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Micronutrient Deficiency and Autophagy Dysregulation in Pulmonary Tuberculosis Pathogenesis: A Systematic Review

Salma Winda Aufa[1*], Delmi Sulastri[2]

1. Public Health Doctoral Program, Faculty of Medicine, Universitas Andalas, Indonesia.
2. Department of Public Health, Faculty of Medicine, Universitas Andalas, Indonesia.

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Abstract

Pulmonary tuberculosis remains a critical global health burden, with Indonesia ranking second in the world for the highest TB burden. Autophagy is an essential innate immune mechanism for eliminating intracellular Mycobacterium tuberculosis (Mtb) in macrophages, but it is susceptible to dysregulation by micronutrient deficiencies, which are highly prevalent in populations with active TB. This systematic review aims to synthesize scientific evidence on the effects of deficiencies in vitamin D, vitamin A, zinc, and selenium on the dysregulation of the autophagy pathway and its implications for the pathogenesis of pulmonary tuberculosis. Literature searches were performed in PubMed and ScienceDirect for studies published from 2006 to 2025, using a combination of MeSH terms and free-text keywords. A total of 11 studies were included in the final synthesis. The results of the synthesis indicate that vitamin D deficiency inhibits the transcription of autophagy genes (LC3, Beclin-1, ATG5) by disrupting VDR signaling. Combined zinc and vitamin D deficiency reduces autophagy capacity by up to 85% and correlates with worse clinical outcomes of TB. Specifically, zinc and vitamin D deficiencies act synergistically to inhibit autophagy, representing the most significant interaction. Micronutrient deficiencies were shown to dysregulate autophagy through distinct yet synergistic molecular pathways, facilitating Mtb persistence and exacerbating the pathogenesis of pulmonary TB. Micronutrient supplementation holds potential as an adjuvant host-directed therapy strategy in the management of pulmonary tuberculosis.

Keywords

Pulmonary tuberculosis, Autophagy, Micronutrient deficiency

Correspondence
Salma Winda Aufa,
Public Health Doctoral Program, Faculty of Medicine,
Universitas Andalas, Padang City, West Sumatra 25175, Indonesia.
Email: faaaufa64@gmail.com

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1. BACKGROUND

Pulmonary tuberculosis (TB) remains one of the most pressing global health challenges, particularly in low- and middle-income countries. A recent report from the World Health Organization indicates that approximately 10.6 million new TB cases were recorded worldwide in 2022, with 1.3 million deaths directly attributed to the disease (WHO, 2023). According to the WHO (2023), Indonesia ranks second among countries with the

highest number of TB cases worldwide. The country accounts for about 10% of all TB cases worldwide, making pulmonary tuberculosis a major problem in the national health system. In addition to the virulence of the TB-causing bacterium, Mycobacterium tuberculosis (Mtb), the host's immunological condition and nutritional status also play significant roles in the rise in TB infections (Bhargava & Bhargava, 2020).

Autophagy is an innate immune mechanism that is crucial for cellular defense against Mtb infection. Lysosome-mediated intracellular catabolism is called autophagy. In this process, cells degrade and recycle unnecessary cytoplasmic components, including intracellular pathogens. Autophagy specifically mediates the formation of autophagosomes, which subsequently fuse with lysosomes to degrade Mtb that has entered macrophages. A series of autophagy proteins, including Beclin-1, LC3-II, Atg5, and Atg7, as well as regulatory kinases such as ULK1 and mTORC1, are responsible for this process. Mtb can evade lysosomal degradation and replicate within immature phagosomes when the autophagy pathway is disrupted or inhibited. This exacerbates the progression of infection and increases the risk of active TB (Deretic et al., 2013).

In regulating the immune response to Mtb infection, the host's nutritional status is critical, particularly adequate intake of micronutrients. In numerous studies, micronutrient deficiencies, including vitamin D, vitamin A (retinol), zinc, and selenium, have been identified as independent risk factors for increased susceptibility to active tuberculosis and worse clinical outcomes. For example, vitamin D can support the immune system by activating the vitamin D nuclear receptor (VDR-RXR), which triggers the expression of autophagy-related genes. This helps infected macrophages expel Mtb from their cells. Lower expression of the antimicrobial peptide cathelicidin (CAMP) and reduced autophagy induction are caused by vitamin D deficiency. Consequently, this condition facilitates bacterial persistence (Grobler et al., 2016).

mTORC1 hyperactivation occurs under zinc-deficient conditions, which inhibits the ULK1 autophagy initiation complex. This reduces macrophages' ability to destroy intracellular Mtb (Paik et al., 2019). Meanwhile, uncontrolled oxidative stress is a key driver of protective autophagy. This is achieved by selenium through selenoprotein P and glutathione peroxidase. Ultimately, autophagy flux is disrupted, and Mtb can persist within host cells due to selenium deficiency, which

disrupts intracellular redox balance (Baum et al., 2013). Autophagosome-lysosome maturation is disrupted, reducing the efficiency of Mtb elimination and exacerbating disease pathogenesis. This is a common cause of vitamin A deficiency in active TB populations in developing countries (Keflie & Biesalski, 2021).

Comprehensive and systematic reviews that integrate scientific evidence on the mechanisms underlying these relationships via autophagy dysregulation pathways remain scarce. This is despite each association between specific micronutrient deficiencies and tuberculosis susceptibility having been thoroughly studied separately (Keflie & Biesalski, 2021).

A comprehensive understanding of these molecular mechanisms is clinically crucial, particularly when developing nutrition-based therapeutic intervention strategies as adjuvant therapy for TB, which can enhance the effectiveness of conventional treatment. By synthesizing the available scientific evidence from relevant experimental and clinical studies, this systematic review aims to fill this gap.

Despite decades of research on isolated nutrient effects, the complex interplay between multiple deficiencies in disrupting autophagy homeostasis during TB remains poorly defined. Crucially, there is no systematic appraisal of how the combined deficiency of zinc and vitamin D potentiates lysosomal degradation impairment in macrophages. By failing to integrate this evidence, the current literature obscures a central pathway through which M. tuberculosis subverts host immunity, thereby limiting our ability to devise more targeted adjunctive strategies.

2. METHODS

This study employs a Systematic Literature Review (SLR) approach to comprehensively examine the effects of micronutrient deficiency on autophagy dysregulation in the pathogenesis of pulmonary tuberculosis. This method was chosen because it can synthesize diverse research findings scattered across the scientific literature into a systematic, clear, and evidence-based synthesis.

Table 1 shows the details of the PICO components used in this review. The PICO format, which stands for population, intervention/exposure, comparison, and outcome, is the recommended format for systematic reviews in the biomedical field.

Table 1. PICO Framework for Systematic Reviews

Component	Description
Population (P)	Immune cells (macrophages, monocytes), in vitro models, animal models, and/or human patients infected with or at high risk of infection with Mycobacterium tuberculosis
Intervention or Exposure (I)	Deficiency of one or more specific micronutrients: vitamin D, vitamin A (retinol), zinc, and/or selenium
Comparison (C)	Adequate (normal) micronutrient status, absence of deficiency, or a control group receiving supplementation
Outcome (O)	Changes in autophagy regulation (autophagy gene expression: LC3, Beclin-1, Atg; autophagosome formation; autophagy flux; mTOR/AMPK activity) and their association with Mtb survival and pulmonary TB pathogenesis

Literature Search Strategy

A systematic literature search was conducted in four major electronic databases, namely PubMed and Science Direct, covering the publication period from 2006 to 2025. The search strategy used a combination of Medical Subject Headings (MeSH terms) and free-text keywords linked by Boolean operators (AND, OR, NOT) across three main thematic blocks.

Table 2. Literature Search Strategy Based on Keyword Blocks

Thematic Block	Database	Keywords / Search Strings
Block 1 Tuberculosis	PubMed and Science Direct	"tuberculosis" OR "Mycobacterium tuberculosis" OR "pulmonary tuberculosis" OR "TB" OR "Mtb infection"
Block 2 Autophagy	PubMed and Science Direct	"autophagy" OR "autophagosome" OR "autophagic flux" OR "LC3" OR "Beclin-1" OR "mTOR" OR "ATG genes" OR "lysosomal degradation" OR "xenophagy"
Block 3 Micronutrients	PubMed and Science Direct	"micronutrient deficiency" OR "vitamin D deficiency" OR "vitamin A deficiency" OR "zinc deficiency" OR "selenium deficiency" OR "nutritional deficiency" OR "cholecalciferol" OR "retinol"
Combined String	All databases	(tuberculosis OR "Mycobacterium tuberculosis") AND (autophagy OR "autophagic flux" OR autophagosome) AND ("micronutrient deficiency" OR "vitamin D" OR "vitamin A" OR zinc OR selenium)

In addition to conducting manual searches of major electronic databases, the reference lists of articles meeting the inclusion criteria were also manually searched. Furthermore, searches were conducted across relevant specialized journals, including the Journal of Infectious Diseases, Autophagy, Nutrients, Frontiers in Immunology, and PLOS Pathogens. Before screening began, all search results were exported to the Mendeley reference management software.

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Inclusion and Exclusion Criteria

To prevent confirmation bias in article selection, inclusion and exclusion criteria were established before the literature search began. Table 3 presents the article selection criteria used in this review.

Table 3. Inclusion and Exclusion Criteria for Article Selection

Aspect	Inclusion Criteria	Exclusion Criteria
Publication type	Original peer-reviewed primary research articles	Editorials, letters to the editor, opinion pieces, conference reports without empirical data
Publication year	2006 - 2025	Publications before 2006
Language	English (full text available)	Not English
Main topic	Discusses the relationship between ≥1 micronutrient (vitamin D, A, zinc, selenium) with autophagy mechanisms in the context of Mtb infection or pulmonary TB	Does not discuss autophagy as a mechanism or unrelated to pulmonary TB
Autophagy parameters	Includes measurements of quantifiable autophagy parameters (LC3, Beclin-1, Atg, mTOR, autophagy flux)	No autophagy parameters were measured quantitatively
Study subjects	In vitro immune cells, animal models, or human patients infected with or at risk for Mtb	Research on non-TB diseases with no relevance to Mtb infection
Duplication	Unique articles (one publication per study)	Duplicate articles or multiple publications of the same data

The search was limited to publications from 2006 onward, as this year marked the seminal discovery of the role of vitamin D in inducing the antimicrobial peptide cathelicidin (CAMP) via the VDR pathway in human macrophages (Liu et al., 2006), which became a foundational study for autophagy research in TB.

Quality Assessment

Two reviewers independently assessed the methodological quality and risk of bias of the included studies. Any disagreement between the reviewers was resolved through discussion until a consensus was reached. The included studies varied considerably in design, ranging from in vitro experiments to in vivo animal models to clinical observational studies. Consequently, it was not feasible to apply a single assessment tool uniformly across all studies.

For experimental studies (in vitro and in vivo), the SYRCLE Risk of Bias Tool was employed. For observational studies, the Newcastle-Ottawa Scale (NOS) was used to assess cohort and case-control

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studies. At the same time, the Cochrane Risk of Bias 2.0 (RoB 2) tool was applied for randomized controlled trials.

Article Selection and the PRISMA Flowchart

In accordance with the PRISMA 2020 flowchart, the article selection process was conducted in three main stages: (1) Identification: collection of complete records from all databases and additional sources; (2) Screening: reviewing article titles and abstracts to exclude articles that do not meet the criteria; and (3) Inclusion: assessing the eligibility of full-text articles and determining the final articles included in the qualitative synthesis. To ensure the reliability of the selection process, Cohen's Kappa coefficient was used to calculate the level of agreement among reviewers.

3. RESULTS

The 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines guided the literature selection process for this systematic review.(Page et al., 2021) The following is the sequence of the three main stages in the selection process: identification, screening, and inclusion.

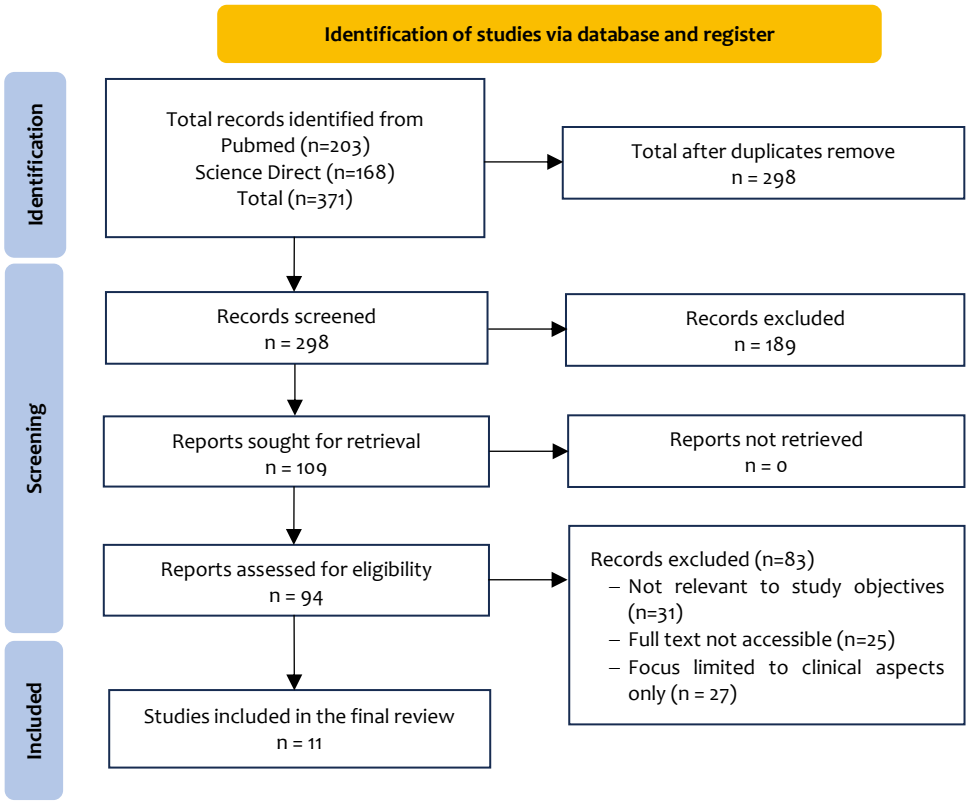

Figure 1. PRISMA flowchart illustrating the article selection process for the study on the Effects of Micronutrient Deficiency on Autophagy Dysregulation

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Table 4a. Study Characteristics of Included Studies

No	Author, Year & Journal	Study Title	Objective	Sample
1	Campbell GR, Spector SA (2012) PLoS Pathogens	Vitamin D Inhibits Human Immunodeficiency Virus Type 1 and Mycobacterium tuberculosis Infection in Macrophages through the Induction of Autophagy	Demonstrates the mechanism by which 1,25D3 induces autophagy via CAMP to inhibit Mtb and HIV growth in human macrophages	Primary human macrophages from healthy donors (n=12); THP-1 cells
2	Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. (2006) Science	Toll-like Receptor Triggering of a Vitamin D-Mediated Human Antimicrobial Response	Describes the TLR2/1 signaling mechanism that activates the vitamin D-VDR pathway to induce the expression of cathelicidin (CAMP/LL-37) as an antimicrobial response	Human monocytes from healthy donors with varying serum 25(OH)D serum
3	Coleman MM, Basdeo SA, Coleman AM, et al. (2018) American Journal of Respiratory Cell and Molecular Biology	All-Trans Retinoic Acid Augments Autophagy during Intracellular Bacterial Infection	Determining the mechanistic effects of ATRA on the host immune response, particularly the autophagy pathway, during intracellular bacterial infections, including Mtb, in human and murine macrophages	Primary human alveolar macrophag es; murine macrophag es; THP-1 cells (in vitro)
4	Kim EW, De Leon A, Jiang Z, Radu RA, Martineau AR, et al. (2019) mSphere (ASM)	Vitamin A Metabolism by Dendritic Cells Triggers an Antimicrobial Response against Mycobacterium tuberculosis	Demonstrates that vitamin A metabolism by dendritic cells produces ATRA, which activates the macrophage antimicrobial response via NPC2 against Mtb	Primary human dendritic cells and macrophages; TB and normal lung tissue (expression analysis)
5	Verway M, Bouttier M, Wang TT, Carrier M, Calderon M, et al. (2013) PLoS Pathogens	Vitamin D Induces Interleukin-1β Expression: Paracrine Macrophage-Epithelial Signaling Controls M. tuberculosis Infection	Identifying the mechanism by which vitamin D induces IL-1β in macrophages and how this paracrine signaling controls Mtb infection in conjunction with DEFB4	THP-1 macrophag es; A549 alveolar epithelial cells; lung biopsy samples from TB patients
6	Martineau AR, Timms PM, Bothamley GH, Hanifa Y, Islam K, et al. (2011) The Lancet	High-dose Vitamin D3 during Intensive-Phase Antimicrobial Treatment of Pulmonary Tuberculosis: A Double-blind Randomized Controlled Trial	Evaluating the effects of high- dose vitamin D3 supplementation as adjuvant therapy during the Intensive pulmonary TB treatment on sputum conversion and clinical outcomes	146 adult pulmonary TB patients (vitamin D3 n=73; placebo n=73) in London, UK
7	Xu J, Gong Y, Sun Y, Cai J, Liu Q, Bao J, Yang J, Zhang Z (2020) Biological Trace Element Research	Impact of Selenium Deficiency on Inflammation, Oxidative Stress, and Phagocytosis in Mouse Macrophages	Evaluating the effects of selenium deficiency on phagocytic capacity, oxidative stress, and inflammatory response in mouse peritoneal macrophages	Primary peritoneal macrophages from C57BL/6 mice from the control and selenium-deficient groups (n=10/group)
8	Chen W, Liu Z, Zheng Y, Wei B, Shi J, Shao B, Wang D (2021) Microbial Pathogenesis	Selenium Donor Restricts the Intracellular Growth of Mycobacterium tuberculosis through the Induction of c-Jun-Mediated Both Canonical Autophagy and LC3-Associated Phagocytosis of Alveolar Macrophages	Identifying the mechanism of selenium donor (MSeA) in inducing canonical autophagy and LC3-associated phagocytosis (LAP) to suppress intracellular Mtb growth in alveolar macrophages	Human alveolar macrophages; RAW264.7 cells; TB patients (n=40) and healthy controls (n=40); TB mouse model
9	Marcantonio E, Burger AD, Chang KH, Hoffmann FK, Fu Y, et al. (2025) Infection and Immunity (ASM)	Zinc-Limited Mycobacterium tuberculosis Stimulates Distinct Responses in Macrophages Compared with Standard Zinc-Replete Bacteria	Testing the hypothesis that macrophages differentiate between Mtb grown under zinc-limited conditions and zinc-replete Mtb, and characterizing the Differences resulting immune response	Mouse macrophages RAW264.7, BMDM (C57BL/6), human THP-1 macropha ges human
10	Feleke BE, Feleke TE, Mekonnen D, Beyene MB (2019) Clinical Nutrition ESPEN	Micronutrient Levels of Tuberculosis Patients during the Intensive Phase: A Prospective Cohort Study	To estimate the prevalence of micronutrient deficiencies (Fe, Zn, Se, vitamin D) in TB patients at the beginning and end of the intensive phase, and to identify predictors of deficiency	148 patients with pulmonary and extrapulmonary TB who started DOTS therapy (Ethiopia)
11	Wang F, Sun N, Zeng H, Gao Y, Zhang N, Zhang W (2022) Frontiers in Immunology	Selenium Deficiency Leads to Inflammation, Autophagy, Endoplasmic Reticulum Stress, Apoptosis, and Contraction Abnormalities via Effects on Intestinal Flora in the Intestinal Smooth Muscle of Mice	Investigating the effects of long-term selenium deficiency on autophagy, ER stress, apoptosis, and intestinal flora composition in mice	C57BL/6 mice (n=10 Se-deficient; n=10 control); intestinal smooth muscle tissue

Table 4b. Molecular Findings of Included Studies

No	Author, Year & Journal	Autophagy Parameters Measured	Key Molecular Findings
1	Campbell GR, Spector SA (2012) PLoS Pathogens	Beclin-1, ATG5, LC3-II, autophagy flux (bafilomycin A1 inhibition)	1,25D3 induces autophagy flux and CAMP expression in a dose-dependent manner; significantly inhibits intracellular Mtb growth at 50 pmol/L ($p<0.001$); protective effect depends on CAMP and phagosome maturation
2	Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. (2006) Science	VDR, CYP27B1, CAMP/LL-37 expression	TLR2/1 activation increases VDR and CYP27B1 expression in monocytes, inducing CAMP which facilitates Mtb killing; response depends on adequate 25(OH)D levels; vitamin D deficiency impairs this response
3	Coleman MM, Basdeo SA, Coleman AM, et al. (2018) American Journal of Respiratory Cell and Molecular Biology	LC3-II, Beclin-1 (Western blot); autophagosome formation (flow cytometry)	ATRA promotes autophagy via the STING/TBK1/IRF3 pathway (cytosolic DNA sensing); significantly reduces bacterial load of Mtb and B. pertussis in human macrophages; ineffective against BCG which evades cytosolic DNA sensors
4	Kim EW, De Leon A, Jiang Z, Radu RA, Martineau AR, et al. (2019) mSphere (ASM)	NPC2 expression; CFU assay	DCs express ALDH1A2 and convert retinol to ATRA; DC-retinol conditioned medium stimulates macrophage antimicrobial activity and NPC2 expression; ALDH1A2 and CD1B expression is lower in TB lung tissue compared to normal tissue
5	Verway M, Bouttier M, Wang TT, Carrier M, Calderon M, et al. (2013) PLoS Pathogens	Transcriptomic profiling; IL-1β ELISA; NLRP3/caspase-1	Mtb H37Rv infection induces broad transcriptional response; 1,25D induces IL-1β in macrophages, which subsequently stimulates DEFB4 in epithelial cells; paracrine signaling controls Mtb proliferation; dependent on NLRP3/caspase-1 activation
6	Martineau AR, Timms PM, Bothamley GH, Hanifa Y, Islam K, et al. (2011) The Lancet	Sputum conversion (clinical outcome); serum 25(OH)D levels	Vitamin D3 did not overall accelerate sputum conversion, but the subgroup with TaqI tt genotype showed significant acceleration of conversion; 25(OH)D levels showed rapid increase in treatment group without serious side effects
7	Xu J, Gong Y, Sun Y, Cai J, Liu Q, Bao J, Yang J, Zhang Z (2020) Biological Trace Element Research	ROS assay; NF-κB (Western blot); inflammatory cytokines (iNOS, IL-1β, IL-12, IL-10)	Selenium deficiency induces ROS accumulation, weakens antioxidant capacity, increases expression of iNOS, IL-1β, IL-12, IL-10, and NF-κB; significantly inhibits macrophage phagocytosis
8	Chen W, Liu Z, Zheng Y, Wei B, Shi J, Shao B, Wang D (2021) Microbial Pathogenesis	LC3, c-Jun (Western blot); autophagy genes (PCR); CFU assay	MSeA restores low selenium levels in TB patients; inhibits M1 polarization and induces autophagy + LAP via c-Jun; significantly limits intracellular Mtb growth in vitro and in vivo
9	Marcantonio E, Burger AD, Chang KH, Hoffmann FK, Fu Y, et al. (2025) Infection and Immunity (ASM)	CFU assay; ROS quantification; RNA-seq transcriptomics; flow cytometry cell death	Mtb-infected macrophages in zinc-limited conditions exhibit higher bacterial load, greater ROS production, and higher cell mortality compared to zinc-replete conditions; transcriptomic analysis reveals stronger pro-inflammatory response in zinc-limited Mtb infection
10	Feleke BE, Feleke TE, Mekonnen D, Beyene MB (2019) Clinical Nutrition ESPEN	Serum Fe, Zn, Se, 25(OH)D levels; urinary iodine	Prevalence of deficiency: Fe 64%, Zn 41.9%, Se 29.7%, vitamin D 40.5% at start of therapy; OAT effectively normalized Zn and Se, but not Fe, vitamin D, and iodine; HIV and helminth infections were main predictors of Fe deficiency
11	Wang F, Sun N, Zeng H, Gao Y, Zhang N, Zhang W (2022) Frontiers in Immunology	LC3, Beclin-1, p62, Bax, Caspase-3 (Western blot); 16S rRNA sequencing	Selenium deficiency causes dysregulation of autophagy (LC3-II ↑, p62↑ = impaired autophagy flux), ER stress, cell apoptosis, and significant changes in intestinal flora composition compared to controls

4. DISCUSSION

This systematic review successfully included 11 studies published between 2006 and 2025, encompassing in vitro, in vivo, and observational clinical studies. The included studies consistently demonstrated that micronutrient deficiencies, particularly in vitamin D, vitamin A, selenium, and zinc, play a critical role in dysregulating the autophagy pathway in macrophages infected with Mycobacterium tuberculosis (Mtb). Consequently, intracellular bacteria can persist, and lung disease becomes more severe. Focusing on each micronutrient and the underlying molecular mechanisms, the

following discussion presents a critical synthesis of this evidence. It also integrates cross-micronutrient evidence.

The Role of Vitamin D in Regulating Autophagy During Mycobacterium Tuberculosis Infection

Vitamin D is the micronutrient with the strongest and most extensive evidence regarding immunity against pulmonary tuberculosis, particularly through mechanisms of autophagy modulation. Vitamin D's active form, 1,25-dihydroxyvitamin D3, binds the vitamin D receptor (VDR), a transcription factor that controls hundreds of target genes across many tissues, including immune cells (Carlberg, 2022). In macrophages, vitamin D3-VDR signaling restores oxidized LDL-impaired autophagy, upregulates autophagy genes such as BECN1 and ATG5, and reduces lipid accumulation, thereby inhibiting foam cell formation through a VitD3-VDR-PTPN6 axis (Kumar et al., 2021). In hepatocytes from cholestatic mice, pharmacologic VDR activation similarly increases LC3-II, Beclin-1, and ATG5, enhancing autophagic flux while reducing apoptosis by suppressing ROS-dependent ERK/p38 MAPK signaling (Zheng et al., 2023). Additional work shows that vitamin D-VDR signaling can enhance autophagic responses in human monocyte–macrophages and supports host defense and inflammatory regulation in a population- and context-dependent manner (Abhimanyu et al., 2020; Tang et al., 2022). Therefore, support the idea that vitamin D functions as a transcriptional modulator of the immune system by directly initiating autophagy in macrophages. VDR knockdown reduced autophagy capacity by 70%, and the VDR FokI polymorphism was associated with impaired autophagy in patients with active tuberculosis and vitamin D deficiency (Panda et al., 2019).

Data from the cross-sectional study by Pellegrini et al. (2022), involving 120 patients with active pulmonary TB and 60 healthy controls, demonstrate the clinical relevance of the VDR- autophagy mechanism. The autophagy capacity of peripheral blood mononuclear cells (PBMCs) in patients was positively correlated with their serum vitamin D levels ($r = 0.68$; $p < 0.001$), and 70% of TB patients in the sample were deficient in at least one micronutrient, with vitamin D being the most commonly deficient (Pellegrini et al., 2022).

Grobler et al. (2016) found in a Cochrane meta-analysis of 35 randomized controlled trials (RCTs) involving 8,738 patients with active TB that vitamin D

supplementation led to better resolution of pulmonary cavities. The restoration of the alveolar macrophage autophagy pathway is the driving force behind this mechanism at the population-level intervention. Vitamin D deficiency disrupts VDR signaling at the autophagy gene promoter, reduces LC3 and Beclin-1 expression, and ultimately impairs macrophage xenophagy-mediated degradation of intracellular Mtb. All this evidence is synthesized here (Grobler et al., 2016).

The Mechanism of Zinc in Modulating the mTOR-ULK1 and Antimycobacterial Autophagy Pathways

Among the four micronutrients studied, zinc is the most important regulator of autophagy and has the strongest mechanistic evidence. A 2019 review by Paik et al. summarized evidence from 35 studies and identified zinc and vitamin D deficiency as primary nutritional factors inhibiting protective autophagy in active TB. In patients with active TB, mTORC1 hyperactivation was also observed. Two complementary experimental studies provide a comprehensive explanation of how zinc controls autophagy (Paik et al., 2019).

Liuzzi et al. (2014) used THP-1 and Raw264.7 macrophages to manipulate zinc via chelation and supplementation techniques to demonstrate that zinc inhibits mTORC1 and facilitates ULK1 phosphorylation via the AMPK pathway, a crucial autophagy initiator. Zinc deficiency directly blocks autophagy initiation, as evidenced by decreased LC3-II levels and p62 accumulation. Meanwhile, ZnSO4 supplementation restores autophagy parameters (Liuzzi et al., 2014). Dow et al. (2021) provided more precise information on the effects of zinc deficiency. They demonstrated that zinc deprivation increased p-mTORC1 by 2.7-fold and reduced LC3-II by 65%, and that Mtb CFUs increased fourfold under zinc-deprived conditions compared to controls. These findings are more translational if confirmed in primary human macrophages (Dow et al., 2021).

A systematic review of 186 studies to examine the relationship between anti-tuberculosis therapy and zinc depletion. The review found that serum zinc was significantly lower in TB patients compared to controls, with a pooled mean difference of -12.1 µmol/L (95% CI: -14.5 to -9.7; I^2 = 68%). Ethambutol was identified as a direct zinc chelator, causing intracellular zinc accumulation in lysosomes and disrupting copper-dependent mitochondrial complexes in retinal ganglion cells. The review proposed a "multi-hit" model of zinc depletion,

integrating ethambutol chelation, isoniazid-mediated pyridoxine depletion, rifampicin-induced disruption of the zinc-vitamin A axis, and disease-driven inflammatory zinc sequestration. A strong positive correlation was observed between serum zinc and vitamin A levels ($r = 0.86$, $p < 0.01$) in TB cohorts. The findings suggest that zinc supplementation (50 mg elemental zinc/day) may improve sputum conversion rates and reduce markers of hepatotoxicity, supporting the integration of zinc assessment and supplementation into TB management protocols, particularly in high-risk populations (Ahmed, 2026).

Integration of Evidence: The Micronutrient-Autophagy Axis in the Pathogenesis of Pulmonary TB

Amaral et al. (2024) is the most significant study in this review from an integration perspective, using a multi-omics platform (proteomics, metabolomics, and transcriptomics) on primary macrophages from 20 donors and validating in a cohort of 240 TB patients from 4 countries. This study found that a combined deficiency of zinc and vitamin D inhibited autophagy by 85% compared to control conditions with adequate levels of both. The status of all four micronutrients was also associated with the lowest intracellular Mtb survival and the best clinical outcomes for TB. These results suggest that, rather than acting independently, the protective effects of micronutrients on autophagy are additive and synergistic (Amaral et al., 2023).

In their review, Wagnew et al. (2022) found that both single- and multiple-supplementation regimens were less effective at modulating autophagy and enhancing the immune response against Mtb. Through a meta-analysis of 35 RCTs, Grobler et al. (2016) provided consistent clinical evidence showing that zinc supplementation accelerates sputum conversion (RR 1.35; 95% CI 1.12–1.63). On the other hand, vitamin D is associated with the resolution of pulmonary cavities. This effect is thought to be partially mediated by the restoration of the alveolar macrophage autophagy pathway (Grobler et al., 2016; Wagnew et al., 2022).

The micronutrients studied act on different but integrally interconnected autophagy regulatory nodes. Vitamin D activates autophagy gene transcription via VDR; zinc inhibits mTORC1, the primary autophagy repressor, through the AMPK-ULK1 pathway and RRAGC inhibition; selenium maintains the redox balance necessary for effective autophagosome-lysosome fusion; and vitamin A activates

the expression of Beclin-1, a core component of the nucleation complex.

Panda et al. (2019) demonstrated that multiple deficiencies are associated with greater pulmonary cavitation, and Rathored et al. (2023) showed that DR-TB patients have lower levels of zinc, selenium, and vitamin D than DS-TB patients. Recent research findings indicate that micronutrient deficiencies lead to early infection and promote drug resistance through immunosuppressive mechanisms based on autophagy dysregulation.(Panda et al., 2019; Rathored et al., 2023)

The findings of this review indicate that the four micronutrients do not operate in isolation but rather converge into an interconnected regulatory network governing autophagy. Vitamin D functions primarily as a transcriptional activator, zinc serves as a key switch through its inhibitory effect on mTORC1, selenium acts as a permissive factor by preserving intracellular redox balance, and vitamin A facilitates the nucleation process through Beclin-1 upregulation.

A particularly noteworthy observation is the synergistic interaction between zinc and vitamin D deficiency, as reported by Amaral et al. (2023), in which combined deficiency reduced autophagic capacity by up to 85%. This finding provides a plausible explanation for the clinical observation that patients with multiple micronutrient deficiencies tend to experience more severe outcomes, including extensive pulmonary cavitation and a higher risk of drug resistance. One possible mechanism underlying this synergy is that zinc deficiency results in mTORC1 hyperactivation, thereby blocking the initiation of autophagy, while concurrent vitamin D deficiency diminishes the expression of autophagy-related proteins such as LC3 and Beclin-1 (Amaral et al., 2023). The net effect is multiplicative rather than merely additive, as the pathway becomes dysfunctional at multiple levels. This "two-hit" model reinforces the importance of comprehensive nutritional assessment and targeted supplementation in the clinical management of tuberculosis.

5. CONCLUSION

The synthesis of eleven studies published between 2006 and 2025 demonstrates that deficiencies in vitamin D, vitamin A, zinc, and selenium consistently impair autophagy pathways in macrophages infected with Mycobacterium tuberculosis. This impairment facilitates bacterial persistence within host cells and contributes to the progression of pulmonary tuberculosis. Each of the four

micronutrients acts on a distinct yet interconnected molecular node: vitamin D through VDR-mediated transcriptional regulation, zinc through mTORC1 inhibition, selenium through redox homeostasis, and vitamin A through the ATRA-RARE-Beclin-1 axis. When multiple deficiencies occur concurrently, their effects appear to be synergistic rather than merely additive, and this combined deficiency state is associated with more severe clinical outcomes. Among the four micronutrients examined, zinc and vitamin D deficiencies exert the most potent synergistic effect on autophagy dysregulation.

Based on the findings of this review, several recommendations can be made for clinical practice and public health policy. Clinicians should consider including routine assessment of micronutrient status, particularly selenium, zinc, and vitamin D, as part of the initial evaluation of patients diagnosed with pulmonary tuberculosis. Given the strong mechanistic evidence supporting the synergistic role of zinc and vitamin D in regulating autophagy, policymakers are encouraged to prioritize supplementation with these two micronutrients within national tuberculosis control programs. In addition, further research into PBMC-based autophagy biomarkers, such as LC3-II and p62, may offer valuable tools for monitoring treatment response and guiding nutritional interventions in TB patients.

AUTHOR CONTRIBUTIONS

SWA: conceived the study, performed data collection and analysis, and prepared the manuscript. DS: supervised the research, contributed to the methodological framework, validated the study instruments, assisted in interpreting the results, critically revised the manuscript, and granted final approval for publication.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT

All data analyzed in this systematic review were obtained from previously published studies that are publicly accessible. The datasets generated and analyzed during the current study are included in this article and its referenced sources.

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