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VITAMIN D: FUTURE THERAPEUTIC WEAPON TO FIGHT TUBERCULOSIS

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ABSTRACT

Vitamin D is well acknowledged for calcium homeostasis is a fat soluble vitamin whose scarcity could cause metabolic disorders infectious diseases and rickets and osteomalacia. *Mycobacterium tuberculosis* (*MTB*), is an ancient pathogen that through an evolutionally developed complex mechanism to immune surveillance and acquire the ability to establish persistent infection, tuberculosis (TB) in its host. There are emerging evidences suggesting the relation of vitamin D deficiency in establishing tuberculosis. This review summarises the importance of Vitamin D for the treatment of tuberculosis. Since the efficacy has depleted of the Bacille Calmette Guerin (BCG), the only approved TB vaccine so there is a need to investigate for a new vaccine candidate. Previous studies suggest that the incidence and severity of tuberculosis are associated with low levels of Vitamin D and it is associated with an increased risk for emerging active TB infection. In vitro logistical data shows that Vitamin D increase innate immune response against the growth of *MTB* giving a high dose of Vitamin D on TB patients. Recent studies concluded that the Vitamin D can be recommended for the adjunctive therapy in treating and prevention of TB, in combination with anti-tuberculosis drugs.

Key words: Tuberculosis, Vitamin D, BCG, Therapy, Diagnosis.

1. INTRODUCTION

Tuberculosis (TB) is one of the most important hazardous diseases and come under among the top 10 diseases in the world. According to World Health Organization (WHO), in the 2019 around 10 million people were affected with TB worldwide, and the count has been dropping frequently **[1]**. However, about one fourth peoples were infected by *Mycobacterium tuberculosis (MTB)* having critical problems such as infection by drug-resistant TB (DR-TB) strains, co-infection with HIV virus, along with latent TB (LTBI) infection. While LTBI individuals are asymptomatic and cannot infect others, but in some cases, they may develop active TB and effects healthy individuals **[2–4]**. The current TB treatment is time consuming and in some cases such as co-infection with HIV, DR-TB, and cases having side effects, therapeutic protocols may

have serious limitations. Therefore, it is urgently needed to develop the novel therapeutic agents to reduce the treatment time and reduce the growth of bacteria**.** Williams first used Vitamin D in 1849 and noticed that fish liver oil improves the powerful effect on TB patients **[5].** Vitamin D has calcitriol, the active biological form of Vitamin D, has in vitro anti-TB effects **[6].** In recent literature has been shown that the serum level of vitamin D has remarkable relationship with TB **[7–9].** Literature also shown that the polymorphisms such as TaqI in the VDR gene also affect the development of TB **[7].** Thus, it shows that vitamin D by refining the immune system responses causes the shorten course of TB treatment, increasing the intercellular elimination of *MTB,* falling transmissibility, and also development of the intensity and strength of infection by DR-TB strains **[10].** Vitamin D is one of the most renowned bioactive compounds that has an vital effect on lowering the pathogenesis of infectious diseases by regulates the immune system responses **(Fig. 1) [11]**.

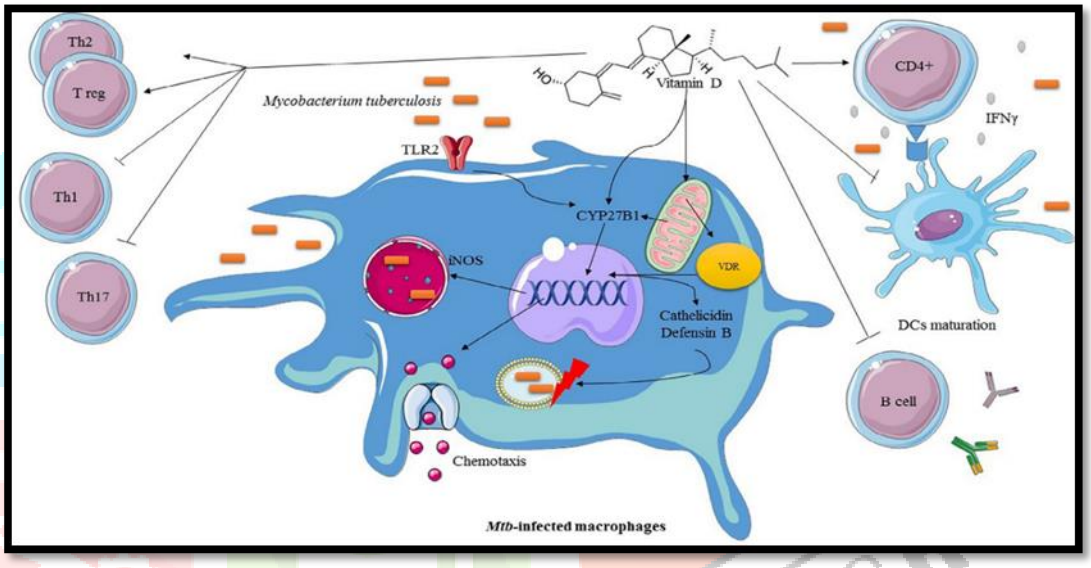

Figure. 1-The vital role of vitamin D in the immunopathogenesis of TB. Vitamin D has immunomodulatory belongings on the immune-system, so that it suppresses Th1, Th17, B cell in addition to DCs maturation. However, it also stimulates the production of T regulatory (T reg) cells, which in turn inhibit the unwarranted T cell-mediated immunity and tissue damage. In the other hand, it also has a definite receptor on the macrophages, vitamin D receptor (VDR). After the binding to the VDR, vitamin D triggers the development such as the production of normal human antimicrobial peptides (AMPs), nitric oxide synthesis and chemotaxis to provoke immune response for approval of *Mtb*.**[11]**

Apart from its well-known effects on bone health and calcium homeostasis, Vitamin D is famous for its immunomodulatory properties that have been investigated in several chronic diseases **[12].** Vitamin D is a fat-soluble vitamin synthesized in the skin upon sunlight exposure. Vitamin D exists as an inactive proform (25(OH)D3) that is converted to an active form (1,25(OH)2D3) by hydroxylation. It is metabolized to 25(OH)D3 in the liver followed by further hydroxylation by 1-α hydroxylase to metabolically active Vitamin D, mainly in the kidney, but also in tissues and immune cells **[13-14].** The major contributing factors for this deficiency include insufficient exposure to sunlight, inadequate diet, application of high percentage sunblock lotions, other chronic conditions such as liver or kidney diseases, or a natural protection due to a high melanin content in the skin (dark skin color) **[13].** From the era of sanatoria to the present days, research on Vitamin D as an immunomodulatory compound that could enhance clinical recovery from TB disease, has been extensively studied. Several in vitro and in vivo studies described the role of Vitamin D in control of TB infection **[15].** Later on, it was found that Vitamin D induces

antimicrobial activity in human *Mtb*-infected macrophages via the induction of LL-37, which reduced intracellular *Mtb* growth substantially **[16].** Vitamin D deficiency is commonly observed in TB disease, although the cause and effect relationship is unclear. But maintaining sufficient levels of Vitamin D, is likely beneficial for promoting host immunity and clinical recovery from TB. Supplementation of Vitamin D to standard anti-TB treatment have been shown to reduce the time to sputum conversion and improve TB treatment outcome including improvement in clinical symptoms and radiological features **[17].** However, several other clinical trials fail to show convincing effects of Vitamin D supplementation **[15].** Importantly, Vitamin D can only be expected to result in significant effects if given to patients or individuals that are Vitamin D deficient, as it would be difficult to supplement someone who already has optimal levels of Vitamin D **[18].** Moreover, the effect of Vitamin D is most likely dependent on the treatment regimen (no bolus dosing, but high doses should be administered frequently **[19].**

Moreover, people with deficient Vitamin D levels may be more susceptible or have a higher risk of contracting TB when exposed to people with active TB infection **[20].**

1.1 Mechanisms for Vitamin D Metabolism &Function

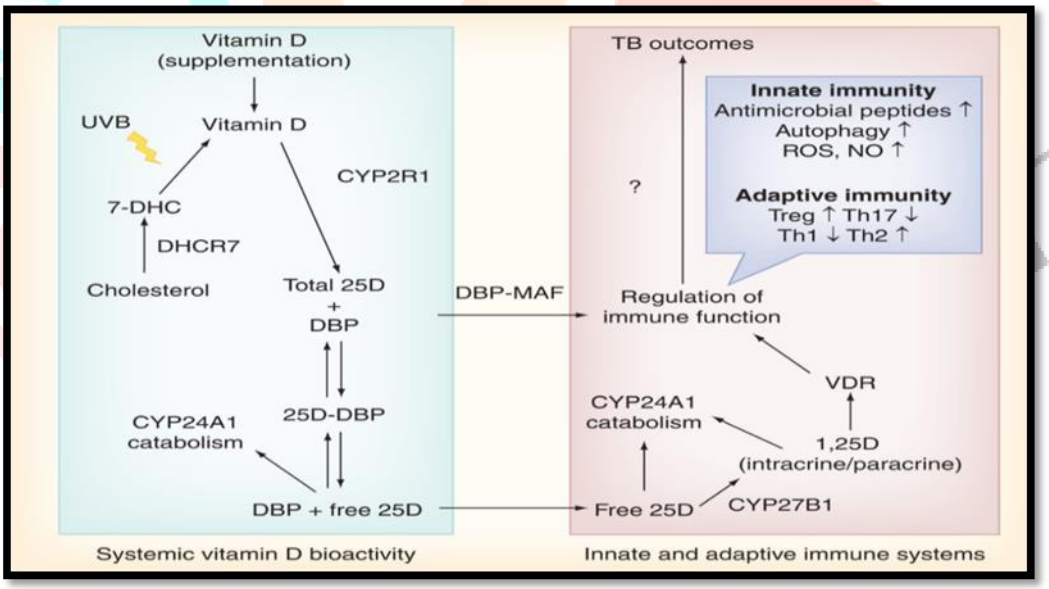

Figure 2. Vitamin D, immune function and TB (Vitamin D is caused in the skin by UVB contact through photoconversion of 7-DHC, produced from cholesterol by the action of DHCR7. Vitamin D can also be found by dietary supplementation. Vitamin D is transformed into 25D by CYP2R1 in the liver. Total 25D levels (vitamin D status) in the blood is chiefly determined by the 25D bound to DBP, even though some 25D is certain to other serum proteins, such as albumin, or existing as 'free' 25D. Glycosylation of DBP causes a MAF (DBP-MAF). Free 25D can arrive into immune cells by simple diffusion and can then be triggered via the enzyme CYP27B1. 1,25D caused in this way can then act in an intracrine manner within the same cell if the VDR is expressed. Alternatively, 1,25D formed by immune cells may act in a paracrine fashion on neighbouring cells communicating VDR. The enzyme CYP24A1 reduces both intracrine and paracrine responses to vitamin D by catabolizing both 25D and 1,25D. Communication between 1,25D and VDR acts to promote the transcriptional instruction of vitamin D target genes. These include genes connected with innate and adaptive immunity. Thus, enough vitamin D (bioavailability) may be a pivotal feature in suitable and adequate immune responses to pathogens such as *MTB*, authorizing protection against or by providing treatment for TB). **[21]**

Vitamin D-binding protein (DBP) bound with albumin by small amount of 25D. Latter 25D has more abundant than DBP but decrease the vitamin D metabolites **[22,23].** In classical vitamin D endocrinology,

the enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) catalyzed by 1,25-dihydroxyvitamin D (1,25D) by the conversion of renal proximal tubule cells. The reactivity of this reaction is explaining the fact that proximal tubular cells also express the vitamin D catabolic enzyme vitaminD-24-hydroxylase (CYP24A1), which converts either 25D or 1,25D to less active 24-hydroxylated metabolites **[24].**

2. VITAMIN D EFFECTS ON COMMON RESPIRATORY DISEASES

Vitamin D effects pulmonary cell biology and immunity. To support this idea, high expression of CYP27B1, which forms the active Vitamin D has been observed in the epithelial cells of lungs**.[25]** Literature says that high consequences between Vitamin D receptor (VDR) polymorphism and lower respiratory tract infections**.[26]** Epidemiological studies says many lung diseases like **[27]** viral respiratory infections**,[28]** chronic rhinitis, rhinosinusitis**,[29]** COPD**,[30]** and asthma,**[31]** were associated with Vitamin D level.

2.1 Asthma

High risk of transmitting disease occurs such as influenza, asthma (simultaneously caused by influenza itself) due to the deficiency of Vitamin D. Chronic asthma and vascular endothelial growth factor cause by hyperplasia and proliferation with smooth muscles and the key factor of this process is fibrinogen and IL-6. Vitamin D can reduce the effect of these factors **[32].** Pathogenesis of asthma are associated with Vitamin D pathway gene, so we can say that Vitamin D and asthma may have a genomic-based relationship **[33].**

Analysis between asthma and Vitamin D have been carried out in higher age group people. Clinical trials show that Vitamin D deficiency causes lungs function; rise airway hyperresponsiveness and can lack response to glucocorticoids **[34]**. Asthma and dysfunction syndrome are same condition but does not response to traditional asthma treatment. High- dose of Vitamin D shows successfully treated for this syndrome **[35].** Results of clinical trials shows that, Vitamin D supplementation had no effect on the asthma exacerbation or viral upper respiratory infections **[36].**

2.2 Chronic Obstructive Pulmonary Disease (COPD)

Recently there are no epidemiological. Data to shows a correlation between childhood Vitamin D deficiency and COPD, but in vivo and in vitro studies recommended a strong role of Vitamin D in lung development. For example, experiments in the emerging rat lung indicate that existence of Vitamin D in alveolar type II cells can rise surfactant synthesis and regulate epithelial-mesenchymal communications **[37,38].** Vitamin D shows confusing effects in COPD. However, studied proved that it can raise the activity of immune cells **[27],** improve the strength of airway muscles, and modulate inflammatory responses **[39].** Pro inflammatory progression occurs insufficiently in airways as a result of down regulation Vitamin D, in COPD patients **[40].**

3. VITAMIN D-ASSOCIATED CYTOKINES

Patients having a congestive heart failure and inflammatory bowel diseases associated with Vitamin D which regulates the production of interleukin IL-6, IL-15 and IL-10 **[41,42].** Serum and supernatants of the QuantiFERON TB Gold-in-Tube (QFT-GIT) test for TB shows Vitamin D level related to cytokines. Kurtzik et al. observed that IL-15 plays an important role against *MTB* and also help in Vitamin D - dependent antimicrobial pathway and also used as vaccination against various disease **[43-46].** IL-32 augments immunity to M. tuberculosis by increasing the expression levels of the vitamin D receptor and antimicrobial peptides, as well as caspase-mediated apoptosis or autophagy **[47,48].** IL-1β increase the level of Vitamin D which protect against the TB **[49].** Study shows the relation between Vitamin D and cytokines sera and QTF-GIT supernatants and may be significant with active and latent TB infection (LTBI) **[50-53].** One epidemiological data in Korean shows that healthy individual having high deficiency of Vitamin D as compared to TB patients **[50].** Arnedo-Pena et al. observed that after TB infection the patients suffer Vitamin D deficiency **[54].** Some in-vitro says that differentiation of macrophages by the cytokines (cytokines include- IL-15 mediates TLR2/1 induced, CYP27b1 and Vitamin D pathway – VDR and Cathelicidin) **[46].** Montaya et al. observed that IL-32 suppressed Vitamin D dependent antimicrobial peptides through macrophages gene network shows defence response by the cytokine IL-15 **[48].** IL-15 activated the Vitamin D in macrophages which decrease the bacterial growth in TB patients and induced paracrine signalling **[49,55].** The logistic data based on the most favourable cytokines of active TB from LTBI. Logistic level of Vitamin D and Vitamin D related to cytokine refers IL-15nil level < 137.2 pg/mL and IL-32TB level ≥ 627.6 pg/ mL in active TB cases. The QFT-GIT probability data was ≥ 0.208 (100% sensitivity and 82.6% specificity) for active TB individual under the IL-15 nil and IL-32 TB cytokines. Study shows that the collaboration between Vitamin D and cytokine level protects against *MTB.* There would be more research needed the efficiency of cytokines with Vitamin D **[56].**

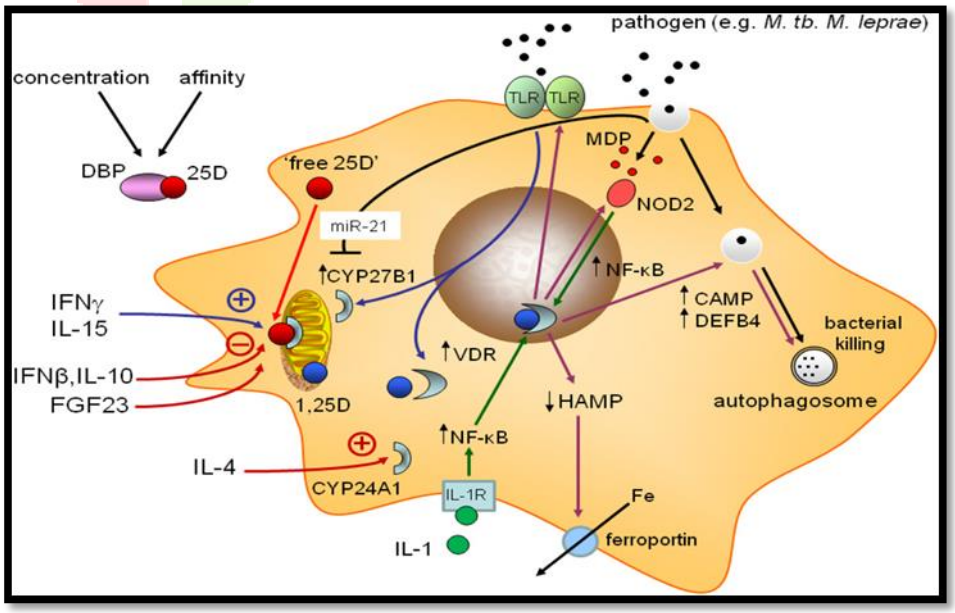

Figure 3. Cytokines Associatedwith Vitamin D (Schematic illustration of monocyte/macrophage responses to infection by a pathogen such as *Mycobacterium tuberculosis (M. tb)*, and related adjunct signals. Positive effects on the vitamin D intracrine system contain: induction of CYP27B1 look by cytokines such as interferon γ (IFNγ) and interleukin-15(IL-15). Negative effects contain suppression of CYP27B1by IL-10andIFNβ, andinductionof24-hydroxylaseactionbyIL-4. Fibroblast Growth factor23(FGF23) as well defeats CYP27B1andmicroRNA-21 (miR-21) connected by some pathogen infections (e.g., M. leprae) can suppress expressionofCYP27B1bydeprivationofRNAand/or translation. The serum vitamin binding protein (DBP)may also attenuate intracrine vitamin by confining monocyte bioavailability of free25D). **[57]**

Vitamin D is an immunomodulatory micronutrient and deficiency is common among people living with HIV while people lacking or having less quantity of it have been at higher risk of pulmonary tuberculosis. Also, the studies have shown that HIV infected patients have large risk of disease progression and mortality. As far as we are awared, the addition of Vitamin-D was the first frequent trial for inhibiting pulmonary tuberculosis. However, no result was found with vitamin D3 supplementation on the risk of mortality among all participants, but supplementation appeared to boost survival for the subgroups of adults initiating antiretroviral therapy (ART) with simultaneous pulmonary tuberculosis or WHO stage IV HIV disease. Vitamin D3 appears to deduce the incidence of sputum smear-positive pulmonary tuberculosis, microbiologically confirmed tuberculosis, and incident high bacillary load (grade ≥2+) sputum smear-positive pulmonary tuberculosis. Vitamin D3 accumulation did not correct or decrease the overall incidence of tuberculosis in this trial. Nonetheless, there was some indication that there might be survival benefits for some subgroups of people with HIV initiating ART. Additionally, vitamin D3 might decrease the rate of smear-positive and high bacillary load pulmonary tuberculosis. But, findings are not definite and additional research is needed to confirm these subgroup and exploratory findings before considering vitamin D3 supplementation as part of a public health programme to decrease the risk of pulmonary tuberculosis or mortality in the context of HIV. **[58]**

In a research, of 101 people were detected with pulmonary tuberculosis patients of which 71 were males and 30 are females while 100 people of non- TB controls were involved into were 58 were males and 42 were females . Studies shows that, the majority of TB patients were suffered from TB decline (36.6%); non-HIV infected individuals (99.1%) or exposed a positive result for AFB (61.4%) in Gene Xpert analysis. Also, there is a vital difference in microscopy assumptions and bacillary levels of AFB, and Rifampicin (RIF) susceptibility pattern of M. tuberculosis strain between sputum samples of TB patients, P-values less 0.0001. Furthermore, showed that TB patients were suffered from vitamin D deficiency. In specificly, the mean of vitamin D level was suggestively much minor in TB patients (26.7 ± 1.6)compared to non-TB controls (117.3 ± 3.2), P-value equal 0.0001. Equally, it's much lower in females, persons of 21–40 years old, and patients with high bacillary levels or individuals infected by Rifampicin resistance strain**[59].**

The incidence of vitamin D deficiency (25 patients vs. 2 healthy individuals; P<0.001) and serum levels of the vitamin D (22.66±15.17 vs. 73.03±25.6 ng/mL; P<0.001) were meaningly higher in patients with TB than healthy subjects. Similarly, the prevalence of vitamin D deficiency in the extrapulmonary TB group was higher than that of the pulmonary TB, but this difference was not statistically noteworthy (P=0 .397). Moreover, there was no significant difference between mean levels of vitamin D in patients with tuberculosis before and after treatment (P = 0.787). Linear reversion analysis showed there was no

significant relationship between vitamin D levels after treatment and age, gender, body site of tuberculosis, and vitamin D levels before treatment, P≥0.68**[60].**

Household contacts who might be accommodating latent tuberculosis are most vulnerable to develop TB. Hence, identifying such cases and prevention of activation of TB in them will help bring down the incidence of new cases. According to studies been performed on bacterial aspects and very few on host aspect. Some environmental, lifestyle and immunological risk factors which devoting towards susceptibility to the disease. Vitamin D, is one such factor and made to assess the role of vitamin D and its associated molecules in the pathophysiology of pulmonary tuberculosis and reduced vitamin D levels were resulted in active pulmonary TB patients as compared to household contacts and healthy controls. Some studies involving clinical trials have shown that vitamin D addition with phenyl butyrate improved the clinical symptoms especially in vitamin D deficient TB patients **[61,62]** providing evidence for protective role of vitamin D in TB patients. Additionally, higher levels of cathelicidin in household contacts were observed as compared to healthy controls. Cathelicidin antimicrobial peptide gene expression was significantly higher in progressive TB, whereas in latent TB it was similar to the control**[63]** group according to recent studies **,**findings have shown, it can be hypothesized that household contacts of TB patients might have undetected latent infection which can be the reason for the increased level of cathelicidin compared to healthy controls, though lower compared to active TB patients where active multiplication of *M.tb*.is going on. Increased levels of cathelicidin in active TB group might be the result of increased bacterial load through the inflammatory pathway **[64,65],** which may not have been enough to control overwhelming bacterial load. Based on the recent findings, vitamin D could be implicated in innate immunity of the host via production of antimicrobial agents to contain bacterial multiplication. High risk household contacts despite being exposed to active TB patients did not develop active disease possibly due to vitamin D levels required for production of cathelicidin and NO levels were sufficient enough to contain the initial infection. However, in case of active TB patients, suboptimal vitamin D levels may have led to initial low production of cathelicidin and NO insufficient to contain the bacilli. However later, increased cathelicidin and NO levels in active TB patients could be attributed to overwhelming bacterial load and may serve as potential biomarkers in diagnosis of TB amongst high risk household contacts of TB. Also, the recent study warrants further studies to complete the role of vitamin D implementation in the prevention and treatment of tuberculosis **[66].**

CONCLUSION

Vitamin D plays a major, undoubtable role in the maintenance of calcium, phosphate and bone metabolism. According to studies immune cells converts 25(OH)D to $1,25(OH)_2D$ in a controlled manner and also dependent on the circulating level of 25(OH)D at least 30 ng/ml (75n mol/L) **[67,68]**. Researches shows that Vitamin D is an immune modulate function with non- genomic form by fixing endothelial membrane **[69].**

Most of the evidence, proposed that care of a healthy vitamin D status is vital for modulating the body's immune function. Low serum levels of 25(OH)D are related with multiple immune-related diseases

including autoimmune disorders and infectious diseases. There is less convincing evidence that vitamin D is an effective treatment strategy for autoimmune diseases and infectious diseases with a few exceptions documented in this review **[70].**

Based on the present studies, Vitamin D enmeshed innate immunity of the host via production of antimicrobial agents for control *MTB* multiplication. Hence, adjunctive vitamin D supplementation may overcome the inflammatory response and enhance patient response to anti-TB treatment which may reduce the treatment duration.

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