



Role of Curcumin as a Potential Immunomodulator to Adjunct Tuberculosis Treatment in Indonesia

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Abstract

This study aimed to highlight and focus on curcumin's role in enhancing the body defense mechanism against tuberculosis (TB) infection, using a narrative review. This review was identified by four search engines: PubMed, Science Direct, Research Gate, and Google Scholar. We found that as an immunomodulator, curcumin reduces the production of specific cytokines by inhibiting the transcription factor. In the same mechanism, curcumin also activates the host macrophages, dendritic maturation, and modulation of the antigen-presenting cell process. Curcumin also increases apoptosis as a defence mechanism against TB infection. Curcumin also increases B-cell proliferation and downregulates oxidative stress on B-cells. As results, curcumin is a potential immunomodulator that complements M. TB treatment, especially in Indonesia. It can be stated that curcumin is proven to be a promising strategy in complementing TB prevention also treatment.

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Introduction

Tuberculosis (TB) is an infectious progressive airborne disease caused by the pathogen named *Mycobacterium tuberculosis* (*M. tuberculosis*) complex, it is transmitted based on droplet nuclei and airborne infection. An accumulation of this bacteria inside our body will affect the primary physiological way in our lungs and cause pulmonary TB. According to the Ministry of Health Indonesia, in 2020, it is stated that Indonesia is one of the eight countries that contribute to 2/3 of TB cases worldwide [1]. Indonesia ranks second after India with 845,000 cases and 98,000 deaths, or equivalent of 11 deaths/h [2].

M. tuberculosis, acid-fast bacillus, is derived from a group of organisms classified as the *M. tuberculosis* complex. *M. tuberculosis* infection is common through exposure to the lungs or mucous membranes to infected aerosols [3]. Bacteria that reach alveoli will be inhibited by T-cells and macrophages by forming granuloma that forms a microenvironment to limit bacteria's spread, resulting in necrosis [4]. However, individuals with a weak immune system are unable to

contain *M. tuberculosis*. Thus, the patient has fibrosis or calcification, resulting in primary progressive TB [5].

T-cell-mediated immunity plays an important role in host defenses against *M. tuberculosis* infection, especially CD4 + Type T-cells T-helper 1 (Th1) which secretes interferon-gamma (IFN- γ) [6]. IFN- γ strengthens the potency phagocytes of macrophages by stimulating fusion phagolysosomes and reactive formation oxygen intermediates/reactive nitrogen intermediates (ROI/RNI) which can destroy the bacteria *M. tuberculosis* [7]. Early secretory antigenic the target 6 kD represents M strain-specific protein TB being a virulent factor, because it inhibits production ROI/RNI for mycobacterium elimination [8].

To prevent the development of *M. tuberculosis* that has entered a person's body, a person needs to have a good immune system and curcumin is the promising solution to strengthen a person's immune system. Mainly, curcumin has a role as an immunomodulator, which can regulate immune responses [9].

Recent studies stated that curcumin has properties such as anti-inflammatory, antioxidant, antidiabetic, and cholesterol-lowering properties. It is

shown that curcumin is a potent immunomodulatory agent in regulating various immune cells such as T-cells, B-cells, macrophages, neutrophils, natural killer (NK) cells, and dendritic cells. Research also stated that, through inactivation of the transcription factor such as nuclear factor (NF)- κ B, curcumin has a role in downregulating the expression of proinflammatory cytokines [10].

This study highlights and focuses on the role of curcumin as a supplement that enhances the body's defense mechanism against TB infection. In Indonesia, the availability of curcumin is abundant. Thus, it has become a leading producer of turmeric globally. Therefore, curcumin could be proven as a promising strategy in TB treatment and prevention [11].

Materials and Methods

This study conducted a narrative review. This review is based on a question-based analysis regarding curcumin's role as an immunomodulator in TB infection. References are systematically sought using keywords such as curcumin, TB, immunomodulator, and immune cells on four search engines PubMed, ResearchGate, ScienceDirect, and Google Scholar. Years of research, article, and review must be included in the past 20 years. The literature searches and article selection were finished during May–June 2021 by two authors which completed the study selection process, and the included studies followed: Identifying duplicates; screening of titles and abstracts; and full-text availability. Data were manually extracted from the study results using the tabulation method and narrative analysis.

Results

We collected 16 scientific publications that were reviewed in this study. As a result, we found the curcumin role in immune response as follow:

T-cell

Based on recent studies, curcumin plays a role in suppressing CD4+ T-cell activation and differentiation. In this experiment, CD4+ T-cells were cultured in a specific appearance of antibody such as CD2/CD3/CD28, and it is coated with beads alone (Act.) or curcumin for 3 days. The figure below shows that, within 3 days, the supernatants were collected, and the total cytokine level (interleukin [IL]-2, IFN-gamma, and IL-10) determined using sandwich enzyme-linked immunosorbent assay (Figure 1). Thus, it can be proved

that curcumin has a role in suppressing the cytokine T-cell activation in producing cytokine [12].

Macrophages

Macrophages are one of the effector cells that phagocytose bacteria and secreting proinflammatory and antimicrobial mediators. Previously study showed that curcumin help controls the intracellular macrophages environment against TB in human. This experiment incubated a human acute monocytic leukemia cell line (THP-1) with curcumin and infected them with *M. tuberculosis*. There is a reduction in the number of TB -infected cells incubated with curcumin compared to controls from the data below (Figure 2). Based on this data, curcumin inhibits *M. tuberculosis* growth in human macrophage by inducing caspase-3-dependent apoptosis and autophagy through inhibit NF- κ B activation [13].

B-cell

Curcumin has the role in increased germinal center (GC) B-cells in lymph nodes. This study showed an increase in the total affinity of immunoglobulin G (IgG) and IgM with the addition of curcumin (Figure 3). It is concluded that curcumin can increase the T follicular helper cells that increase the production of GC B-cells and antibodies [14].

Natural killer cells

Curcumin has a role in activating NK cells. South *et al.* showed that curcumin with a dose of 40 mg/kg can elevate IgG level in the NK cells [10]. Furthermore, A low dosage of curcumin report the ability of NK cells to upregulate Th1 and NO production. Other studies also reported that curcumin has a role in normal NK cell immunomodulation and also increases cell death in NK/T-cell lymphoma (NKTL) cell lines [15].

Dendritic cells

In dendritic cells, Kim *et al.* stated that curcumin can depress CD80, CD86, and Major Histocompatibility Complex (MHC) II expression. Kim *et al.* also found that curcumin can block the lipopolysaccharide (LPS)-induction expression of IL-12 and inflammatory cytokines. Suppression by curcumin weakens the T-cell-mediated immune system as well as disrupts the stability of antigen presentation by dendritic cells [16].

Discussion

Curcumin is the main natural polyphenol in the rhizome found in turmeric or *Curcuma longa*.

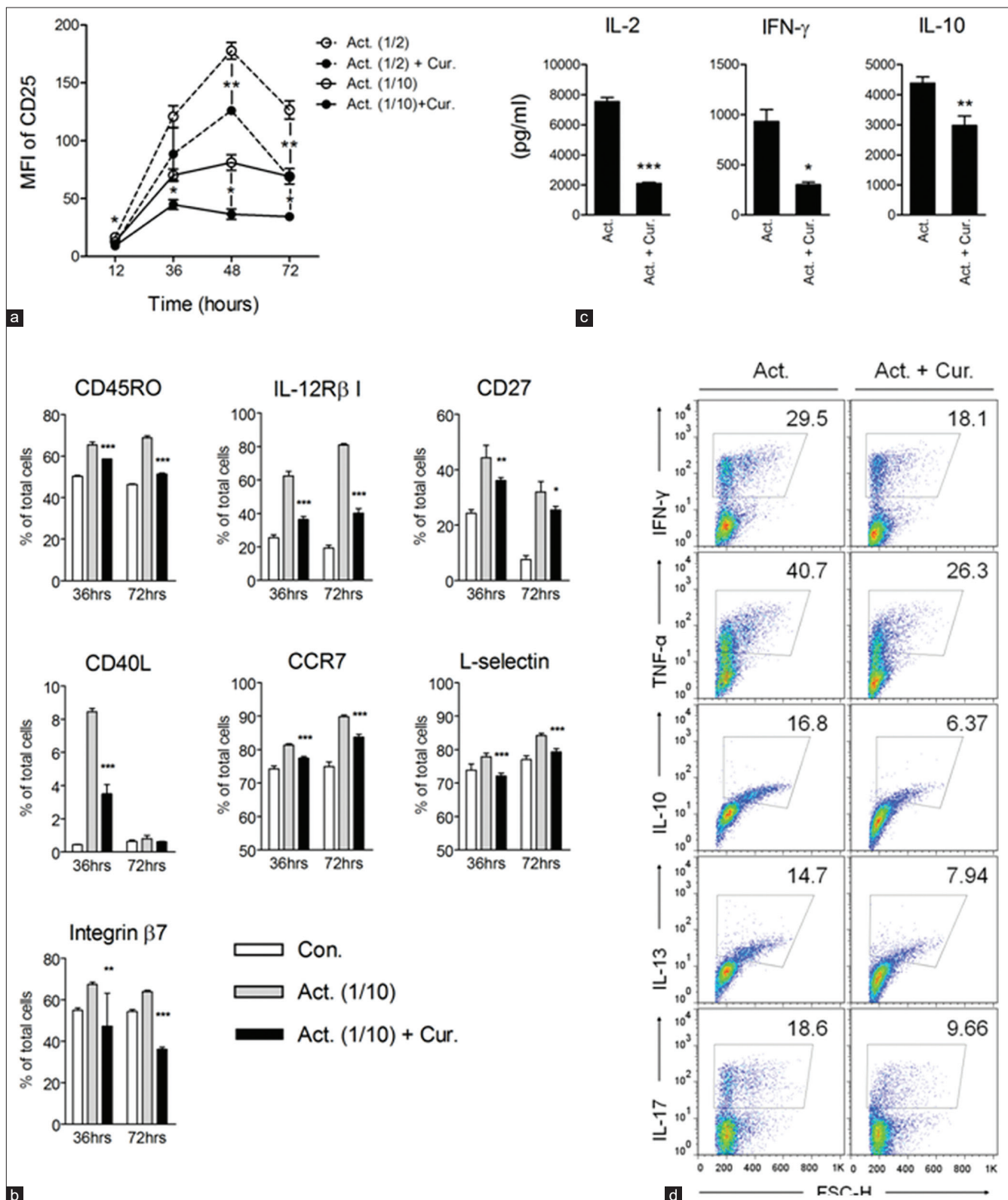


Figure 1: (a-d) The role of curcumin in T-cell activation and differentiation [12]

Turmeric has been used in many products and known well for thousands of years before. Recently, it is shown that turmeric has natural ability as a medicinal herb, specifically as antioxidant, antimicrobial, anti-inflammation, antimutagenic, and anticancer agents [17]. In our country, Indonesia, curcumin is known for its functionality as an immune booster found in a traditional

herbal drink called *jamu* [17]. Our study found that (1) Curcumin regulating T-cells against *M. tuberculosis*, (2) Curcumin-induced macrophage apoptosis and autophagy, (3) Curcumin modulates the activation of (NK) cells, (4) Curcumin suppressed the expression of dendritic cells, and (5) Curcumin boost our immune system by regulating B-cells (Figure 4).

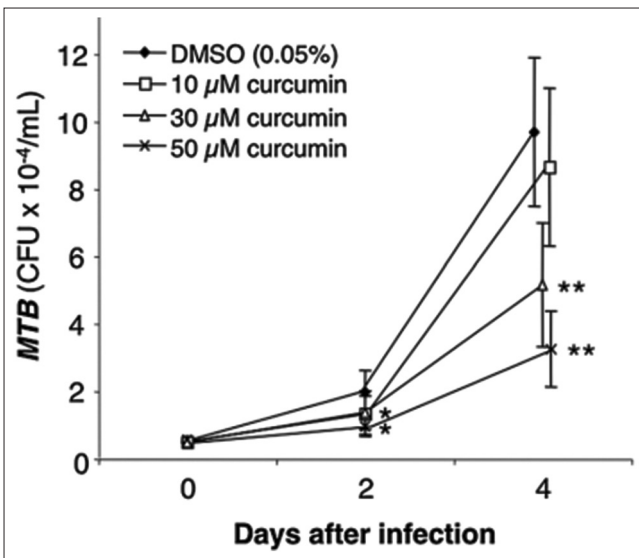


Figure 2: The role of curcumin in alveolar human macrophages [13]

Curcumin regulating T-cells against Mycobacterium tuberculosis

Th cells play a role in fighting intracellular pathogens, including *M. tuberculosis*, by producing IFN-γ and proinflammatory cytokines. Excessive activation of Th can cause tissue damage [18], [19]. Various evidence based on research has been conducted to prove the curcumin availability in modulating the proliferation by inhibiting concanavalin (Con A), phytohemagglutinin, and phorbol-12-myristate-13-acetate in lymphocytes of the human spleen. Moreover, T-cell activation is also regulated by curcumin. By its ability to regulate NF-κB activation, curcumin also suppresses the synthesis and induces the proliferation of IL-2. In conclusion, through the NF-κB, Signal Transducer and Activator of Transcription (STAT), and Activator Protein 1 (AP1) signaling pathways, curcumin can reduce the production of IFN-γ, TNF-α, IL-1, and IL-8 [18], [19].

Curcumin-induced macrophage apoptosis and autophagy

Macrophage has a role in our immune system, and it is shown that curcumin also acts in

modulating macrophages. Curcumin causes and promotes apoptosis in macrophage cells infected with *M. tuberculosis* [20]. In addition, curcumin also blocks the TLR2-mediated signaling pathway, which reduces the ability of macrophages to generate reactive oxygen species (ROS) response [19]. In infected macrophages, ROS are produced in high levels to counteract and kill the mycobacteria. Madhur *et al.* stated that the survivability of *M. tuberculosis* also depends on the level of ROS produced by host immune cells. The pathogen will have the ability to survive and proliferate inside the host cells if the ROS levels are overwhelmed by *M. tuberculosis* antioxidant system. On the other hand, a high level of excess production of ROS will initiate various chemical reactions, leading to the damage of cellular components such as lipid, protein, and nucleic acid. Moreover, ROS will initiate a signaling cascade in inflammation through protein kinase pathways, transcription factors, and genomic expression in the proinflammatory regulator. As a result, this mechanism will make an overactivated immune system [21]. Curcumin also affects by inhibits the activation of NF-κB and The Janus kinase-signal transducer and activator of transcription (JAK-STAT)-STAT signaling pathways, resulting in the activation of the host macrophages by suppressing Th1 and NO [22]. This will lead to dendritic cell maturation and modulation of the antigen-presenting cell (APC) process [19].

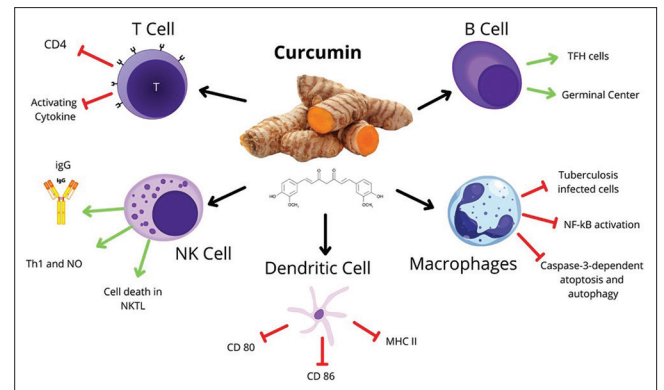


Figure 4: Model of the role of curcumin as a potential immunomodulator to adjunct tuberculosis

Curcumin modulates the activation of natural killer cells

NK cells are part of innate lymphocytes granular and have the capacity as a potent cytolytic. In correlation with TB, in immunocompromised individuals, NK cells have an essential role in combating *M. tuberculosis*. Furthermore, NK cells also modulate mycobacterial growth through immune stimulation and macrophage activation by cytotoxic mechanism [23]. In an investigation, it is said that curcumin increases NK cells' cytotoxicity [10]. NK cells also produce IFN-γ and IL-22, leads to the increasing activity of phagolysosome fusion that has a role in inhibiting *M. tuberculosis* growth. Curcumin modulates the activation of the NK cells. Moreover, curcumin also increases apoptosis in refractory NKTL or

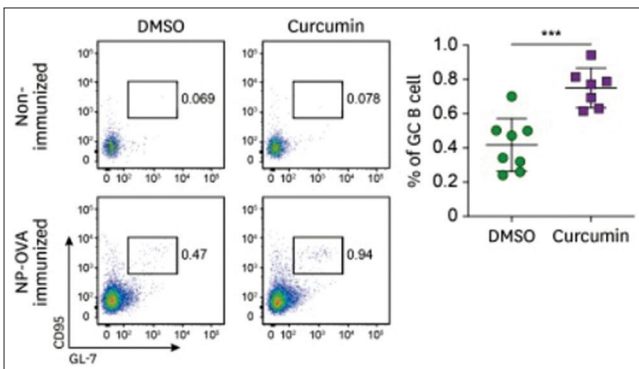


Figure 3: The role of curcumin in elevates GC B-cell response [14]. GC: Germinal center

abbreviated as NKTL. This mechanism will downregulate the transcription factor (NF- κ B) [10], [24].

Curcumin suppressed the expression of dendritic cells

Dendritic cells are known for their professional APCs for initiating T-cell responses to microbial pathogens. In TB, Th1 mediated IFN- γ response leads to restriction in growth and proliferation against *M. tuberculosis* infection. However, Th1 has an essential role in helping the elimination of those pathogen. An excessive amount of these cells can lead to various immune-associated diseases inhibiting the excessive amount of Th-1 cells by reducing IL-12 and other proinflammatory cytokines secretion [25], [26]. As an immunomodulatory agent in our body, curcumin plays a role in suppressing the expression of CD80, CD86, and MHC Class II antigens. Curcumin may help in capturing the AG through mannose receptor-mediated endocytosis. Curcumin also efficiently blocks the LPS-induced expression in IL-12 and other inflammatory cytokines such as IL-1 β , IL-6, and TNF- α . Moreover, curcumin will suppress the LPS-induced phosphorylation of Mitogen-Activated Protein Kinase (MAPK) and NF- κ B. This complex activity will attenuate the T-cell-mediated immune response by disrupting and regulating the antigen presentation in dendritic cells [10].

Curcumin boost our immune system by regulating B-cells

Despite the involvement of B-cells in controlling TB humans is still unclear, some research has shown that B-cell depletion leads to delay the progression of mainly T-cell-mediated. Plasma cells will secrete that antibody will contribute to control the *M. tuberculosis* prevention and infection. Antibodies regulate effectors functions, including opsonization mechanism, antibody-dependent cellular cytotoxicity, and secreted antigen. Moreover, antibody secretion will enhance granuloma formation in the early inflammatory response of Bacillus Calmette Guérin infected mice. As an immunomodulator in our immune system, curcumin on B-cells will boost our immune system by increasing B-cell proliferation [27]. The effect of curcumin also plays in downregulating oxidative stress that was previously induced by cyclosporine and hydrogen peroxide. Research has stated that curcumin treatment also has immunomodulatory activity and its role in stimulating the proliferation of B-cells. It is found that curcumin will reduce the proliferation of immature B-cells due to its ability to influence apoptosis [10].

Implication for clinical practice and further research

This review summarized the evidence that curcumin has the potential to prevent and treat TB.

However, we are unable to make a recommendation, because the evidence for our review came from a small number of studies. More Randomized controlled trials on curcumin for TB prevention and treatment are urgently needed. This review summarizes existing evidence that could be used to help shape future trial designs. To reduce potential biases in trials evaluating the effectiveness of curcumin for the prevention and treatment of TB, both study investigators and authors should ensure a strict methodology and proper reporting.

Limitation

We are consider of the limitations in our study especially in the number of the study. The small number of studies included in this review was most significant limitation. Furthermore, this review article is limited by including only Indonesian and English article and has been sought on four databases only, with specific set of keywords which were used for our findings, Consequently, the steps of filtering relevant research articles may not have been retrieved. Therefore, further studies should address the efficacy of curcumin in human also taking account for the effect on demographical factors and disease severity. Standard formulations and dose regimens are suggested to directly compare between each of the results.

Conclusion

Curcumin has a role as an immunomodulator which is useful as an adjunct TB treatment. Information regarding the relationship between curcumin and TB is still limited. Therefore, further research is advised. Curcumin has the ability in modulating cell in immune response against TB infection. With an enormous amount produced in Indonesia, curcumin is one of the solutions for the Indonesian population to adjunct treatment in most TB cases. As the further advances of managing COVID-19, curcumin has the most promising novel therapeutic agents and advised for further targeted experiments on curcumin, which are needed to analyze and identify effect on various severity in COVID-19. Considered, as promising therapeutic agents, utilization of curcumin should be implemented by various drug-making industry and advocate holistically in Nongovernmental and Governmental Organizations to be supplement therapy for COVID-19 publicly.

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