



The Curcumin Effects on Immune-Response and Its Potential Properties against Tuberculosis

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Abstract

There is numerous evidence for the efficacy of curcumin on the treatment of infectious disease particularly tuberculosis infection. According to review of the literature, curcumin could be considered as a therapeutic option against tuberculosis; but given that immunomodulatory of curcumin in immune-response and limitation of data about the main mechanism of curcumin during tuberculosis infection; we discuss the probability of curcumin as a novel treatment option for tuberculosis disease using current evidence.

Keywords: Curcumin; *Mycobacterium tuberculosis*; Treatment; Tuberculosis

Introduction

Tuberculosis (TB) remains as one of the most important infectious diseases in worldwide. According to WHO reports in 2018, there are 10.7 million new TB-cases, also it estimated 1.3 million deaths [1]. The lack of BCG vaccine efficacy in TB-adults and the emergence and extension of DR-TB (drug resistant-TB) strains are the cause of limit efficacy of current standard treatment of tuberculosis. In addition, anti-tuberculosis drugs particularly Isoniazid has a serious side-effect such as hepatotoxicity during the course of treatment [2,3]. Therefore, it necessary to introduce a novel generation of anti-tuberculosis therapeutic option which has efficient against both strain of susceptible and drug-resistant-TB without serious side-effects.

Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadien-3,5-dione] is natural polyphenol extract of *Curcuma longa* plants. curcumin has several activities such as anti-oxidant, anti-inflammatory, anti-cancer and antimicrobial effects [4,5]. Furthermore, curcumin not cytotoxicity on human cell lines [5]. In recent years there are several documents of anti-tuberculosis effects of curcumin during experimental studies and clinical trials [6,7]. Although the main mechanism of Curcumin against *Mycobacterium tuberculosis* (*Mtb*) remains unknown; But curcumin has immune-modulatory the effects on immune-system during tuberculosis infection [6-8]. The aim of this study was discussed

about effects of curcumin on immune-system and answer this question that can curcumin be used as an anti-TB drug?.

Discussion

Immune-system against Tuberculosis infection

Mycobacterium tuberculosis is commonly entered to the human body via inhalation of infected droplets from smear-positive TB individuals; innate immunity such as mucosa membrane, natural killer (NKs) and alveolar macrophage is active to fight with *Mtb* infection [9]. Overall, there are four possible outcomes following infection with tubercle bacillus including: 1) aborted infection and *Mtb* clearance, 2) primary TB infection caused by active *Mtb* replication and intracellular growth, 3) latent-TB infection without clinical symptoms, and 4) Reactivation of previous TB infection via infection with multiple *Mtb* strains or fallen into immune-disorder complications [10]. Although the innate immune response is immediately activated to fight with TB infection, the innate immune system is commonly not enough [11]. Usually, innate immune cells such as dendritic cells (DCs), antigen-presenting cells (APC), alveolar macrophages and epithelial cells are inducing inflammatory process and provoke cell mediate immune-system by recognition of pathogen-associated molecular pattern molecules (PAMPs) throughout mannose receptors, complement receptors, Toll-like receptors (TLRs), Fcγ receptors, and scavenger receptors and production of pro-inflammatory cytokines [12]. Cell-mediated immunity particularly Th1 cells are responsible for appropriate response to intracellular pathogens such as *Mtb* infection via various pathway including 1) production of cytokines such as IL-2, IL-12, IL-1β, TNF-α and IFN-γ, 2) activation of macrophage for increasing ROS, 3) Apoptosis of infected cells by induction of CD8+ cells (CTLs), and 4) Autophagy promotion [13]. Th17 is a subgroup of Th cells which promoted recruitments of neutrophils and other PMNs to infected sites and solid granuloma formation via the production of various pro-inflammatory cytokines such as IL-6, IL-17A, IL-23 [14]. But, changing immune-response into an extension of Th2 and T regulatory cells is cause to caseous necrosis, *Mtb* multiply, and reactivation of previous TB infection (Table 1 and Figure 1) [15].

Submitted: 20 May 2019 | **Accepted:** 03 June 2019 | **Published:** 05 June 2019

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Citation: Karbalaeei M, Keikha M (2019) The Curcumin Effects on Immune-Response and Its Potential Properties against Tuberculosis. JSM Clin Cytol Pathol 4: 4.

Curcumin effects on dendritic cells

According to the review of the literature, curcumin has inhibitory effects on maturation of dendritic cells (DCs) by decreasing the expression of CD80, CD86, and presentation of functional MHC II surface molecules [16]. In addition, Shirley et al., have shown that Curcumin can impair expression of IL-12 and other pro-inflammatory cytokines in bone marrow-derived DCs (BMDCs) of murine models; this process leads to inhibition of Th1 activation which supports intracellular growth of Tubercle bacilli within macrophages [17].

Curcumin effects on alveolar macrophages

Li et al., have found that curcumin can induce apoptosis of *Mtb*-infected macrophages. In previous reports, it has been suggested that apoptosis of *Mtb*-infected macrophages is playing important role in the destruction of tubercle bacilli reservoirs cells from the body; In addition, increasing antigen presentation cells (APCs) after apoptosis of *Mtb*-infected macrophages can lead to activation of Th1 cells against TB [6,18]. In contrast, Shuto et al., have shown that curcumin can also inhibit the TLR2-mediated signaling pathway in macrophages which blocked Reactive oxygen species (ROS) response of *Mtb*-infected macrophages [19]. In addition, curcumin has inhibitory effects on NF-κB and

JAK/STAT pathway which is dysregulated activation of T helpers, activation of macrophages, maturation of DCs and modulate APCs process [20].

Curcumin effects on Th1 cells

According to present evidence, curcumin can reduce the expression and production of IFN-γ, TNF-α, IL-1, and IL-8 by its influence on NF-κB, STAT, and AP1 signaling pathways [20,21]. Castro et al., have suggested that curcumin can reduce the proliferation of Th1 cells throughout the impairment of NF-κB and T-bet signaling pathways [22]. Th1 cells activities have play determinative role against intracellular pathogens particularly, Mycobacterium tuberculosis infection by production of IFN-γ and pro-inflammatory cytokines such as IL-2 [10]. Although exacerbate activation of Th1 response can cause to host damage and tissue destruction, but cell-mediated immune-response is main responsible for the prevention of intracellular pathogens [23]. Therefore, inhibition of Th1 cells mediated activities during TB infection can associate with milliary-TB and high-actively proliferation of tubercle bacilli within macrophages [24].

Curcumin effects on Th17 cells

Th17 cells are responsible for the recruitment and activation

Table 1: Different tuberculosis outcomes, Immune-system changes and status of bacteria.

Outcomes	Immune-system changes	Bacterial replication state
Aborted infection	Innate immune-response particularly macrophages	Killing TB bacilli
Primary active-TB	Deficient immunity, extension of T regulatory and Th2 response, production of IL-10 and TGF-β	Actively multiply <i>Mtb</i>
Latent-TB infection	Th1 and Th17, solid granuloma formation, CTLs and production of IL-1β, IL-2, IL-6, IL-12, IL-17A, IL-23, TNF-α and IFN-γ	VBNC and intracellular growth
Reactivation	Th2 and T regulatory response	Actively multiply <i>Mtb</i>

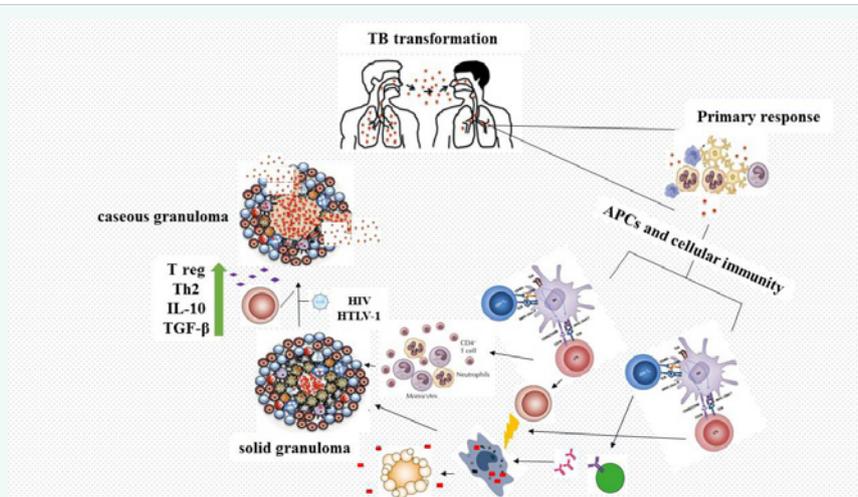


Figure 1 Immune-pathogenesis of tuberculosis. The alveolar macrophages and DCs are uptake *M. tuberculosis* and invoke CD4+ and CD8+ T cells response; The solid granuloma is created following efficient immune-response, but infection with retroviruses or suppression of immune-response (due to extension of T regulatory response) cause to caseous necrosis and reactivation of TB..

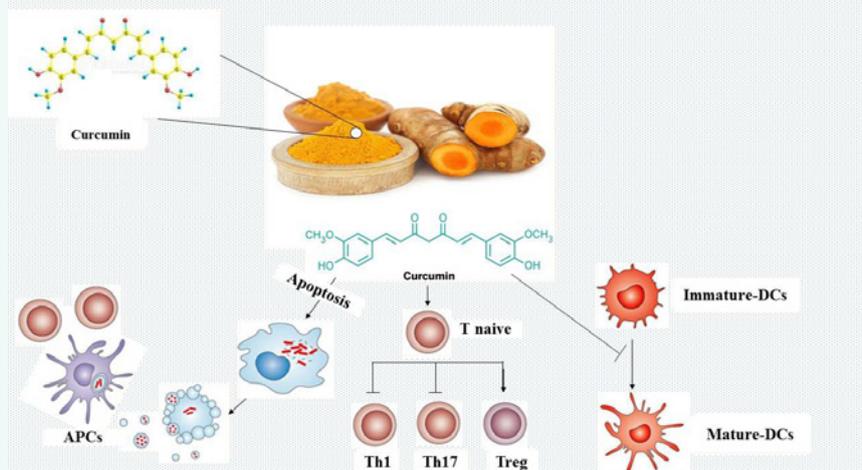


Figure 2 Immune-modulatory effects of curcumin on immune-system; curcumin can have impaired CD4+ T cells response by apoptosis of Mtb-infected macrophages, provoke T regulatory response, blockade DCs maturation and suppressive activity on induction to Th1 and Th17.

of neutrophils against TB infection [25]. These cells are derived from naïve T cells by ROR γ t transcription factor in the effects of the production of pro-inflammatory cytokines such as IL-6 and IL-23 [26]. Th17 cells produce pro-inflammatory cytokines particularly IL-17A-F, IL-22, and IL-21 which cause the invention of innate-immune cells such as polymorphonuclear cells (PMNs) into inflammation sites and cause to create solid granuloma formation during tuberculosis infection [25,27]. Xie et al., have shown that curcumin has suppressive activities on the production of Th17 by intervention in the production of IL-17, IL-6, IL-21, ROR γ t, and STAT3 signaling pathway [28]. Carbone et al have found that curcumin can down-regulate expression levels of ROR γ t and IL-17 [29].

Curcumin effects on T regulatory cells

It has been approved that curcumin can provoke the production of T regulatory cells via activation of JAK3-STAT5 signaling pathway and over-expression of TGF- β [30]. Sakaguchi et al have shown that oral administration of curcumin could decrease immune-response in inflammatory bowel disease (IBD) cause to evaluate levels of T regulatory cells [31]. In addition, there are several experimental evidence for increasing of CD4+ and CD8+ T reg cells in murine models due to curcumin-treated allogeneic splenocytes [32,33]. T regulatory cells can suppress Th1 activities by production of IL-10 and TGF- β ; there are several evidence for increasing of T regulatory cells in disseminated-TB patients [34]. Also, according to Babu et al., there are the false-negative response of TST test in latent-TB individuals due to increasing levels of T regulatory cells [35].

Whereas, the presence of numerous documents for the efficacy of curcumin against tuberculosis infections; but the information is controversial, curcumin has immune-modulatory effects on immune-systems and influenced several types of human cell lines (Figure 2) [4-8,36]. Therefore, according to present the evidence, curcumin could not be considered as therapeutic option as anti-tuberculosis drug due to its effects on immune-response

activities particularly Th1 cells [37]. In addition, curcumin has low serum half-life and has no efficient bioavailability capacity as a pharmaceutical compound [37,38].

Conclusion

Information about curcumin effects on tuberculosis infection it's limited and controversial; according to present suggestions, curcumin could not be considered as a therapeutic option against tuberculosis due to lack of selectivity, low bioavailability and modulating immune-system. Although it suggested that administration of curcumin nanoparticles can reduced hepatotoxicity effects following the isoniazid therapy.

Ethical Considerations

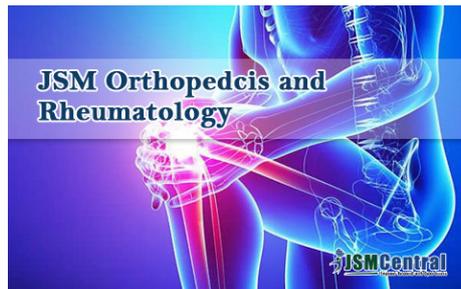
The Ethics Committee of Mashhad University of Medical Sciences was approved the study.

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