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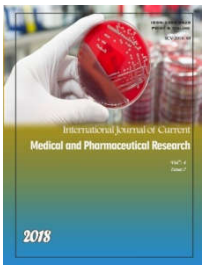

EFFECT OF CURCUMIN ON MYCOBACTERIUM TUBERCULOSIS INFECTION

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ABSTRACT

Tuberculosis is a world-wide menace putting mankind under huge financial burden and life threat. Attempts have been made to eradicate mycobacterium tuberculosis infection but without much success due to the emergence of resistance to various anti tubercular drugs either as MDR, XDR or TDR. Current first line, second line and even newer drugs targets only the causative organisms and thereby leave behind the chances of drug resistance and disease reactivation or reinfection, even after the treatment. Agents which target and enhance the host immunity, are devoid of limitations of conventional anti tubercular drugs. Curcumin targets the host immunity, hence becomes a preferred adjunct to the conventional anti tubercular drugs. It lacks the serious adverse drug reactions of the anti tubercular drugs. The various mechanisms for its anti tubercular actions are the enhancement of apoptosis and autophagy of macrophages, harbouring tubercular bacilli, blocking of human Kv 1.3 potassium channels, expression of anti microbial peptide cathelicidin, inhibition of mycobacterial enzyme pantothenate synthetase, activation of PPAR γ. Anti inflammatory, immunomodulatory, antioxidant and free radical scavenging properties of curcumin contribute to its anti tubercular potential. Curcumin and it's analogues have proved their merit as an adjunct anti tubercular agent. Their use can be encouraged and regularized in the treatment of tuberculosis by conducting extensive clinical studies.

INTRODUCTION

Tuberculosis [TB] is a major health problem affecting both the developed and developing countries, inflicting a huge financial burden on the society. The current first line, second line and newer drugs have many limitations like prolonged duration of therapy, their adverse effects and high cost resulting into reduced drug compliance. Emergence of the drug resistant mycobacterial [Mtb] strains add to the problem. The drug resistance can be either multi drug resistance [MDR], extended drug resistance [XDR] or even total drug resistance [TDR] [1-4] Isoniazid causes toxicity to the antigen activated T cells leading to the elimination of antigen responding T cells, resulting in to immune dysfunction and enhancing the susceptibility for the disease reactivation and reinfection as seen in animal studies.[5] Patients treated with anti TB drugs are found to be more prone for disease reactivation and reinfection.[6,7] Introduction of the newer anti TB drugs are likely to be misused leading to the development of resistance against them.

Present line of drug treatment for tuberculosis is not very effective to control the process of the development of drug resistance as they target Mtb organisms only and not the host defense mechanism. Hence the agents which target host defense mechanism and not only the pathogens are preferred.[8] Curcumin is a potent immunomodulator known to enhance the host immunity against Mtb infection. Curcumin targets the host defense mechanism, hence is less prone for the development of drug resistance. It shortens the course of anti TB drugs, has minimal adverse drug reactions and on the contrary it prevents the hepatotoxicity induced by anti TB drugs like Isoniazid. Curcumin minimises the chances of reinfection by the complete clearance of Mtb bacilli.[9]

The role of macrophages in the control of Mtb infection-Mtb has the ability to modify signals involved in the production of immunomodulatory cytokines and the effector molecules in the host.[10] Hence host immunomodulation forms the preferred strategy to control Mtb infection.

Evasion of both the innate and adaptive host immune responses favor the growth of pathogens and the prolongation of infection.[11-13] The host cell innate immune response against microbia include the generation of reactive oxygen species [ROS], reactive nitrogen species [RNS] and the use of phagosomal activity or autophagy pathway to destroy intracellular pathogens.[14,15] When the Mtb organisms enter the host cell, the host defense mechanism is activated through macrophages to achieve the phagocytosis of the organisms. Usually the phagocytosis is effective in internalizing and clearing the bacillary load. After the activation by appropriate stimuli, alveolar macrophages transfer the phagocytosed Mtb bacilli for their destruction to the lysosome after the fusion of

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phagosome to lysosome. Formation of the granuloma by the host is an attempt of localizing the infection. The activated macrophages in the granuloma, process and present Mtb antigen to the surrounding T cells. Activated T cells secrete cytokines and chemokines which keep the macrophages in the activated state along with the recruitment of other immune cells at the site of infection.[16]

Tuberculosis as a disease constitutes components like infection, inflammation, immune disturbances and the generation of oxidative stress. Curcumin was found to address all these components of tubercular disease and also minimizes the chances of reactivation and reinfection. It has minimal adverse drug reactions. Anti TB drugs available at present deal only with the infection part and also cause many adverse drug reactions. They also enhance the chances of reactivation and reinfection.[17]

Curcumin is a yellow pigment, and a principle polyphenolic curcuminoid of curcuma longa. It was found to have various medicinal properties like antiinflammatory, antioxidant, immunomodulatory, antimicrobial, antiproliferative and anticancer.[18]

Antitubercular mechanism of curcumin- Curcumin is known to inhibit the growth of microorganisms like Escherichia coli, Bacilus subtilis, Helicobacter pylori and Mtb.[19-21]

The various mechanisms studied by researchers for the anti tubercular potential of curcumin are- the blocking of Kv 1.3 potassium channels in the effector memory T [TEM] cells, [22] enhancement of the apoptosis and autophagy of macrophages, harbouring Mtb bacilli,[23] expression of the anti microbial peptide cathelicidin,[24] inhibition of mycobacterial enzyme pantothenate synthetase[25] and the activation of peroxisome proliferator activated receptor γ.[26] Possibly the inhibition of mycobacterial lipoprotein 19-kappa Da by curcumin also contributes for it's anti mycobacterial action.[27] Anti inflammatory, immunomodulatory, antioxidant and free radical scavenging action of curcumin play an important role in it's anti-mycobacterial action.[18]

Kv1.3 potassium channel plays an important role in the functioning of the TEM cells. It has an implication in the autoimmune diseases like multiple sclerosis, psoriasis and type 1 diabetes mellitus. Clofazamine, an antimycobacterial drug was found to inhibit human Kv1.3 potassium channels and intracellular T cell receptor mediated signaling resulting in to transcriptional activation of human interleukin-2 genes in the T cells. By blocking these channels oscillation frequency of the calcium release activated calcium channel get disturbed resulting in to the inhibition of calcineurin-NFAT signaling pathway. Thus clofazamine acts as an immunomodulatory drug .[28]

Curcumin was found to be useful in the treatment of autoimmune diseases through various mechanisms. TEM cells play an important role in the pathogenesis of T cell mediated autoimmune diseases like multiple sclerosis and rheumatoid arthritis. Kv1.3 potassium channels are predominantly expressed in TEM cells and control their activities. Curcumin was found to block these channels in human [hKv1.3], in concentration and time dependent manner. Curcumin also significantly inhibited the proliferation and secretion of interferon γ by TEM cells. Thus curcumin inhibits the proliferation and pro inflammatory cytokine secretion of TEM cells possibly by inhibiting hKv1.3 channels which makes it a potential agent in the treatment of diseases like TB where the immunity plays an important role.[22]

Curcumin provides post infection prophylaxis as it prevents the apoptosis of the antigen presenting T cells and stimulates memory T cell response. Curcumin is an inhibitor of Kv1.3 and it alters the ratio of the central memory T cells to effecter memory T cells [TCM:TEM], enhances the host immunity and provides protection against post treatment infection.[9]

Macrophages infected with Mtb bacilli undergo apoptosis. This enhances the killing of MTB bacilli. This process facilitates the antigen presentation to the T cells through either MHC class 1 or CD 1 molecule and enhances host immunity against Mtb bacilli.[29-32] Curcumin inhibits the activation of Nf-kB and reduces the viability of Mtb bacilli in human macrophages through the induction of autophagy and apoptosis in the macrophages. Induction of caspase -3 contributes to apoptosis.[23]19-kappa Da lipoprotein secreted by Mtb bacilli is a virulence factor of these organisms. It's inhibition by curcumin decreases the virulence of Mtb bacilli.[27]

Changtam *et al* showed the direct anti TB activity of curcumin against Mtb H37Rv, but at high concentration of more than 250muM.[21] Baldwin *et al* used monocarbonyl analogues of curcumin and they were found to inhibit the growth of Mtb organisms at low concentration of less than 50muM.[33]

Curcumin has been proved to induce the expression of antimicrobial peptide cathelicidin in human monocyte cell line U- 937.[34] Cathelicidin was shown to kill the intracellular Mtb in murine macrophages. Cathelicidin mediated killing of Mtb organisms is one of the important mechanism for the anti tubercular action of curcumin.[24]

Effect of curcumin on enzyme pantothenate synthetase- Enzyme pantothenate synthetase [PS] is a protein found in the microorganisms including Mtb. It's function is to synthesize pantothenate, an essential precursor of coenzyme A [CoA] and acyl carrier protein [ACP].For the metabolism of the cells these two factors are essential. Biosynthetic pathway of pantothenate is also essential for the virulence of Mtb bacilli as observed in experimental studies.[35] Inhibition of synthesis of pantothenate proves detrimental to Mtb bacilli. Humans lack enzyme PS. Hence enzyme PS is considered as a potential target for anti tubercular agents.[36] Study done by Catrina Theresa M Yang *et al* revealed that curcumin and its analogues 3, 16 and 18 were potent inhibitors of PS than nafronyl oxalate, a known competitive inhibitor of PS. When curcumin and its analogues have been docked to the enzyme PS, exhibited the best binding interaction with PS. It's binding energy as well as that of curcumin and its two analogues inhibit the enzyme PS.[25]

Studies have shown that peroxisome proliferator activated receptor γ [PPAR γ] plays an important role in the inflammation. Activation of PPAR γ by thiozolidinediones have an anti inflammatory effect. Their beneficial effects were associated with the reduction of lkB kinase complex, JNK activation and the reduction of transcription factor nuclear factor kappa B[Nf-kB] and AP-1 pathways.[37-39] Mechanisms responsible for the apoptosis induced by the curcumin involves the inhibition of cell signaling pathways, AKt, Nf-kB, AP-1 or JNK. It is suggested that curcumin induced anti inflammatory effect is caused by the up regulation of PPAR γ and is associated with the inhibition of the activation of Nf-kB

pathway.[40] Curcumin induces the apoptosis of human neutrophils through the mediation of activation of P38 and caspase-3 activity.[26]

Anti inflammatory and immunomodulatory mechanism of curcumin- Various in vitro and animal studies suggested the anti-inflammatory mechanism of curcumin. Curcumin was found to inhibit various inflammatory mediators like cycloxygenase-2, lipoxygenase, leukotrienes, thromboxane, prostaglandins, nitric oxide, collagenase, elastase, hyaluronidase, monocyte chemoattractant protein -1 [MCP-1], interferon inducible protein, tumor necrosis factor α [TNF α] and interleukin 12.It was also found to inhibit the activation of pro inflammatory transcription factors Nf-KB and AP-1.[41] Inhibition of the activation of Nf-kB by curcumin was found to reduce the viability of Mtb organisms in human macrophages and it also enhanced macrophage effector function against Mtb bacilli.[23] Curcumin is a potent inducer of apoptosis which is an effective mechanism used by the macrophages to kill intracellular Mtb bacilli. Induction of apoptosis and autophagy by curcumin was found to reduce the intracellular burden of Mtb infected macrophages. Macrophages infected with Mtb bacilli when undergo apoptosis, enhance their killing as well as facilitate the antigen presentation to T cells through either CD1 molecule or MHC class 1.[29-32] This increased apoptosis of Mtb bacilli infected macrophages enhances the host immunity against Mtb. Study done by Xiyuan Bai *et al* found that curcumin was an inducer of caspase-3 dependent apoptosis and autophagy.[42] Pramodkumar Gupta *et al* observed the dose dependent inhibition of the intracellular survival of Mtb strains in macrophages.[43]

Curcumin was found to be a potent immunomodulatory agent. It modulates the activation of T cells, B cells, macrophages, neutrophils, natural killer cells and dendritic cells. It also down regulates the expression of various pro inflammatory chemokines and cytokines like TNF α, IL-1,2,6,8 and 12 through the inactivation of transcription factor Nf-kB. Curcumin modulates both the proliferation and activation of T cells. It also inhibited the synthesis of IL-2 and related proliferation of lymphocytes which was correlated with the suppressed activation of Nf-kB. [44,45] Immunomodulatory action of curcumin targets Toll like receptors [TLRs] which regulate innate and adaptive immune responses.[46,47]

Antioxidant and free radical scavenging potential of curcumin- Antioxidant and free radical scavenging potential of curcumin can be attributed to it's polyphenolic contents. It donates hydrogen ions and bears the potential to neutralize reactive oxygen species [ROS].In the studies done by Sai Krishna Bora curcumin exhibited the potential of scavenging of 1,1-diphenyl-2-picryl-hydrazil [DPPH], superoxide, nitric oxide and hydrogen peroxide radicals in the dose dependent manner. Curcumin inhibited erythrocyte membrane lipid peroxidation and scavenged the peroxy radicals which are known to induce RBC haemolysis.[48]

Effect of curcumin analogues on MTB infection- Monocarbonyl derivatives of curcumin have superior efficacy than curcumin itself.[49-52] Study done by Baldwin *et al* showed that monocarbonyl analogues are also effective against Rifampicin resistant strains of MTB and mycobacterium marinum strain.[53]

To improve the bioavailability of the curcumin it's nano particles of size about 200nm were prepared which were found to be more effective than curcumin. Treatment with these nano particles in experimental animals was found to reduce the hepatotoxicity induced by anti TB drugs and the incidence of disease reactivation and reinfection as a result of enhanced T cell mediated immunity. It also reduced the total duration of anti TB drugs required to eradicate the infection. Curcumin nano particles are the promising adjuncts to the conventional anti TB drugs and are expected to reduce the incidence of MDR and XDR TB.[9]

The benzylidene acetate analogue of curcumin was tested against Mtb H37Rv infection. This analogue of curcumin having chlor moiety was found to have better activity of inhibiting MTB.[54]

Curcuminoid constituents-curcumin, demethoxy curcumin and bis-demethoxycurcumin- were structurally modified to 55 analogues. Among these analogues isoxazole analogues were the most active group, mono-O-methyl curcumin isoxazole -53 being the most active compound. It was 1131 fold more active than curcumin-1 and was about 18 and 2 times more active than kanamycin and isoniazid respectively. This compound exhibited high activity against the clinical isolates of MDR Mtb. The presence of isoxazole ring and 2 unsaturated bonds on heptyl chain of curcuminoid analogue is a structural requirement to exhibit anti TB activity.[21]

Medicinal activity of curcuminoid is known to be enhanced by complex formation with various inorganic species like metal ions. The synthesized 3 ligands and their copper complexes were prepared and tested in vitro for anti Mtb activity against Mtb H37Rv. It was observed that the copper complexes of all the derivatives showed more anti TB activity than ligands. This can be explained on the basis of chelation theory. Chelation can reduce the polarity of metal ions considerably. This increases the lipophilic character of the chelate, favoring the interaction between metal ions and the lipids of the cell wall and membrane. This leads to the breakdown of permeability barrier of the cell which interferes normal cell functions.[55]

Curcumin was found to be more effective in animals than in humans. This may be due it's less bioavailability as a result of poor GI absorption, rapid metabolism and excretion.[56] Efforts have been made to enhance the bioavailability of curcumin by various techniques like heat, pH, complexations with metal ions, polymers or serum. By the use of heat, solubility of curcumin was raised up to 12 fold.[57] To overcome the low bioavailability of curcumin, some new approaches are tried, like the use of adjuncts which can block it's metabolic pathways such as glucorunidation,[58] adopting effective delivery system like the use of phopholipid complexes,[59] micelles,[60] liposomes,[61] and nanoparticals.[62-64] In rat model nano curcumin showed 22 fold increase in the oral bioavailability than curcumin.[65]

Curcumin has been proved to be an anti tubercular drug by virtue of its various mechanisms. Hence it can be concluded that the use of various pharmaceutical preparations of curcumin and its analogues, as an adjunct to conventional anti TB drugs, can be encouraged after extensive clinical studies.

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