

## The Effect of Vitamin D Supplementation on Sputum Conversion in TB Patients: A Literature Review

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| Vitamin D Supplementation;<br>Pulmonary Tuberculosis; Sputum<br>Smear Conversion | <p>Tuberculosis (TB) remains a major global health challenge, with delayed sputum smear conversion continuing to affect treatment outcomes and disease transmission control. Vitamin D has received increasing attention as an adjunctive therapy in TB management due to its immunomodulatory role in enhancing macrophage activation and antimicrobial responses. However, evidence regarding the effectiveness of vitamin D supplementation in accelerating sputum conversion remains inconsistent across different populations and treatment protocols. This study aimed to evaluate the effect of vitamin D supplementation on sputum smear conversion among pulmonary tuberculosis patients and identify factors contributing to variations in treatment outcomes. A systematic literature review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Relevant studies published between 2016 and 2024 were identified through PubMed, Scopus, and Google Scholar databases using predefined keywords related to vitamin D supplementation, tuberculosis, and sputum conversion. Eligible primary studies, including randomized controlled trials, clinical trials, quasi-experimental studies, and observational studies, were analyzed descriptively. The findings revealed heterogeneous results, with several studies demonstrating accelerated sputum conversion following vitamin D supplementation, particularly among patients with baseline vitamin D deficiency and adequate supplementation dosage and duration. However, other studies reported no significant improvement, potentially due to differences in supplementation protocols, patient characteristics, and geographical factors. In conclusion, vitamin D supplementation shows potential as an adjunctive therapy for pulmonary tuberculosis, but current evidence remains insufficient to support universal application. Further standardized clinical studies are required to determine optimal dosage, duration, and target populations.</p> |

## INTRODUCTION

Pulmonary tuberculosis (TB), a communicable disease caused by *Mycobacterium tuberculosis*, remains a major global public health challenge. According to the Global Tuberculosis Report 2024 by the World Health Organization (WHO), an estimated 10.8 million new TB cases occurred worldwide in 2023, representing a slight yet steady increase compared to previous years. Despite a gradual decline in TB-related mortality from 1.40 million in 2020 to 1.25 million in 2023, TB continues to rank among the leading causes of death from a single infectious agent, particularly in the post COVID-19 era (World Health Association, 2024).

In Indonesia, which holds the second highest TB burden globally after India, case notifications reached 724,309 in 2022, the highest figure in the past decade and surpassing pre-pandemic levels. Primary healthcare centres (*Puskesmas*) accounted for the largest share of detected TB cases, contributing 72% of all suspected cases and 43% of confirmed notifications, whereas private clinics and independent medical practices contributed only 1% in both categories. Geographically, the highest proportion of suspected TB cases detected by private healthcare facilities was reported in West Java (21%), while Yogyakarta recorded the highest proportion of confirmed TB cases (42%). The steady increase in TB notifications from private healthcare facilities, from 21% of all national cases in 2018 to 28% in 2022, reflects the growing engagement of the private sector in TB control efforts (P2PM DKKR, 2023).

The substantial disease burden underscores the need for control strategies that extend beyond case detection and notification to ensuring optimal treatment outcomes. A key clinical target in TB management is achieving sputum smear conversion, defined as the change from acid-fast bacilli (AFB) positive to AFB negative status following the intensive phase of therapy. Sputum conversion not only serves as a critical marker of treatment efficacy but also plays a pivotal role in reducing disease transmission. Nevertheless, delayed or failed sputum conversion remains a challenge in some patients, influenced by factors such as nutritional deficiencies, comorbidities, treatment adherence, and micronutrient adequacy, including vitamin D, an essential modulator of macrophage activation and antimicrobial peptide production such as cathelicidin (Chung et al., 2020). Deficiency in vitamin D has been frequently observed among TB patients and is thought to impair phagocytic activity, delay bacterial clearance, and reduce treatment responsiveness (Patti et al., 2021).

Previous studies available in international databases such as Scopus and Google Scholar have provided diverse evidence regarding the relationship between vitamin D supplementation and TB treatment outcomes. Maulidar et al. (2021) reported that vitamin D supplementation combined with anti-tuberculosis medication improved sputum conversion among pulmonary TB patients in Indonesia. Similarly, Afzal et al. (2018) through a randomized clinical trial in Pakistan found that vitamin D supplementation contributed to earlier sputum conversion among smear-positive pulmonary TB patients. Lubis (2017) also demonstrated beneficial effects of complementary vitamin D therapy among TB patients. However, contrasting findings were reported by Ganmaa et al.

(2017), who conducted a large randomized controlled trial in Mongolia and found that high-dose vitamin D3 supplementation did not significantly accelerate sputum conversion. These contradictory findings indicate that the therapeutic effects of vitamin D may depend on specific conditions, including dosage, duration, baseline vitamin D status, and patient characteristics.

Further evidence from systematic reviews and meta-analyses also reveals uncertainty regarding the effectiveness of vitamin D as an adjunctive TB therapy. Jolliffe et al. (2019) conducted an individual participant data meta-analysis and suggested that vitamin D supplementation may provide benefits among individuals with specific genetic variations or baseline deficiency. Zhang et al. (2019) and Wang et al. (2018) similarly evaluated randomized controlled trials and found heterogeneous outcomes regarding vitamin D supplementation in pulmonary tuberculosis management. More recently, Meng et al. (2024) emphasized that although vitamin D plays an important immunological role in TB prevention and treatment, the available clinical evidence remains insufficient to establish universal recommendations. These studies suggest that existing evidence has not fully explained why vitamin D supplementation produces different outcomes across populations and treatment settings.

The inconsistency among previous studies represents an important research gap. Many previous investigations have focused on individual clinical trials or broad meta-analyses without deeply examining methodological differences that may contribute to conflicting findings. Variations in vitamin D dosage, supplementation duration, administration route, baseline serum vitamin D levels, geographical characteristics, and participant profiles may influence treatment responses but have not always been systematically synthesized. In addition, previous reviews often combined various types of evidence, including secondary studies, which may limit understanding of the direct clinical effects derived from primary research. Therefore, a comprehensive synthesis focusing specifically on primary studies, including randomized controlled trials and observational studies, is required to provide clearer evidence regarding the role of vitamin D supplementation in sputum smear conversion among pulmonary TB patients.

The urgency of this research is strengthened by the continued global burden of tuberculosis and the need for complementary approaches to improve treatment effectiveness. Although anti-tuberculosis drugs remain the cornerstone of TB management, treatment failure, delayed conversion, and prolonged infectious periods continue to create challenges for TB control programs. Identifying supportive interventions that can enhance host immunity may provide valuable clinical implications, especially in populations with nutritional deficiencies. Vitamin D supplementation represents a relatively accessible and affordable intervention; however, its implementation requires stronger evidence regarding which patient groups are most likely to benefit. Therefore, evaluating existing evidence systematically is essential to support evidence-based decision-making in tuberculosis management.

This research provides novelty by focusing exclusively on the synthesis of primary scientific evidence regarding the effect of vitamin D supplementation on sputum smear

conversion among pulmonary tuberculosis patients. Unlike previous reviews that mainly emphasized pooled statistical outcomes, this study examines variations in study characteristics, intervention protocols, patient conditions, and contextual factors that may explain differences in findings. By identifying determinants associated with positive or negative treatment responses, this research contributes a more comprehensive understanding of when vitamin D supplementation may be clinically beneficial. The novelty also lies in highlighting the importance of baseline vitamin D status, dosage standardization, supplementation duration, and population characteristics as critical considerations for future clinical research.

Based on these considerations, this study aims to evaluate the effect of vitamin D supplementation on sputum smear conversion among pulmonary tuberculosis patients through a systematic literature review approach. Specifically, this research seeks to identify patterns of effectiveness, compare findings across previous studies, and explore factors contributing to variations in treatment outcomes. The contribution of this study is expected to enrich scientific knowledge regarding nutritional immunomodulation in tuberculosis therapy and provide evidence for researchers, healthcare professionals, and policymakers in developing more targeted adjunctive treatment strategies. Furthermore, the findings may serve as a foundation for future clinical trials by emphasizing the need for standardized methodologies, appropriate patient selection, and comprehensive assessment of vitamin D status before supplementation.

## **METHOD**

This systematic literature review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review aimed to evaluate the effect of vitamin D supplementation on sputum smear conversion among patients with pulmonary tuberculosis.

### **Search Strategy**

A systematic search was performed across PubMed, Scopus, and Google Scholar for articles published between 2016 and 2024. Boolean operators were used to combine the following terms:

1. “vitamin D” OR “cholecalciferol” OR “calcitriol”
2. “tuberculosis” OR “pulmonary TB”
3. “sputum conversion” OR “sputum smear” OR “AFB conversion”

The full search string for PubMed was:

**(“vitamin D” OR cholecalciferol OR calcitriol) AND (“tuberculosis” OR “pulmonary TB”) AND (“sputum conversion” OR “sputum smear” OR “AFB”).**

Reference lists of included articles were manually screened to identify additional eligible studies (snowballing).

## **RESULTS AND DISCUSSION**

The selection of articles in this literature review was primarily guided by the research objective, which is to evaluate the effect of vitamin D supplementation on AFB

conversion in pulmonary tuberculosis patients. A total of 10 articles, published between 2016 and 2024, were identified as relevant through databases such as PubMed, Google Scholar, and Scopus.

These studies were analyzed based on specific details, including authorship, data collection design, study location, and key results related to the effectiveness of vitamin D in tuberculosis management. A summary table was constructed to facilitate comparison and mapping of findings across studies. This descriptive overview aims to provide insight into the patterns and trends observed in different settings and research methodologies.

**Table 1. Characteristics of Studies on the Effect of Vitamin D Supplementation on Sputum AFB Conversion in Pulmonary Tuberculosis Patients**

| No. | Authors                          | Study Design and Period                                                               | Study Location                                    | Outcome       |
|-----|----------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------|---------------|
| 1   | Rina Maulidar et al. (2021)      | Quasi-experimental pre-post control group over 4 months in 2019                       | Pidie District, Indonesia                         | Effective     |
| 2   | Arbab Afzal et al. (2018)        | Randomized clinical trial (Nov 2015 – Aug 2016)                                       | Mayo Hospital, Lahore, Pakistan                   | Effective     |
| 3   | Nita Andriani Lubis (2017)       | Randomized controlled trial (Nov 2015 – Jun 2016)                                     | Community Health Centers, Deli Serdang, Indonesia | Effective     |
| 5   | Haibo Yang et al. (2022)         | Cohort study (Jun 2020 – May 2021)                                                    | Linyi People's Hospital, China                    | Not Effective |
| 6   | Yatish Byndoor et al. (2023)     | Prospective, randomized, double-blind, placebo-controlled trial                       | Tertiary Care Center, South India                 | Effective     |
| 7   | Erica, et al. (2019)             | Quasi-experimental (May – Oct 2017)                                                   | Medan Community Health Area, Indonesia            | Not Effective |
| 8   | Davaasambuu Ganmaa et al. (2017) | Randomized clinical trial on 390 adult TB patients during intensive phase (2012–2014) | Ulaanbaatar, Mongolia                             | Not Effective |
| 10  | Youli Wen et al. (2022)          | Single-blind controlled clinical trial (Jun 2016 – Apr 2017)                          | Zigong First People's Hospital, China             | Effective     |
| 12  | Alam et al. (2019)               | Randomized placebo-controlled trial (Jun – Nov 2017)                                  | Nishtar Hospital, Multan, Pakistan                | Not Effective |
| 15  | Sinha et al. (2023)              | Randomized double-blind placebo-controlled trial (Feb 2017 – Feb 2021)                | India                                             | Not Effective |

Based on the literature reviewed, the effect of vitamin D supplementation on sputum smear conversion among patients with pulmonary tuberculosis demonstrates considerable variability across studies. Such discrepancies in findings are likely

influenced by several interrelated factors, including variations in dosage and duration of supplementation, the route of administration, baseline vitamin D status prior to intervention, and the geographical as well as population characteristics of the study settings. A critical examination of these factors is essential to better elucidate the potential role of vitamin D as an adjuvant therapy in pulmonary tuberculosis management, while also identifying existing research gaps that warrant further investigation.

### **Variation in Dosage and Duration of Administration**

The dosage and duration of vitamin D supplementation are critical determinants of its efficacy as an adjuvant therapy for various diseases, including pulmonary tuberculosis. From a pharmacological perspective, an optimal dosage is required to achieve sufficient serum concentrations, whereas the duration of administration influences the sustainability of vitamin D's immunomodulatory effects throughout the treatment phase. Variability in these two factors may partly explain the inconsistencies reported in studies evaluating the effect of vitamin D on sputum smear conversion.

Several studies have supported this relationship by demonstrating improved clinical outcomes with specific dosage and duration protocols. Daily oral supplementation of 5,000 IU of vitamin D for four months was associated with a faster sputum smear conversion among pulmonary tuberculosis patients. Similarly, intramuscular administration of 100,000 IU vitamin D given every two weeks during the intensive phase, with a total of four doses, also resulted in a significant improvement in sputum conversion by the eighth week. Comparable positive effects were observed with oral doses of 2.5 mg per day, 0.25 mg daily over a six-week period, and calcitriol supplementation at a dose of 0.25 µg twice daily, particularly in individuals with low baseline serum vitamin D levels.

However, not all studies have yielded consistent results. Several investigations utilizing lower doses or shorter supplementation periods failed to demonstrate a significant effect on sputum smear conversion. For instance, although vitamin D levels were shown to modulate T-cell immune responses, no significant improvement in conversion time was reported in patients receiving lower-dose regimens. Similarly, a trial involving four doses of 140,000 IU administered during the intensive phase did not result in accelerated conversion rates (Soeharto et al., 2019). Additional studies also support this trend, suggesting that limited duration and variability in baseline serum vitamin D levels may attenuate the potential clinical benefits of supplementation, even when high doses are used periodically (Ganmaa et al., 2017).

These observations suggest that the efficacy of vitamin D supplementation in accelerating AFB sputum conversion is influenced not only by the magnitude of the dose but also by the duration of administration and the consistency of the supplementation protocol. Standardizing both dosage and duration in future clinical trials is essential to ensure more consistent outcomes and facilitate meaningful comparisons across studies.

### **Route of Vitamin D Supplementation**

The route of vitamin D supplementation can influence its bioavailability, absorption kinetics, and the resulting serum concentration, thereby potentially affecting

its efficacy in accelerating sputum smear conversion among patients with pulmonary tuberculosis. From a pharmacokinetic perspective, intramuscular administration may lead to a more rapid and sustained increase in serum vitamin D levels, whereas oral administration is more dependent on patient adherence, gastrointestinal function, and dietary interactions. Variability in the route of administration across studies may thus contribute to the heterogeneity of reported outcomes.

Several studies have reported favorable outcomes with intramuscular administration of vitamin D. For example, administration of 100,000 IU intramuscularly every two weeks for a total of four doses during the intensive treatment phase was associated with significantly faster sputum smear conversion compared to control groups. These findings suggest that intramuscular delivery may help maintain optimal serum vitamin D levels over time, potentially enhancing the host immune response against *Mycobacterium tuberculosis* and improving treatment outcomes.

In addition to intramuscular administration, several studies utilizing oral supplementation have also reported positive effects. Daily administration of 5,000 IU of vitamin D for four months was shown to accelerate sputum smear conversion among patients with pulmonary tuberculosis. Comparable improvements were observed with daily oral doses of 2.5 mg and 0.25 mg over a six-week period[1]. Oral supplementation is considered more feasible for implementation in primary care settings; however, its effectiveness may be influenced by factors such as patient adherence, gastrointestinal absorption, and dietary interactions.

Overall, both oral and intramuscular forms of vitamin D administration can yield effective outcomes when combined with adequate dosage and duration. Nevertheless, intramuscular administration has the potential to achieve more stable serum concentrations, whereas oral administration offers greater practicality but requires a high level of patient adherence. Further controlled studies are warranted to directly compare the effectiveness of these two administration routes in homogeneous populations.

### **Baseline Vitamin D Levels**

Baseline serum vitamin D levels represent a critical determinant of patient responsiveness to supplementation. Physiologically, individuals with severe vitamin D deficiency are more likely to exhibit a pronounced response to supplementation compared with those whose baseline levels are normal or near-normal. This enhanced responsiveness is primarily attributed to the increased sensitivity of the immune system to vitamin D restoration, particularly through pathways involving macrophage activation and the induction of antimicrobial peptides. Variations in baseline vitamin D status across study populations may therefore partly explain the heterogeneity in reported outcomes regarding the effect of supplementation on sputum smear conversion.

Several investigations that incorporated baseline serum vitamin D assessments prior to supplementation have reported a positive correlation between lower initial levels and enhanced treatment outcomes. One study measured pre- and post-supplementation serum vitamin D using the ELISA method and observed that individuals receiving vitamin D supplementation exhibited faster sputum smear conversion than those in the

placebo group. Similarly, another study evaluating 25-hydroxyvitamin D levels at the start of treatment and at week eight found that increases in serum levels were associated with shorter time to sputum conversion. These findings underscore the importance of monitoring baseline vitamin D status to better predict patient responsiveness and optimize the efficacy of adjunctive therapy in pulmonary tuberculosis.

In contrast, other studies that also assessed baseline serum vitamin D levels reported no consistent association between initial concentrations and sputum smear conversion outcomes. One investigation found that although serum vitamin D levels increased following intramuscular supplementation, the improvement in sputum conversion time was not observed uniformly across all patient subgroups. Another study reported that the use of calcitriol resulted in accelerated conversion only among individuals with low baseline levels, whereas those with normal serum concentrations exhibited no significant change in treatment response (Soeharto et al., 2019). These findings imply that the therapeutic benefit of vitamin D supplementation may be confined primarily to patients with documented deficiency prior to intervention.

Overall, baseline vitamin D status appears to be a key determinant of responsiveness to supplementation, particularly among patients with severe deficiency. Therefore, assessing serum vitamin D levels prior to initiating supplementation could be an important step toward personalizing adjunctive therapy for pulmonary tuberculosis. Further studies incorporating consistent baseline and post-intervention measurements are warranted to clarify this relationship.

### **Geographical and Population Characteristics**

Geographical and population characteristics may influence the effectiveness of vitamin D supplementation in patients with pulmonary tuberculosis through several mechanisms, including sunlight exposure, dietary patterns, nutritional status, and the prevalence of vitamin D deficiency in specific regions. These factors play an important role in determining patients' baseline vitamin D levels prior to intervention and their subsequent response to supplementation. In addition, genetic variations affecting vitamin D metabolism and differences in healthcare system capacity across countries may contribute to the heterogeneity of study outcomes.

Several investigations conducted in tropical regions with abundant sunlight exposure, including Indonesia and India, have yielded mixed findings regarding the effectiveness of vitamin D supplementation in accelerating sputum smear conversion. In one study conducted in Pidie, Indonesia, supplementation with 5,000 IU of vitamin D daily over four months resulted in a faster conversion time. Comparable outcomes were documented in Deli Serdang, Indonesia, and in southern India, where patients receiving daily oral vitamin D showed improved sputum conversion rates (Byndoor et al., 2023). These findings suggest that, despite high environmental availability of ultraviolet B radiation, vitamin D deficiency remains prevalent in these regions. Contributing factors may include limited sun exposure due to clothing practices, indoor lifestyles, and inadequate dietary intake, all of which can compromise endogenous vitamin D synthesis and reduce responsiveness to supplementation.

In contrast to studies conducted in tropical regions, research from China has further emphasized the influence of baseline vitamin D status on treatment outcomes. In one investigation, participants with sufficient serum vitamin D levels demonstrated enhanced CD4+ and CD8+ T cell responses following supplementation, although no significant improvement was observed in the time to sputum smear conversion[6]. Conversely, a separate study found that individuals with low baseline vitamin D levels who received calcitriol supplementation exhibited significantly accelerated sputum conversion compared to their counterparts. These findings support the hypothesis that vitamin D supplementation may confer the greatest clinical benefit among patients with pre-existing deficiency, particularly in populations residing in regions with lower sunlight exposure.

Overall, geographical and population characteristics play a pivotal role in determining baseline vitamin D status, which in turn can influence the success of supplementation in accelerating sputum smear conversion. Future studies should explicitly account for these factors in their design, including the measurement of sunlight exposure, dietary intake of vitamin D-rich foods, and lifestyle habits that affect vitamin D metabolism.

Based on the synthesis of available literature, the effectiveness of vitamin D supplementation in expediting sputum smear conversion among patients with pulmonary tuberculosis is influenced by a set of interrelated factors, including variations in dosage and duration of administration, the form of supplementation, baseline vitamin D levels prior to intervention, and the geographical and demographic characteristics of the study population. Studies employing adequate dosages, sufficient duration, and baseline level monitoring generally report more consistent results, whereas those with heterogeneous protocols and limited assessment of contributing factors tend to yield mixed findings. Differences in the route of administration, whether oral or intramuscular, also affect bioavailability and clinical response, which may further be shaped by patient adherence and nutritional status. Geographic variability adds another layer of complexity, as differences in sunlight exposure, dietary patterns, and lifestyle practices contribute to population-level vitamin D status. Therefore, future research should adopt more standardized designs that comprehensively account for these determinants, enabling a clearer understanding of the role of vitamin D as an adjuvant therapy in the management of pulmonary tuberculosis.

### **Summary**

Based on a review of 10 publications encompassing controlled clinical trials, cohort studies, meta-analyses, and systematic reviews, the impact of vitamin D supplementation on the acceleration of sputum smear conversion in patients with pulmonary tuberculosis demonstrates heterogeneous findings. Among these studies, five reported positive effects, particularly in populations with baseline vitamin D deficiency, the use of adequate dosage and supplementation duration, and regular monitoring of serum levels during therapy. In contrast, nine studies did not find a significant association, which may be attributed to variations in study design, sample size, vitamin D formulation

(oral, intramuscular, or active form), supplementation duration, and the diversity of baseline vitamin D levels among participants.

Geographical variability also emerged as a contributing factor to the inconsistency of findings. Several large-scale randomized clinical trials and multinational meta-analyses reported no significant benefit of high-dose vitamin D supplementation in accelerating sputum smear conversion among pulmonary tuberculosis patients [8]. In contrast, studies conducted in Indonesia demonstrated more favorable outcomes, with accelerated sputum conversion observed following consistent daily supplementation [9]. These regional discrepancies underscore the potential influence of environmental exposure, baseline nutritional status, and population-specific characteristics on the effectiveness of adjunctive vitamin D therapy.

Overall, the current body of evidence remains insufficient to support the routine use of vitamin D supplementation as an adjunctive therapy for all patients with pulmonary tuberculosis. Future research should employ more standardized study designs, enroll populations with measured vitamin D levels both before and after the intervention, and account for factors such as dosage, duration, mode of administration, and population-specific characteristics. Such considerations are essential to generate more definitive and clinically relevant conclusions that can inform practice.

## CONCLUSION

This systematic literature review found that vitamin D supplementation shows potential benefit in accelerating sputum smear conversion among pulmonary tuberculosis patients, particularly in individuals with baseline vitamin D deficiency and when adequate doses and durations are used; however, the overall evidence remains inconsistent across studies. These findings highlight that vitamin D may serve as a supportive adjunct in TB management, especially in populations at risk for deficiency, although the current evidence is insufficient to recommend routine supplementation as part of standard care. Compared with previous meta-analyses, this review offers a novel contribution by exclusively synthesizing primary research namely randomized controlled trials and observational studies allowing a clearer appraisal of study heterogeneity and methodological differences that may explain the conflicting results reported in the literature. Moving forward, future studies should adopt more standardized research methods, include pre- and post-supplementation serum vitamin D assessments, and take into account nutritional status, geographical differences, and population characteristics in order to more accurately determine the clinical effectiveness of vitamin D supplementation in TB patients.

## REFERENSI

- Afzal A, Rathore R, Butt NF, Randhawa FA. Efficacy of vitamin D supplementation in achieving an early sputum conversion in smear positive pulmonary tuberculosis. *Pak J Med Sci*. 2018;34:849–54. <https://doi.org/10.12669/pjms.344.14397>.
- Alam M, Tahir A, Ullah R. Effect of Vitamin D supplements and pulmonary tuberculosis prognosis in known diabetic patients. *Pakistan Journal of Medical and Health Sciences*. 2019;13:903–5.
- Bilezikian JP, Formenti AM, Adler RA, Binkley N, Bouillon R, Lazaretti-Castro M, et al. Vitamin D: Dosing, levels, form, and route of administration: Does one approach fit all? *Rev Endocr Metab Disord*. 2021;22:1201–18. <https://doi.org/10.1007/s11154-021-09693-7>.
- Bösch ES, Spörri J, Scherr J. Vitamin Metabolism and Its Dependency on Genetic Variations Among Healthy Adults: A Systematic Review for Precision Nutrition Strategies. *Nutrients*. 2025;17:1–19. <https://doi.org/10.3390/nu17020242>.
- Byndoor Y, Sagar TV, Patil RH, Veeraiah D. Vitamin D as Supplementary Treatment for Newly Diagnosed Pulmonary Tuberculosis patients. *Res J Pharm Technol*. 2023;16:4924–8. <https://doi.org/10.52711/0974-360X.2023.00798>.
- Chung C, Silwal P, Kim I, Modlin RL, Jo EK. Vitamin D-cathelicidin axis: At the crossroads between protective immunity and pathological inflammation during infection. *Immune Network*. 2020;20(2).
- Diguilio KM, Rybakovsky E, Abdavies R, Chamoun R, Flounders CA, Shepley-McTaggart A, et al. Micronutrient Improvement of Epithelial Barrier Function in Various Disease States: A Case for Adjuvant Therapy. *Int J Mol Sci*. 2022;23. <https://doi.org/10.3390/ijms23062995>.
- El Abd A, Dasari H, Dodin P, Trottier H, Ducharme FM. The effects of vitamin D supplementation on inflammatory biomarkers in patients with asthma: a systematic review and meta-analysis of randomized controlled trials. *Front Immunol*. 2024;15. <https://doi.org/10.3389/fimmu.2024.1335968>.
- Erica E, Sari DK, Siregar DIS, Mega JY. Vitamin D and hemostasis parameters in human immunodeficiency virus/acquired immunodeficiency syndrome patients with pulmonary tuberculosis coinfections. *Open Access Maced J Med Sci*. 2020;8:312–8. <https://doi.org/10.3889/oamjms.2020.4283>.
- Ganmaa D, Munkhzul B, Fawzi W, Spiegelman D, Willett WC, Bayasgalan P, et al. High-dose Vitamin D3 during tuberculosis treatment in Mongolia a randomized controlled trial. *Am J Respir Crit Care Med*. 2017;196:628–37. <https://doi.org/10.1164/rccm.201705-0936OC>.
- Jolliffe DA, Ganmaa D, Wejse C, Raqib R, Haq MA, Salahuddin N, et al. Adjunctive vitamin D in tuberculosis treatment: Meta-analysis of individual participant data. *European Respiratory Journal*. 2019;53(3).
- Lubis NA. The Effect of Complementary Vitamin D on Sputum Conversion in Pulmonary TB Patients. *Indonesian Journal of Medicine*. 2017;2:169–74. <https://doi.org/10.26911/theijmed.2017.02.03.04>.

- Maulidar R, Nurjannah N, Adamy A, Iskandar I. Pengaruh pemberian obat anti tuberkulosis dengan vitamin D terhadap perubahan BTA pada penderita tuberkulosis paru di Kabupaten Pidie. *Jurnal SAGO Gizi Dan Kesehatan*. 2021;2:25. <https://doi.org/10.30867/gikes.v2i1.442>.
- Meng J, Li X, Wu Y, Liu P, Gao S. The Role of Vitamin D in the Prevention and Treatment of Tuberculosis: A Meta-analysis of Randomized Controlled Trials. 2024.
- Murugaiha JS. Micronutrient Deficiency in Pulmonary Tuberculosis - Perspective on Hepatic Drug Metabolism and Pharmacokinetic Variability of First-line Anti-Tuberculosis Drugs: Special Reference to Fat-soluble Vitamins A, D, & E and Nutri-epigenetics. *Drug Metab Lett*. 2021;14:166–76. <https://doi.org/10.2174/1872312814999211130093625>.
- P2PM DKKR. Laporan Program Penanggulangan Tuberkulosis Tahun 2022. Kemenkes RI. 2023;1–139.
- Patti G, Pellegrino C, Ricciardi A, Novara R, Cotugno S, Papagni R, et al. Potential role of vitamins A, B, C, D and E in TB treatment and prevention: A narrative review. *Antibiotics*. 2021;10(11):1–16.
- Santana KV de S de, Oliver SL, Mendes MM, Lanham-New S, Charlton KE, Ribeiro H. Association between vitamin D status and lifestyle factors in Brazilian women: Implications of Sun Exposure Levels, Diet, and Health. *EClinicalMedicine*. 2022;47:1–12. <https://doi.org/10.1016/j.eclim.2022.101400>.
- Sinha S, Thukral H, Shareef I, Desai D, Singh BK, Das BK, et al. Prevention of relapse in drug sensitive pulmonary tuberculosis patients with and without vitamin D3 supplementation: A double blinded randomized control clinical trial. *PLoS One*. 2023;18:1–15. <https://doi.org/10.1371/journal.pone.0272682>.
- Soeharto DA, Rifai DA, Marsudidjadja S, Roekman AE, Assegaf CK, Louisa M. Vitamin D as an Adjunctive Treatment to Standard Drugs in Pulmonary Tuberculosis Patients: An Evidence-Based Case Report. *Adv Prev Med*. 2019;2019:1–10.
- Wang J, Feng M, Ying S, Zhou J, Li X. Efficacy and safety of vitamin D supplementation for pulmonary tuberculosis: A systematic review and meta-analysis. *Iran J Public Health*. 2018;47(4):466–72.
- Wen Y, Li L, Deng Z. Calcitriol supplementation accelerates the recovery of patients with tuberculosis who have vitamin D deficiency: a randomized, single-blind, controlled clinical trial. *BMC Infect Dis*. 2022;22. <https://doi.org/10.1186/s12879-022-07427-x>.
- Wohlin C, Kalinowski M, Romero Felizardo K, Mendes E. Successful combination of database search and snowballing for identification of primary studies in systematic literature studies. *Inf Softw Technol*. 2022;147:106908. <https://doi.org/10.1016/j.infsof.2022.106908>.
- World Health Association. 2024 Global tuberculosis report. 2024.
- Yang H, Chen H, Ma Y, Dong Z, Ni M, Lin Y, et al. Effects of 25-hydroxy vitamin D on T lymphocyte subsets and sputum smear conversion during antituberculosis

treatment. *International Journal of Infectious Diseases*. 2022;121:17–23.  
<https://doi.org/10.1016/j.ijid.2022.04.056>.

Zhang J, Chen C, Yang J. Effectiveness of vitamin D supplementation on the outcome of pulmonary tuberculosis treatment in adults: A meta-analysis of randomized controlled trials. *Chin Med J (Engl)*. 2019;132(24):2950–9.