JCARR
JOURNAL OF CLINICAL ADVANCES AND RESEARCH REVIEWS

Available online on http://www.jcarr.in/
Journal of Clinical Advances and Research Reviews 2024; 01(01); 05-10

Review Article

Medicinal Effect of Curcumin as an Anti-tuberculosis

Amruta Bapu Lokhande*[1], Ankit Raju Waghmare[1], Madhuri Bharat Yadav[1]
[1]*Mandesh Institute of Pharmaceutical Science and Research Centre Mhaswad*

Received: 20-01-2024 / Revised: 20-02-2024 / Accepted: 26-02-2024
Corresponding Author: Amruta Bapu Lokhande
Email: amrutalokhande642@gmail.com
Conflict of interest: Nil

Abstract:
Since very early times, people have been afflicted by the disease known as tuberculosis (TB). Anti-TB allopathic drugs have been administered to manage the disease's symptoms, but they include side effects such hepatitis, hypersensitivity responses, nausea, and vomiting, among others. Ayurvedic (Indian traditional medicine) and foreign medicinal herbs origin have been used to treat TB with success. In this particular review, turmeric with potential anti-tubercular action were described. curcumin is the principal curcuminoid obtained from the plant curcuma longa and has been extensively studied for its biological and chemical properties, including antimicrobial, antiinflammatory, antioxidant, and antitumor activity. These include antimycobacterial activity, modulation of the host immune response and enhancement of BCG vaccine efficacy.

Keywords: *Anti–tubercular, Mycobacterium*

Introduction:
Tuberculosis (TB) is a bacterial infection mainly caused by mycobacterium tuberculosis (MTB). The development of paleopathology and paleoepidemiology in infectious diseases has proven the very ancient origin of this disease TB is the most common cause of death due to a single infectious agent worldwide in adults. In 1993, the World Health Organization (WHO) took an unprecedented step and declared TB to be a global emergency [1]. Tuberculosis is primarily a poor-country disease, with developing countries accounting for 95% of cases and 98% of facilities underdeveloped nations, tuberculosis is the primary parasitic HIV/AIDS [2].In the two decades (1944–1955) that the medications used to treat tuberculosis were developed, a relatively small number of scientists made significant discoveries. A thorough investigation was conducted in several industrial and academic laboratories. There are numerous factors for the waning enthusiasm for the development of fresh tuberculosis medications [3]. First, short-course chemotherapy that used combinations of these drugs was successful. Availability of potent medications caused the inaccurate a belief that other people weren't really needed products. Second, extensive screening techniques for the identification of novel anti-tuberculosis drugs especially labor-intensive and problematic pertaining to how the pathogen is handled. Lastly, the anti-tuberculosis medication takes longer to develop time and personnel than the creation of different antibiotics. Lastly, and likely most Victor Arya [4]. In addition to eliminating pathogenic M. tuberculosis, they choose for drug subsequently effective against those medications' target microorganisms ineffective. Global monitoring has demonstrated that drug Now a threat, resistant TB is pervasive to control initiatives in numerous nation [5].

Biochemistry Of Tuberculosis:
It needs oxygen to grow, which is a requirement for M. tuberculosis. Because of the high lipid content of its wall, it does not require any bacteriological stain and is never classified as either Gram-positive or Gram-negative. Ziehl-Neelsen staining, also known as acid-fast staining, is therefore utilized. The lack of an outer cell membrane causes the mycobacteria to be classed as acid-fast Gram-positive bacteria even though they do not appear to fall under the empirically defined category of Gram-positive bacteria (i.e., they do not maintain the crystal violet stain). In comparison to other bacteria, whose division periods are often measured in minutes, M. tuberculosis replicates every 15-20 hours, which is incredibly slowly. Early endosomal auto antigen 1 (EEA1), a bridge molecule, is specifically blocked by M. tuberculosis, however this blockage does not stop the fusion of vesicles filled with nutrients. Consequently, the bacteria multiply unchecked within the macrophage. The bacteria also carried the UreC gene, which

prevents acidification of the phagosome. The bacteria also evade macrophage-killing by causing the neutralization of reactive nitrogen intermediates [6].

Natural ingredients as TB-fighting agents:

Plants, animals, and minerals are examples of natural resources that have been used to treat human diseases. The history of medicine begins almost with the existence of civilization in humans. the presentaccepted allopathy or modern medicine has gradually built created over time by scientific and scientists' observing efforts [7]. Humans have chosen natural items as raw materials with efficacy against a variety of ailments over many centuries of practical experience. Such Experiential evaluation differs from scientific evaluation. Western medicine appraisal is undervalued. Sometimes, Despite the abundance of effective drugs, such as ephedrine, morphine, aspirin, atropine, digitoxin and reserpine were created from natural products [8]. Almost all societies have employed medicinal plants as a source of medicine from the dawn of mankind. Health care and natural medicines are often used preparations, such as those mentioned in historical sources like such as the Bible and the Vedas, and derived from traditional herbs and plants used for healing, has been linked to natural product occurrence having therapeutic qualities [9].

History and philosophy of tuberculor therapy:

Despite the fact that tuberculosis has been around for a very long time, there have never been any viable treatments. The surgical approach became the gold standard after Carlo Forlanini discovered the positive effects of the artificially induced pneumothorax in 1927. Initially, the pre antibiotic therapy was represented by isolation in sanatoria to reduce the likelihood of Mycobacterium tuberculosis transmission to healthy contacts, with rest, adequate nutrition, and sunlight exposure; then, the surgical approach represented the gold standard [10]. Streptomycin, a naturally occurring chemical derived from Streptomyces griseus, was destined for a different fate after demonstrating its efficiency first in animals and subsequently in people. Due to the drug's bactericidal effect, Schatz and Waksman declared in 1944 that it may be given for the treatment of tuberculosis. The United Kingdom Medical Research Council Tuberculosis Unit demonstrated its six-month short-term efficacy in 1946, reducing mortality from 27% to 7%. As a result of the developed antibiotic resistance, no differences between individuals who had been exposed to streptomycin and those who had not were discovered after 5 years [11]. The marketing of bedaquiline and delamanid has recently been approved. Bedaquiline-containing regimens boost the likelihood of culture conversion in tuberculosis cases that are multidrug resistant by a factor of 12 and stop new drug resistance from developing against the medications in the backbone regimens. In the first six months of exposure, the time to culture conversion is sped up (hazard ratio: 2.3). When compared to other anti tuberculosis medications, the safety and tolerability profile is favorable (e.g., acne, bilateral hearing loss, extremities and non cardiac chest discomfort). However, compared to the control group, the frequency of nausea was noticeably higher during various research trials[12].

Curcumin's chemical, physiological, and pharmacological properties:

Curcumin I (77%), curcumin II (demethoxycurcumin 17%), and curcumin III (bisdemethoxycurcumin 3%) constitute the curcuminoids isolated from turmeric.The natural analogs demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC) possess biological activity similar to that of curcumin [13]In addition to curcuminoids, turmeric comprises carbohydrate (69.4%), protein (6.3%), fat (5.1%), minerals (3.5%), and moisture (13.1%)[14]Curcumin is soluble in solvents like acetone, methanol, and ethanol. Curcumin is a keto-enol tautomeric compound that exists in a predominant keto-form in acid or neutral solutions and the enol-form in alkali solutions exhibiting the properties of metal ion chelator [15]. Curcumin has substantial protective and preventive effects against various diseases such as cancer, autoimmune, neurological, metabolic, lung, liver, and cardiovascular diseases as the keto-enol forms endow curcumin with antiangiogenic, anti-inflammatory, antimicrobial, antimutagenic, antioxidant, and antiplatelet aggregation properties. Due to its light sensitivity, it is recommended that curcumin-containing samples be protected from light [15,16,17].

Curcumin As Anti-Mycobacterial Agent:

Curcumin presents itself as a novel and robust strategy to combat the virulence and antibiotic resistance of *Mycobacterium abscessus*. Curcumin at minimum inhibitory concentrations (MIC) of 128 µg/mL reduction exhibited synergistic activity with amikacin, ciprofloxacin, clarithromycin, and linezolid against a clinical strain of *M. abscessus*. Curcumin significantly ($p < 0.05$) reduced the motility of *M. abscessus* at 1/8th the concentration of MIC. The biofilm formed by MTB contributes to its virulence and drug tolerance, and at a concentration four times higher than the MIC curcumin completely inhibited day four and eight mature biofilms in terms of biomass reduction [18].

Through Altering the Host Immune Response, Curcumin Demonstrates Antitubercular Activity:

Curcumin modulates the clearance of MTB by macrophages via the induction of apoptosis. Preincubation of human THP-1 monocytes and primary human alveolar macrophages with curcumin at a concentration of 10, 30, and 50 µM for 1 h before infection with MTB H37Rv have reduced the burden of intracellular MTB. Compared to the control cells, which were incubated with 0.05% DMSO, incubation with curcumin exhibited a significant reduction ($p < 0.05$) in the number of MTB recovered at two and four days after infection. However, curcumin at concentrations up to 50 µM did not significantly affect MTB growth in the absence of macrophages, indicating that curcumin aids in the

clearance of the MTB by enhancing macrophage activity. TUNEL assay of the MTB-infected THP-1 cells revealed that curcumin induced apoptosis in macrophages in a dose-dependent manner. The enhanced clearance of MTB in the differentiated THP-1 human monocytes and primary human alveolar macrophages was by curcumin-induced caspase-3-dependent apoptosis and autophagy [19]. MTB activates NFκB, causing inhibition of both apoptosis and autophagy in infected human macrophages, and evades host clearance [20,21,22]. Curcumin induces an anti-MTB cellular response in the macrophages via inhibition of the p65 NFκB, binding to its consensus oligonucleotide and activation of the NFκB and induction of apoptosis, causing a substantial reduction in bacterial viability [19]. Depicts the various mechanisms of curcumin antitubercular activity via modulation of the host immune response. However, the results of another study contradict this, showing that curcumin at low doses (10 and 20 μM) protected MTB infected macrophages from 19-kDa lipoprotein (P19) and induced inflammation and apoptosis. P19, a virulence factor secreted by the MTB, activates Toll-like receptor 2 (TLR2) and mitogen-activated protein kinases (MAPKs) in MTB infected macrophages. However, curcumin affects the extracellular signal-regulated protein kinase (ERK), showing that curcumin inhibits apoptosis of macrophages mediated by P19 by regulating the JNK pathway [23]. Blocking of the p38 mitogen-activated protein kinases (p38 MAPK) signaling pathway in human macrophages cell line WBC264-9C with the concomitant treatment of curcumin at a concentration of 20 and 40 μmol/L and the MTB P19 revealed that curcumin modulates the inflammatory responses and apoptosis induced by P19. Curcumin attenuated the P19-induced growth inhibition significantly ($p < 0.01$), as shown by significantly lowered expression of the cytokines IL-1β, IL-6, TNF-α, the signal transducer and transcription activator 3 (STAT3), and apoptotic proteins P53, Bax, Bcl2, and phospho-p38 MAPK expression measured in the presence and absence of the antagonist of p38 MAPK [24]. Overall, antitubercular activity of curcumin via modulation of the host immune response remains unclear and needs to be further studied to elucidate its protective role in MTB infected macrophages.

Acetamiprid (ACE) is an insecticide belonging to the neonicotinoid family, which induces immunosuppression of specific humoral and cellular responses against the MTB virulence factor CFP32. Curcumin treatment at the dose of 100 mg/kg partially restored this Acetamiprid (ACE) mediated immunosuppression in Swiss Albino mice after exposure to ACE at the dose of 5 mg/kg. Treatment for 61 days showed significant ($p < 0.05$) restoration in the humoral immune response when assessed by ELISA with anti-rCFP32 antibody concentrations in the serum compared to Swiss Albino mice treated with ACE only. The cellular immune response was also partially restored when assessed by the cellular proliferation of the splenocytes stimulated by rCFP32, showing that the use of curcumin could be a new potential strategy to reduce the ACE-induced immunotoxicity, especially in the population involved in the agricultural sector [29].

Influencing host immune responses, curcumin nanoparticles increase the effectiveness of the Mycobacterium bovis BCG vaccine:

The only available vaccine against TB that is effective against disseminated and meningeal TB in young children is *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) [30]. The main drawback of BCG is its inefficacy in protecting against adult pulmonary TB, which is mainly due to the decline with time in the host-protective immune responses that it induces [31]. Curcumin nanoparticles (nanocurcumin) enhance the functions of dendritic cells, macrophages, Langerhans cells, and B cells, which are the host antigen-presenting cells (APC) and modulate the host immune responses via autophagy, costimulatory activity, and the production of inflammatory cytokines. Further, nanocurcumin enhanced the efficacy of BCG in the induction of T cells with long-lasting central memory T (TCM) cells of the Th1 and Th17 lineages, which elevate host immune protection against MTB infection. Nanocurcumin reduced the bacterial burden ($p \leq 0.05$) of MTB H37Rv-infected peritoneal macrophages at a concentration of 60 nM in a time-dependent fashion. Nanocurcumin treatment at 60 nM significantly ($p \leq 0.05$) enhanced cellular activation, autophagy of the macrophages, and production of TNF-α (the cytokine involved in the production of NO and other free radicals), which together clear MTB. The cytokine IL-10 suppresses protective immune responses by the downregulation of the expression of major histocompatibility complex (MHC) class II (MHCII) and costimulatory molecules. Nanocurcumin significantly ($p \leq 0.05$) down regulated the levels of IL-10 in H37Rv-infected macrophages. The efficacy of the BCG vaccine was also enhanced by nanocurcumin in the C57BL/6 murine TB infection model. Subcutaneous administration of the BGC vaccine and subsequent treatment with nanocurcumin for 30 days, followed by a resting period of 30 days, causes a significant ($p \leq 0.05$) reduction in bacterial burden and reduction of granulomatous regions in the organs of the mice when challenged with MTB-H37Rv aerosol at a low dose of approximately 110 Colony Forming Units (CFU) showing the enhancement of the BCG vaccine [32].Curcumin nanoparticles also exhibited fivefold enhanced bioavailability. By themselves, curcumin nanoparticles inhibited the growth of the MTB H37Rv strain by at best 1-log in the mice and accelerated the clearance of the MTB from the lung and spleen of BALB/c mice by promoting an antitubercular response, which in turn reduced the duration of therapy. Curcumin nanoparticles restored the isoniazid (INH)-induced suppression in antigen-specific cytokine, the proliferation of T cells suppressed by INH, and reduced hepatotoxicity in mice induced by antitubercular antibiotics.

Far more intriguing, curcumin nanoparticle treatment raised the total number of splenocytes, enhanced the frequency and activation of both $CD4^+$ and $CD8^+$ T cells, and also reduced the risk for TB reactivation and reinfection [33].
To improve intramacrophage delivery and improved MTB clearance, rifampicin (RIF) and curcumin were co-encapsulated in polymeric nanoparticles with an average size of ~400 nm, low polydispersity, and zeta potential of 26.89 ± 2.9 mV. Both rifampicin and the curcumin were released in the lysosomal fluid, indicating that the drugs were released by the nanoparticles only after the macrophage internalization. These nanoparticles were nontoxic to RAW 264.7 macrophages and increased the drug internalization 1.5-fold compared to free drugs as determined by confocal microscopy. Encapsulation did not affect the drug properties as confirmed by the comparable minimum inhibitory concentration of free RIF, free curcumin, and nanoparticle encapsulated RIF and curcumin. The nanoencapsulation method is suggested to be a promising tool to tackle TB as high efficacy was exhibited by the RIF-CUR nanoparticles, which cleared the MTB infected macrophages at 25× MIC (98.03 ± 2.5%) as well as complete clearance above 50× MIC [34].

Conclusions:

Several efforts have been made over the years to learn more about curcumin's and its derivatives' which shows antimycobacterial properties. Every year after that, researchers have discovered additional synthetic compounds, targets, and modes of action for curcumin. Curcumin and its derivatives have been demonstrated to enhance the outcome of TB infection in both animal experiments and human trials, suggesting the potential utility of curcumin as a medicinal agent in the treatment of TB. Although the specific molecular mechanisms underlying curcumin's antitubercular activity are still not fully understood, it is possible that many of the molecular pathways involved in the pathophysiology of TB are associated to this compound's activity. Curcumin is predicted to influence a wide array of physiological and biochemical systems.

References:

1. Godreuil S, Tazi L, Banuls AL. ‘‘Pulmonary Tuberculosis and Mycobacterium Tuberculosis: Modern Molecular Epidemiology and Perspectives’’. Encyclopedia of Infectious Diseases: Modern Methodologies 2007; 1: 1-29
2. Joseph P, Severe P, Ferdinand S, Goh KS, Sola C, Haas DW, Johnson WD, Rastogi N, Pape JW, Fitzgerald DW. ‘‘Multidrug-resistant tuberculosis at an HIV testing center in Haiti’’. AIDS 2006; 2(3): 415-418.
3. Sensi P. ‘‘Approaches to the Development of New Anti-tuberculosis Drugs’’. Reviews of infectious diseases 1989; 2(2): S467-S470.
4. Sharma SK, Mohan A. ‘‘Multidrug-resistant tuberculosis’’. Indian J Med Res. 2004; 120: 354-376
5. Johnson R, Elizabeth MS, Louw GE, Warren RM, Helden PDV and Victor TC. ‘‘Drug Resistance in Mycobacterium tuberculosis’’. Curr. Issues Mol. Biol. 2006; 8: 97–112.
6. Sam Burcher and Mae-Wan Ho,1996. Prac. Global strategy for traditional medicine research: 142-144.
7. Patwardhan B, Vaidya ADB, Chorghade M. ‘‘Ayurveda and natural products drug discovery’’. Current science 2004; 86(6): 789- 799.
8. Kurokawa M, Shimizu T, Watanabe W, Shirak K. ‘‘Development of New Antiviral Agents from Natural Products’’. The Open Antimicrobial Agents Journal, 2010, 2: 49-57.
9. Hoareau L, DaSilva EJ. ‘‘Medicinal plants: a reemerging health aid’’. Electronic Journal of Biotechnology 1999; 2(2): 56-70.
10. Rosenblatt MB. 1973. Pulmonary tuberculosis: Evolution of modern therapy. Bull NY Acad Med 49: 163–196.
11. Schatz A, Bugie E, Waksman SA. 1944. Streptomycin, a substance exhibiting antibiotic activity against Gram-positive and Gram-negative bacteria. ProcSoc Exp Biol Med 55: 66–69.
12. Diacon AH, Pym A, Grobusch M, Patientia R, Rustomjee R, Page-Shipp L, Pistorius C, Krause R, Bogoshi M, Churchyard G, et al. 2009. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med 360: 2397–2405.
13. Soleimani V., Sahebkar A., Hosseinzadeh H. Turmeric (*Curcuma longa*) and its major constituent (curcumin) as nontoxic and safe substances. *Phytother. Res.* 2018;32:985–995. doi: 10.1002/ptr.6054.
14. Eke-Okoro U.J., Raffa R.B., Pergolizzi J.V., Jr., Breve F., Taylor R., Jr., NEMA Research Group Curcumin in turmeric: Basic and clinical evidence for a potential role in analgesia. *J. Clin. Pharm. Ther.* 2018;43:460–466. doi: 10.1111/jcpt.12703. [PubMed] [CrossRef] [Google Scholar]
15. Tomeh M.A., Hadianamrei R., Zhao X. A review of curcumin and its derivatives as anticancer agents. *Int. J. Mol. Sci.* 2019;20:1033. doi: 10.3390/ijms20051033. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
16. Abrahams S., Haylett W.L., Johnson G., Carr J.A., Bardien S. Antioxidant effects of curcumin in models of neurodegeneration, aging, oxidative and nitrosative stress: A review. *Neuroscience.* 2019;406:1–21. doi: 10.1016/j.neuroscience.2019.02.020. [PubMed] [CrossRef] [Google Scholar]

17. Pivari F., Mingione A., Brasacchio C., Soldati L. Curcumin and type 2 diabetes mellitus: Prevention and treatment. *Nutrients.* 2019;11:1837. doi: 10.3390/nu11081837. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
18. Patel S.S., Acharya A., Ray R.S., Agrawal R., Raghuwanshi R., Jain P. Cellular and molecular mechanisms of curcumin in prevention and treatment of disease. *Crit. Rev. Food. Sci. Nutr.* 2020;60:887–939. doi: 10.1080/10408398.2018.1552244. [PubMed] [CrossRef] [Google Scholar]
19. Marini E., Di Giulio M., Magi G., Di Lodovico S., Cimarelli M.E., Brenciani A., Nostro A., Cellini L., Facinelli B. Curcumin, an antibiotic resistance breaker against a multiresistant clinical isolate of Mycobacterium abscessus. *Phytother. Res.* 2018;32:488–495. doi: 10.1002/ptr.5994. [PubMed] [CrossRef] [Google Scholar]
20. Bai X., Oberley-Deegan R.E., Bai A., Ovrutsky A.R., Kinney W.H., Weaver M., Zhang G., Honda J.R., Chan E.D. Curcumin enhances human macrophage control of Mycobacterium tuberculosis infection. *Respirology.* 2016;21:951–957. doi: 10.1111/resp.12762. [PubMed] [CrossRef] [Google Scholar]
21. Shariq M., Quadir N., Sharma N., Singh J., Sheikh J.A., Khubaib M., Hasnain S.E., Ehtesham N.Z. *Mycobacterium tuberculosis* RipA Dampens TLR4-Mediated Host Protective Response Using a Multi-Pronged Approach Involving Autophagy, Apoptosis, Metabolic Repurposing, and Immune Modulation. *Front. Immunol.* 2021;12:434. doi: 10.3389/fimmu.2021.636644. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
22. Arnett E., Weaver A.M., Woodyard K.C., Montoya M.J., Li M., Hoang K.V., Hayhurst A., Azad A.K., Schlesinger L.S. PPARγ is critical for Mycobacterium tuberculosis induction of Mcl-1 and limitation of human macrophage apoptosis. *PLoS Pathog.* 2018;14:e1007100. doi: 10.1371/journal.ppat.1007100. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
23. Bah A., Sanicas M., Nigou J., Guilhot C., Astarie-Dequeker C., Vergne I. The lipid virulence factors of Mycobacterium tuberculosis exert multilayered control over autophagy-related pathways in infected human macrophages. *Cells.* 2020;9:666. doi: 10.3390/cells9030666. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
24. Li M.Y., Wang H.L., Huang J., Shi G.C., Wan Y.G., Wang J.X., Xi X.E. Curcumin inhibits 19-kDa lipoprotein of *Mycobacterium tuberculosis* induced macrophage apoptosis via regulation of the JNK pathway. *Biochem. Bioph. Res. Commun.* 2014;446:626–632. [PubMed] [Google Scholar]
25. Liu L., Liu J., Niu G., Wu Q., Li W., Zhou Y. The effects of curcumin on the 19 000 Mycobacterium tuberculosis protein-induced inflammatory and apoptotic reaction and the expression of p38 mitogen-activated protein kinases in WBC264-9C macrophages. *Chin. J. Tuberc. Respir. Dis.* 2014;37:421–426. [PubMed] [Google Scholar]
26. Marzouki S., Bini Dhouib I., Benabdessalem C., Rekik R., Doghri R., Maroueni A., Bellasfar Z., Fazaa S., Bettaieb J., Barbouche M.R., et al. Specific immune responses in mice following subchronic exposure to acetamiprid. *Life Sci.* 2017;188:10–16. doi: 10.1016/j.lfs.2017.08.022. [PubMed] [CrossRef] [Google Scholar]
27. Erokhina M.V., Lepekha L.N., Voronezhskaya E.E., Nezlin L.P., Avdienko V.G., Ergeshov A.E. Application of Laser Scanning Confocal Microscopy for the Visualization of M. tuberculosis in Lung Tissue Samples with Weak Ziehl–Neelsen Staining. *J. Clin. Med.* 2019;8:1185. doi: 10.3390/jcm8081185. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
28. Urbanowski M.E., Ordonez A.A., Ruiz-Bedoya C.A., Jain S.K., Bishai W.R. Cavitary tuberculosis: The gateway of disease transmission. *Lancet Infect. Dis.* 2020;20:e117–e128. doi: 10.1016/S1473-3099(20)30148-1. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
29. Odashima K., Kagiyama N., Kanauchi T., Ishiguro T., Takayanagi N. Incidence and etiology of chronic pulmonary infections in patients with idiopathic pulmonary fibrosis. *PLoS ONE.* 2020;15:e0230746. doi: 10.1371/journal.pone.0230746. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
30. Lee H., Hua H., Wang C., Yu M., Chen B., Lin A.C. Mycobacterium tuberculosis induces connective tissue growth factor expression through the TLR2-JNK-AP-1 pathway in human lung fibroblasts. *FASEB J.* 2019;33:12554–12564. doi: 10.1096/fj.201900487R. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
31. Machlaurin A., Dolk F.C.K., Setiawan D., Werf T.S., Postma M.J. Cost-Effectiveness Analysis of BCG Vaccination against Tuberculosis in Indonesia: A Model-Based Study. *Vaccines.* 2020;8:707. doi: 10.3390/vaccines8040707. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
32. Whitlow E., Mustafa A.S., Hanif S.N.M. An Overview of the Development of New Vaccines for Tuberculosis. *Vaccines.* 2020;8:586. doi: 10.3390/vaccines8040586. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
33. Ahmad S., Bhattacharya D., Kar S., Ranganathan A., Van Kaer L., Das G. Curcumin Nanoparticles Enhance Mycobacterium bovis BCG Vaccine Efficacy by Modulating Host Immune Responses. *Infect.*

Immun. 2019;87:e00291-19. doi: 10.1128/IAI.00291-19. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

34. Tousif S., Singh D.K., Mukherjee S., Ahmad S., Arya R., Nanda R., Ranganathan A., Bhattacharyya M., Van Kaer L., Kar S.K., et al. Nanoparticle-Formulated Curcumin Prevents Posttherapeutic Disease Reactivation and Reinfection with *Mycobacterium tuberculosis* following Isoniazid Therapy. *Front. Immunol.* 2017;8:739. doi: 10.3389/fimmu.2017.00739. [PMC free article] [PubMed] [CrossRef] [Google Scholar].