**). Indonesia has one of the highest concentrations of active volcanoes in the world, generating volcanic soil ecosystems characterized by extreme conditions such as high temperatures, acidic pH, and distinctive mineral compositions. These conditions support unique communities of extremophilic microorganisms, providing a reservoir of biomolecules with structural and immunological properties that may differ from those of microorganisms inhabiting mesophilic environments [5].

Volcanic soil microbiomes are known to produce a wide range of bioactive molecules involved in host-microbe interactions, including membrane lipids, polysaccharides, and secondary metabolites capable of modulating innate immune responses. Adaptation of these microorganisms to extreme environmental stress may result in biomolecules with enhanced structural stability and resistance to degradation, potentially increasing their biological effectiveness within the human immune system [5]. These properties are particularly relevant for the development of immunomodulators targeting chronic infectious diseases such as TB [21].

Within the context of TB immunotherapy, the GeoImmunology Nusantara framework positions volcanic biomolecules as host-directed therapy agents that act by strengthening the host immune response rather than by exerting direct bactericidal effects (**Figure 2**). Activation of innate immune pathways through PRRs may enhance antigen presentation and promote differentiation of T helper type 1 cells, which are essential for control of *M. tuberculosis* [21,22]. Accordingly, biomolecules derived from volcanic soil microbiomes may function as supportive immunomodulators that complement standard antibiotic therapy [21].

This framework also aligns with the concept of trained immunity, whereby exposure to selected biomolecules induces epigenetic and metabolic reprogramming in innate immune cells, thereby enhancing their ability to respond to intracellular infection in a sustained manner. In endemic diseases such as TB, which require prolonged immune engagement, this strategy may strengthen population-level immune resilience without increasing the risk of antimicrobial resistance [22]. Therefore, GeoImmunology Nusantara is not only scientifically relevant, but also strategically important from a public health perspective [27].

Beyond its immunological implications, the GeoImmunology Nusantara framework offers a contextual approach that links Indonesia's geological potential with the development of locally grounded health innovation [5]. Utilization of volcanic soil microbiome resources as a basis for TB immunotherapy may support the principles of sustainability, research independence, and translational relevance in countries with a high TB burden [27]. GeoImmunology Nusantara may

therefore be viewed as an integrative paradigm that bridges earth science, microbiology, and immunology in support of TB control in Indonesia [21].

Although this concept remains at the conceptual and preclinical stages, synthesis of the current literature indicates that GeoImmunology Nusantara has a strong biological foundation for further development as a framework for identifying host-directed TB immunomodulators [22,26]. Further research is required to identify specific candidate biomolecules, define their immunological mechanisms, and evaluate their safety and translational potential [26].

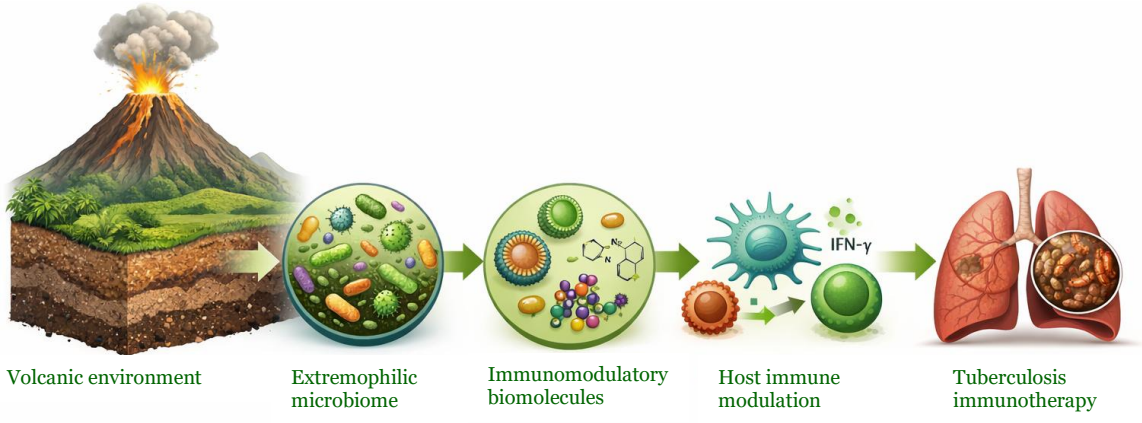

Figure 2. Schematic representation of GeoImmunology Nusantara as a conceptual framework for tuberculosis (TB) immunotherapy, linking volcanic ecosystems, extremophilic microbiomes, immunomodulatory biomolecules, host immune modulation, and TB treatment. Volcanic ecosystems may serve as reservoirs of extremophilic microorganisms that produce bioactive compounds with immunomodulatory potential. Through modulation of host immune pathways, these biomolecules may contribute to host-directed therapeutic approaches that complement conventional TB treatment.

Comparison of volcanic natural immunomodulators with conventional TB immunotherapy agents

Current advances in TB immunotherapy largely focus on host-directed therapy, an approach that seeks to modulate host immune responses in order to improve control of *M. tuberculosis* without applying direct selective pressure on the pathogen [21]. Within this framework, a range of conventional immunotherapeutic agents has been explored, including recombinant cytokines, synthetic adjuvants, and modulators of specific immune pathways targeting T-cell or macrophage responses. Although promising, these approaches often face limitations related to mechanistic complexity, production costs, and the risk of adverse effects arising from highly specific immune stimulation [28].

Conventional TB immunotherapy agents typically act by targeting specific immune pathways, such as enhancement of IFN-γ signaling, modulation of tumor necrosis factor alpha, or manipulation of immune checkpoints to promote T-cell activation. These highly targeted strategies offer mechanistic precision, but they may also increase the risk of immune imbalance or excessive inflammation if not carefully regulated [29]. In addition, most of these agents remain in early clinical development or require complex manufacturing infrastructure, thereby limiting accessibility in high-burden countries [28].

In contrast, natural immunomodulators derived from volcanic soil microbiomes may provide a broader and more adaptive strategy through pattern recognition receptor-based stimulation of innate immunity [22]. Extremophile-derived biomolecules, including archaeal lipids and metabolites from thermophilic microbes, may prime innate immune pathways and subsequently strengthen adaptive immune responses [25]. This mechanism is consistent with the concept of trained immunity, in which initial stimulation enhances immune responsiveness over the medium term without dependence on a single molecular target [22].

Another fundamental difference lies in the degree of immunological specificity. Conventional TB immunotherapy agents are generally designed to target one or a few defined immune pathways, whereas natural immunomodulators derived from volcanic environments

may promote a more balanced form of immune modulation through activation of multiple pathways. Such a multi-pathway approach may be particularly relevant in TB, a chronic disease characterized by complex and heterogeneous immune dynamics across individuals [21].

From the perspectives of safety and sustainability, natural immunomodulators may carry a lower risk of resistance because they do not directly target the pathogen [22]. In addition, biomolecules derived from Indonesia's volcanic environments offer an opportunity to develop locally sourced immunotherapies that may be more affordable and contextually appropriate than imported synthetic or recombinant agents [5]. Nevertheless, variability in natural biomolecular composition and the limited availability of toxicological data remain important challenges that require further investigation [26].

Overall, this comparison indicates that conventional TB immunotherapy agents and volcanic-derived natural immunomodulators possess distinct but potentially complementary advantages [21]. Conventional agents offer mechanistic precision, whereas natural immunomodulators may provide immunological flexibility and compatibility with locally grounded host-directed therapy approaches [22]. Within the GeoImmunology Nusantara framework, volcanic immunomodulators are therefore best viewed not as replacements for conventional therapy, but as strategic complements with the potential to enhance TB immunotherapy in a more holistic and sustainable manner [21].

Conclusion

Volcanic soil microbiomes may represent a promising source of immunomodulatory biomolecules capable of activating and regulating both innate and adaptive immune responses relevant to TB control. The GeoImmunology Nusantara framework offers a host-directed therapy perspective based on local natural resources and provides a conceptual basis for exploring Indonesia's volcanic biodiversity for TB immunotherapy. The exploration and utilization of Indonesia's volcanic soil microbiome merit further attention for the development of immunology-based TB interventions. Future studies should focus on elucidating the underlying immunological mechanisms, evaluating safety, and assessing the translational potential of candidate biomolecules for TB immunotherapy.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available publicly from the studies cited.

Declaration of artificial intelligence use

AI-based language models, ChatGPT, was employed for language refinement only (improving grammar, sentence structure, and readability of the manuscript). We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

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