REVIEW ARTICLE

Therapeutic effects of curcumin in inflammatory and immune-mediated diseases: A nature-made jack-of-all-trades?

Running title: Immunomodulatory and anti-inflammatory effects of curcumin

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Abstract

Curcumin is a dietary polyphenol from turmeric with numerous pharmacological activities. Novel animal and human studies indicate that curcumin can affect different immune cells, such as various T lymphocyte subsets, macrophages, dendritic cells, B lymphocytes and natural killer cells, which results in decreasing severity of various diseases with immunological etiology. The present review provides a comprehensive overview of the effects of curcumin on different immune cells and immune system-related diseases. This article is protected by copyright. All rights reserved

Key words: Curcumin; Immune system; Autoimmune disease; Inflammation
1. Introduction

Curcumin is a polyphenolic dietary phytochemical, and the bioactive pigment present in the roots of *Curcuma longa* L. (turmeric) (Figure 1) [1]. Turmeric and its chemical constituents have been used in traditional medicine and Asian cooking as a food color and food additive for thousands of years [2]. Regarding its safety, there is extensive evidence from human trials on the lack of toxicity of curcumin even at doses as high as 10 g/day [3, 4].

Curcumin shows a wide range pharmacological activities, including antioxidant, pro-oxidant, chemopreventive, proapoptotic, anti-inflammatory, antifungal, anti-ischemic, hepatoprotective anti-parasitic, antimicrobial, and chemotherapeutic activity (Figure 2) [5-31]. Furthermore, there is accumulating scientific evidence suggesting the immunomodulatory potential of curcumin.

Curcumin has been found to modulate the activation of T cells, B cells, macrophages, neutrophils, natural killer (NK) cells and dendritic cells (DCs), as well as the secretion of immune cytokines in the normal body [32-39].

2. Immunomodulatory properties of curcumin

2.1. Mechanisms of actions, molecular and cellular targets

A variety of pharmacological activities of curcumin stem from its ability to interact with different biological targets and signaling pathways [40]. Toll-like receptors (TLRs) are integral to the recognition and innate immune defence against antigens of microbial origin [41]. Some studies suggest that the immunomodulatory activity of curcumin may involve direct targeting (activation) of TLRs (such as TLR4: a receptor of LPS) by pathogen-associated molecular patterns (PAMPs). PAMPs are microbial products that are recognized by cell surface receptors such as TLRs and cytosolic receptors [42-46].
Other mechanisms underlying curcumin modulation of immune responses are attributed to the regulation of various transcription factors such as nuclear factor (NF-κB), activator protein 1 (AP-1), signal transducer and activator of transcription (STAT) and also their downstream signaling pathways [47-53].

NF-κB exerts a key role in producing pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-2 (IL-2) and interferon-γ (IFNγ) in T-cells [54-57]. Pleiotropic effects of curcumin (such as inhibition of IL-1 production) are believed to stem from suppression of NF-κB activity via inhibition of I kappa B kinase-a (IKK-a) phosphorylation and prevention of nuclear translocation of the NF-κB p65 subunit [58-60].

BLYS (B Lymphocyte Stimulator) is an important cytokine for B cell proliferation and autoantibody secretion in autoimmune diseases [61]. Curcumin has the potential to serve as an efficacious therapy for autoimmune disorders such as systemic lupus erythematosus (SLE) and Rheumatoid Arthritis (RA) by targeting BLYS. The inhibitory effect of curcumin on BLYS expression is due to reduction of NF-κB activity by inhibiting DNA binding of NF-κB and the nuclear translocation of p65 [62]. The mTOR (mammalian target of rapamycin) signaling is known to have an important role in xenograft (transplantation of tissues or organs from one species to another) rejection [63]. Inhibition of mTOR by curcumin is another mechanism to regulate immune responses through suppression of cytokine (e.g., IL-2) production. This effect of curcumin is thought to be a mechanism involved with preventing xenograft rejection [63].

2.2. The effects of curcumin on DCs

Mature DCs are key mediators in preserving central and peripheral tolerance to immune responses [64, 65]. Curcumin has been found to inhibit the maturation of DCs and to reduce co-stimulatory molecules (CD80 and CD86), major histocompatibility complex (MHC) class II, and
CD40 expression on the surfaces of DCs in a dose-dependent manner. The curcumin-treated DCs have a high capacity at antigen capture (property of DCs) through mannose receptor-mediated endocytosis. The maturation inhibition by curcumin is similar to the activity of corticosteroids, IL-10, TGF-B, cyclosporine, 1,25-dihydroxyvitamin D3, and aspirin [66-73]. Human DCs expressing indoleamine 2,3-dioxygenase (IDO) are capable of maturation [74]. Curcumin has been found to suppress maturation of DCs by inhibition of IDO expression through a cyclooxygenase (COX-2)/prostaglandin E2 (PG-E2) dependent pathway [64, 65, 74].

Adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) (CD54), are pivotal in regulating cellular adhesion and T cell responses. CD11c, a protein belonging to the integrin family, is also an important regulator of cell adhesion, and is highly expressed on DCs. Curcumin significantly reduces the expression of both markers mentioned above on the DC surface. The reduced CD11c could be the result of curcumin-induced AP-1 inhibition. AP-1 is a transcription factor that controls cellular response to different stimuli, including cytokines, growth factors, and bacterial and viral infections; thus affecting cell differentiation, proliferation, and apoptosis [75].

2.3. The effects of curcumin on neutrophils and macrophages

There are several lines of studies that show curcumin can reduce neutrophil recruitment to inflamed tissues by a direct effect on neutrophil chemotaxis and chemokinesis [76-78]. The inhibition of chemotaxis can be attributed to downregulation of PI3K (Phosphoinositide 3-kinase) activity, O$_2^{\cdot-}$ (superoxide) , iNOS , AKT phosphorylation and NF-KB activation[79]. Curcumin attenuates lipopolysaccharide (LPS)-stimulated expression and secretion of macrophage inflammatory protein-2 (MIP-2), IL-1b, keratinocyte chemoattractant (KC), IL-8 (mediates chemotaxis of human neutrophils) and MIP-1a in neutrophils and macrophages. It also
reduces the levels of inducible NO synthase, IFN-γ and IL-12 through inhibition of the NF-κB signaling pathway in monocytes/macrophages [79]. In several studies, a significant increase in macrophage phagocytic activity in the presence of curcumin has also been observed [80-83]. These studies suggest the potential benefits of curcumin for reducing oxidative and lipid-mediated damages in macrophages [84-86]. Furthermore, pretreatment with curcumin was reported to significantly inhibit IL-12 production by down-regulating NF-κB in LPS-stimulated macrophages, which resulted in inhibition of IFN-γ production and enhancement of IL-4 production by CD4⁺ T cells [87].

2.4. The effects of curcumin on B cells

The effects of curcumin on B cell activity have been investigated in several studies. Curcumin can decrease antibody production (IgG2a, IgE and IgG1, and particularly IgG1) in response to LPS by rat splenocytes [88, 89]. The TLRs signaling leading to NF-κB activation can involve B cell activation [88]. Curcumin can also inhibit NF-κB activation through inhibiting the TLR signaling pathway [88]. Another study revealed that curcumin can down-regulate activation-induced cytosine deaminase (AID), which is a master regulator in immunoglobulin class switch recombination and somatic hypermutation [90]. This activity of curcumin lead to the prevention of immunoglobulin class switch recombination and somatic hyper-mutation. Curcumin has also been reported to enhance intestinal immune function in high-fat fed animals by increasing IgA production or suppression of IgA degradation [91]. These observations suggest the potential effects of curcumin in the treatment of B cell-mediated autoimmune diseases.

2.5. The effects of curcumin on T cell subsets and NK Cells

In a recent study, the effect of curcumin on absolute lymphocyte count (ALC), T cell populations and NK cells in patients with Chronic Lymphocytic Leukemia (CLL) was evaluated. Curcumin
was found to have therapeutic effects on a small percentage of early CLL patients by decreasing their ALC, perhaps by stimulating an immune response that increased the number of CD4\(^+\), CD8\(^+\), and NK cells [92]. Similarly, an in vivo study in a mouse model showed that curcumin can increase CD8\(^+\) T cell and NK cell populations [93, 94].

The immunomodulation effect of curcumin on CD8\(^+\) and CD4\(^+\) T cell subsets has been frequently found in previous studies [95]. Cytotoxic T Cells (CTLs) with CD8 marker defend against tumor cells and viral infected cells. Mechanistically, some studies show that curcumin can attenuate tumor-induced depletion of T cells and restore antitumor activity to CD8\(^+\) T cells by increasing the number of CD4\(^+\) (from 2.5% to 4.5%) and CD8\(^+\) T cells (from 2.5% to 6%) at the tumor micro-environment in tumor-bearing animal models [95].

CD4\(^+\) T helper (Th) lymphocytes can be divided to several distinct subsets of effector cells including Th1, Th2, Th17, and T regulatory cells (Tregs), which are known to have different profiles of cytokine and transcription factor expression [96]. Th1 cell subsets secrete cytokines usually associated with inflammation such as IFN-\(\gamma\) and tumor necrosis factor-\(\beta\) (TNF-\(\beta\)), and induces cell-mediated immune responses. Th2 cell subset plays a central role in allergic diseases and produces cytokines such as IL-4, IL-5, and IL-13. These cytokines induce B cell proliferation and differentiation that are associated with humoral immune responses [96].

Curcumin can inhibit the production of the Th1 cytokine profile in CD4\(^+\) T cells by suppressing IL-12 production in macrophages; therefore, curcumin may possess a possible therapeutic effect on Th1-mediated immune diseases. Curcumin was reported to decrease the expression of Th1 cytokines (IL-12, IFN-\(\gamma\), TNF-\(\alpha\), IL-1) and increase the expression of Th2 cytokines (IL-4 and IL-10) in colon mucosa. It was also found to increase the IFN-\(\gamma\)/IL-4 ratio in splenocytes and the circulation [87].
TH17 cells have an important role in host defense against bacterial, fungal, and viral infections at mucosal surfaces. It was recently demonstrated that TH17 cells are crucial in the pathogenesis of inflammatory and autoimmune diseases [97]. These cells produce IL-17 and IL-21 cytokines. RORγt (RAR-related orphan receptor gamma) is the master transcription factor in Th17 cells. Some evidence indicates that curcumin inhibits differentiation and development of Th17 cells by down-regulating the expression of IL-6, IL-21, IL-17, and RORγt signaling, as well as inhibiting STAT3-phosphorylation [98, 99].

Treg cells modulate innate and adaptive immune responses. These cells produce immunosuppressive cytokines, such as transforming Growth Factor Beta (TGF-β) and IL-10, which play a critical role in the maintenance of tolerance in the immune system [97, 100]. These cells comprise a predominate population of the CD4^+CD25^+ T cells. Additionally, the transcription factor forkhead winged helix protein-3 (FoxP3) is widely accepted as the most specific marker for Treg cells [101]. It was reported that treatment of DCs with curcumin may induce development of FoxP3^+ Treg cells [64]. Curcumin was also associated with an up-regulation of IL-10, and CD4^+CD25^+ Foxp3^+ Treg cells in the CNS and lymphoid organs [98].

2.6. The effects of curcumin on cytokine production and inflammatory mediators

A key mechanism for the modulatory effects of curcumin on pro inflammatory cytokines is the suppression of NF-κB [102, 103]. Upon binding of IL-1 (a potent inflammatory cytokine) to IL-1 Receptor-I (IL-1RI), NF-κB is activated via various signaling pathways, such as activation of several mediators, for example, IRAK, MyD88, and Tollip [104]. Curcumin blocks IL-1-mediated recruitment of IL-1 receptor-associated kinase (IRAK) to the IL-1RI in murine Thymoma EL-4 cells and thereby inhibits NF-κB activation [104]. Curcumin has been found to reduce serum levels of various inflammatory mediators such as cytokines, chemokines, and
surface receptors including IL-1β, IL-6, soluble CD40 ligand, IL-8, macrophage inflammatory protein-1 (MIP-1), macrophage chemotactic protein-1 (MCP-1), TNF-α, adhesion molecules, C-Reactive Protein (CRP), CXCR-4, PGE2, and soluble vascular cell adhesion molecule-1, as well as the erythrocyte sedimentation rate (ESR) [32, 44, 105-108]. The effects of curcumin on the production of key cytokines and chemokines is shown in Table 1.

3. Therapeutic potential of curcumin in inflammatory and immune-related diseases

The effects of curcumin on various immune system disorders are discussed in the following sections (Tables 2-4).

3.1. Curcumin and anti-tumor immunity

Curcumin has been identified as a promising anti-tumor compound [8, 34, 40] capable of suppressing tumor initiation, promotion, invasion, and metastasis [109, 110]. The anticarcinogenic effects of curcumin have been well documented and are attributed to an increase in the activation of macrophages and NK cells [111]. Curcumin can enhance NK cell cytotoxicity and thereby plays a crucial modulatory role in the remission of tumor progression [112].

It has been found that curcumin (20 mg/animal/day) can increase NO production by NK cells, which leads to a regression of subcutaneously transplanted AK-5 tumors and thus exhibits an anti-tumor effect [113]. Cytokines, such as IL-2, IFN-γ, and IL-12, play a critical role in the activation of host immune cells, which, in turn, participate in the rejection of tumors [113]. The levels of both IFN-γ and IL-12 produced by NK cells and macrophages are increased in the presence of a tumor. In addition, results have shown that NO production by NK cells increases with curcumin plasma concentrations (2.5-20 μM) [113]. Another study in 3LL lung tumor-bearing mice revealed that high-dose curcumin treatment (100 mg/kg) inhibits the expansion and function of immune cells, while low-dose curcumin (50 mg/kg) treatment increased the
frequency and number of Th1 and TCD8+ cells and increased IFN-γ secretion leading to an enhanced immune response. The lower (25 mg/kg) dose was less effective in vivo [114]. In contrast, an in vitro study on human melanoma cell lines indicated that although curcumin can induce apoptosis in melanoma cells, it inhibits NK cell activity [115]. Mechanistically, it was suggested that curcumin (20 μmol/L) inhibits the phosphorylation of the STAT1 protein and downstream gene transcription, which leads to a diminution of IFN-γ gene expression (an important cytokine in the induction of CD8+ cells differentiation) [116]. This, in turn, leads to adverse effects on the production of tumor suppressive-cytokines by NK cells [115]. This paradox may be due to the use of different concentrations of curcumin in various studies. Consequently, it is necessary to find an optimum therapeutic dose for curcumin, which can induce tumor cell apoptosis and enhance antitumor immunity [114]. Curcumin was also found to reduce the levels of TGF-β and IL-10 in Treg cells and decrease the number of Treg cells in tumor-bearing animal models. Furthermore, curcumin treatment improves the ability of effector T cells to kill tumor cells. It has also been reported that curcumin can prevent the loss of T cells, expand effector memory T cell (TEM) and central memory T cell (TCM) populations, and attenuate tumor-induced inhibition of T-cell proliferation and Th2 cells responses (that induce tumor progression) in tumor-bearing hosts [114].

In summary, curcumin (in a dose dependent manner) can enhance tumor immunity by augmenting the cytotoxicity of NK cells, increasing the production of cytokines (particularly IFN-γ), and expanding the population of memory T cells. In addition, curcumin can attenuate the activation and secretion of cytokines of cells that contribute to tumor progression (Th2 and Treg cells).
3.2. Rheumatoid arthritis and osteoarthritis

Rheumatoid Arthritis (RA) is known to be a systemic inflammatory disease. In RA, recruitment of inflammatory cells, such as neutrophils, to the joint is an important process in the pathogenesis of this autoimmune disease [117]. In addition, increased levels of pro-inflammatory cytokines, CRP and ESR, have been shown with a streptococcal cell wall (SCW)-induced arthritis rat model of RA [117]. Curcumin (23 mg/kg/day) was found to decrease the expression of pro-inflammatory cytokines (such as IL-1β), chemokine (such as MCP-1), and growth-related oncogene/keratinocyte chemoattractant (GRO/KC) [118]. The anti-inflammatory effects of curcumin were found to be associated with the prevention of both synovitis and granulomatous inflammation. Curcumin also significantly inhibits granuloma formation in the liver and spleen[118]. In RA, endothelial cells in the synovium activate and express adhesion molecules that increase the recruitment of inflammatory cells into the joint [118]. Curcumin can decrease the gene expression of adhesion molecules, β3 and β7 integrins, and thereby decrease joint inflammation in RA [118].

Clinical efficacy of curcumin in patients suffering from knee osteoarthritis (OA) have also been evaluated [119]. These anti-inflammatory properties were verified in cultured chondrocytes that were isolated from normal and healthy articular cartilage. Pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6 exacerbate local tissue inflammation by stimulating chondrocytes and synoviocytes to secrete additional pro-inflammatory cytokines [119]. Mechanistically, curcumin (50 µM) has been known to exert anti-inflammatory effects on OA through the inhibition of NF-κB and the suppression of important regulators of inflammation such as TNF-α, IL-1β, IL-6, MCP-1, prostaglandin E2, cyclooxygenase-II, activator protein-1, as well as JNK, MAPK, and PI3K/Akt pathways [119, 120].
Activating expression of proteolytic enzymes such as matrix metalloproteinases (MMPs) in chondrocytes and synoviocytes leads to cartilage matrix breakdown [121]. Activation of certain caspases, such as caspase-3, and loss of collagen type-II expression play a key role in initiating chondrocyte apoptosis. In addition, the cell-matrix signal transduction receptor B1-integrin plays an important role in mediating cell matrix interactions in the surveillance of chondrocytes. IL-1β leads to inhibition of collagen type II and B1-integrin synthesis on the cell surface [121]. It has been shown that curcumin (50 µM) can protect human chondrocytes against IL-1β-induced inhibition of collagen type II and B1-integrin expression and activation of caspase-3. Curcumin’s anti-inflammatory properties may reduce cartilage breakdown in degenerative joint diseases [121].

3.3. Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic relapsing immune disorder that is characterized by leucocyte infiltration and up-regulation in the levels of Th1 cytokines (IL-12, IFN-γ, TNF-α, IL-1) and Th17 cytokines (IL-17), as well as downregulation in the levels of Th2 cytokines (IL-4, IL-5, IL-10) in the intestinal mucosa [122]. IBD comprises two illnesses; Crohn’s disease (CD) and ulcerative colitis (UC), that are both characterized by inflammatory conditions in the colon [123]. Curcumin (30 mg/kg) can inhibit Th1 and enhance the synthesis of Th2 cytokines and therefore, can be an appropriate therapeutic agent for IBD [122]. Curcumin has shown contradictory effects on the profile expression of Th2 cytokines in IBD. A study strongly reported that IL-4 could not be detected in all the experimental animals treated with curcumin (0.75–7.5 g/kg) [124], but another study indicated that curcumin (50 mg/kg) increased the expression of IL-4 in Th2 cells [125].
IL-10 is a regulatory cytokine secreted by Treg cells. Another study demonstrated that in IL-10 gene-deficient mice, curcumin (200 mg/kg) could ameliorate the complications associated with colitis. In addition, curcumin was effective in decreasing the levels of inflammatory cytokines (IFN-γ and IL-17) and MPO in both the colon and cecum of these mice [126].

Recruitment and activation of neutrophils to the site of injury is one of the hallmarks of active IBD [127]. The results of an in vitro study clarify that curcumin (50 µg/ml) diminishes mucosal neutrophil infiltration and also the expression and secretion of MIP-2, IL-1b, KC and MIP-1α in colonic epithelial cells (CECs) and in macrophages. Likewise, curcumin significantly inhibited neutrophil chemotaxis towards MIP-2 and KC, as well as the IL-8-mediated chemotaxis of human neutrophils [127].

Nod-2 (Nucleotide-binding oligomerization domain-containing protein-2) is an intracellular pattern recognition receptor (PRR) that recognizes bacterial peptidoglycans [58]. The activation of Nod-2 signaling leads to the expression of pro-inflammatory genes that are mediated by the phosphorylation of a cascade of effector proteins, which include IK-B and NF-κB-p65 [128]. In human colonic epithelial cell, curcumin was reported to inhibit the Nod2-downstream signaling pathway by suppression of NF-κB activation and the gene expression of IL-8 [128].

Furthermore, there are several studies that have shown therapeutic effects of curcumin on colitis. Curcumin can alleviate colitis by regulating the shift from Th1 to Th2 [2, 87, 122, 129]. One study evaluated the therapeutic effects of curcumin, Dex (dexamethasone), and a combination of curcumin-Dex on the balance of Th1/Th2 cytokines in trinitrobenzene sulphonic acid (TNBS)-induced colitis in mouse model [130]. In this study curcumin not only decreased the mRNA expression of Th1 cytokines, but also increased the mRNA of Th2 cytokines in the mucosa of colon. Curcumin also decreased the proportion of IFN-γ/IL-4 in splenocytes and the circulation.
While the combination of curcumin-Dex decreased the expression of Th1 cytokines, there was no significant effect on the expression of Th2 cytokines and the proportion of IFN-γ/IL-4 [130]. It was found that recognition of LPS by TLR4 in colonic epithelial cells initiates the signaling pathway, which includes the recruitment of myeloid differentiation factor (MyD88). This, in turn, leads to NF-κB activation. NF-κB induces various pro-inflammatory and inflammatory mediators, inflammatory cytokines, and growth factors and has been implicated in the pathogenesis of IBD [131]. It has been demonstrated that amelioration of colitis by curcumin in an experimental model was mediated through inhibition of NF-κB that is regulated by signaling mechanisms associated with TLR-4 and MyD88 [131].

Briefly, curcumin can decrease the severity of IBD by attenuating inflammation caused by innate immune mediators (receptors, cells, cytokines, chemokines) including membrane (TLRs, particularly TLR4) and cytosolic (NOD-2) receptors and related signaling pathways (particularly NF-κB), macrophage, neutrophils and related cytokines (such as IL-1) and chemokines (such as IL-8, KC, MIP-1). Cellular targets of curcumin in adoptive immune responses are Th1 and Th2 cells and related cytokines. Curcumin can enhance Th2 (producing IL-4) responses and diminish adverse Th1 (producing IFN-γ) responses. Consequently, curcumin can be considered a good candidate for alleviating inflammatory diseases such as IBD.

3.4. Immune-mediated liver injury and pancreatitis

TLRs are widely expressed on Kupffer cells, hepatocytes, sinusoidal endothelial cells, and hepatic dendritic cells. Indeed, the TLRs signaling pathway is involved in almost all liver diseases [132]. TLR2, TLR4, and TLR9 signaling in concanavalin (Con) A-induced liver contribute to increases in plasma ALT and AST levels in response to Con A injections in mice [132]. Previous clinical reports have also indicated that IFN-γ is positively associated with
elevated levels of ALT in chronic hepatitis B [133]. The beneficial effect of curcumin (200 mg/kg) can be attributed to the inhibition of TLR2, TLR4, and TLR-9 expression, as well as the reduction in the expression levels of ICAM-1 and CXCL10 in the liver [132]. It was found that pretreatment with curcumin can significantly reduce pro-inflammatory cytokine levels (TNF-α and IFN-γ) as well as plasma aminotransferase levels and liver necrosis in Con A-induced hepatitis [132]. Importantly, curcumin can increase anti-inflammatory IL-10 levels and consequently can prevent inflammation of the liver [132].

Hepatic fibrosis occurs in response to chronic hepatic injury induced by alcohol abuse, viral infection, and cholestasis [134]. TNF-α and IL-6 stimulate the development of hepatic fibrosis. Moreover, IL-6 induces hepatic inflammation and collagen synthesis in vivo [135]. IL-6 produced by activated hepatic stellate cells (HSC) facilitates the production of type I collagen, which leads to hepatic fibrosis [135]. It has been shown that oral administration of curcumin (200 and 400 mg/kg) can decrease liver TNF-α and IL-6 levels in the carbon tetrachloride (CCL4)-induced rat model of hepatic fibrosis. Curcumin (200 and 400 mg/kg) reduced the levels of TGF-β in this model. TGF-β is the crucial pro-fibrogenic factor that causes hepatic fibrogenesis [134].

The beneficial effects of curcumin (100 mg/kg) in pancreatitis have also been demonstrated. It was reported that intragastric administration of curcumin significantly reduces IL-1 and TNF-α serum levels in a sodium taurocholate infusion model of acute pancreatitis [136]. Suppression of TNF-α levels by curcumin was found to be associated with decreased pancreatic injury in a mouse model of acute pancreatitis [137].

In conclusion, curcumin may have beneficial effects on alleviating pancreatitis and liver inflammation or liver fibrosis by inhibition of pro-inflammatory cytokines (IL-1β, TNF-α),
ligands of adhesion molecules (I-CAM-1), chemokines (CXCL10), and pro-fibrogenic factor (TGF-β). Curcumin can also modulate inflammation mediated by the TLR signaling pathway.

3.5. Periodontal disease

Periodontal disease is characterized by inflammation of the tissues surrounding the teeth in response to a bacterial infection. The host immune response to infection leads to an overproduction of inflammatory cytokines and prostaglandins and, consequently, periodontal attachment loss and bone resorption [138]. Curcumin (30 and 100 mg/kg) was reported to reduce the number of inflammatory cells, IL-6, and TNF-α gene expression and increase the collagen content in the gingival tissues in ligature-induced periodontitis in rats [138]. In an experimental study using the LPS model of periodontal disease, curcumin was orally administered to rats at doses of 30 and 100 mg/kg. Results showed that both low (30 mg/kg) and high doses of curcumin (100 mg/kg) significantly decreased the expression of the pro-inflammatory mediators such as PGE2, TNF-α, and IL-6 in the gingival tissues, while low-dose curcumin was only able to inhibit NF-κB expression. Activation of NF-κB is known to be pivotal for the expression of inflammatory cytokines involved in the pathogenesis of periodontal disease [42]. This suggests that curcumin (at higher doses) may modulate signaling pathways downstream of TLR activation that are implicated in the expression of pro-inflammatory cytokines [42].

3.6. Chronic lung disease

Curcumin can be regarded as a therapeutic option in the treatment of chronic lung disease (CLD). For example, CLD is represented by hyaline membrane disease in preterm infants [139]. In these infants, the expression of pro-inflammatory cytokines, including TNFα, IL-1 b, and IL-8, have been up-regulated. Ongoing inflammation in the lungs of these infants may be facilitated by the expression of pro-inflammatory cytokines including TNF α, IL-1 b, and IL-8 [139].

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Curcumin (20 uM) was shown to inhibit the expression of IL-1β and IL-8 in lung inflammatory cells when evaluated in vitro [139].

3.7. Intracerebral hemorrhage

Curcumin can inhibit T lymphocyte proliferation and migration. Following an intracerebral hemorrhage (ICH), immune responses may cause secondary brain injury [140]. It has been demonstrated that treatment with curcumin can reduce the number of cerebral T lymphocytes in mice with experimentally-induced ICH. Results showed that curcumin-treated mice with ICH display attenuated brain edema and a suppression in the expression of various pro-inflammatory cytokines, such as INF-γ and IL-17, in the brain [140].

3.8. Obesity-induced inflammation

Inflammation is a key process in obesity and is known to be associated with increased levels of pro-inflammatory cytokines such as IL-1β, IL-4, and VEGF [141]. A randomized, cross-over trial demonstrated that curcumin exerts immunomodulatory effects by reducing the circulating levels of IL-1β, IL-4, and VEGF in obese subjects [141]. Curcumin can also reduce the serum levels of CRP level, which is an important inflammatory factor in patients with cardiovascular disease [142].

3.9. Autoimmune encephalomyelitis and multiple sclerosis

Multiple sclerosis (MS) is an inflammatory demyelinating disorder of the central nervous system (CNS) [143]. Experimental autoimmune encephalomyelitis (EAE) is a CD4⁺ T cell-mediated demyelinating disease of the CNS in animal models [144]. Various cells including antigen presenting cells (APCs), such as macrophages, microglia, and specific Th1/Th17 cells, are involved in the pathogenesis of this disease [143, 144]. Curcumin has been reported to be an
efficient candidate in the treatment of MS and EAE Th17-mediated inflammatory diseases [145, 146].

In EAE-induced rats, treatment with curcumin was found to significantly decrease the number of inflammatory cell that infiltrated the spinal cord [146]. Curcumin treatment was also associated with up-regulation of IL-10 levels and increased percentages of CD4+ CD25+− Foxp3+ Treg cells in the CNS and lymphoid organs in EAE-induced C57BL/6 mice. In addition, curcumin ameliorates EAE in SJL/J mice by inhibiting the IL-12 signal through the JAK-STAT pathway, which results in a decrease in Th1 differentiation [98].

Some studies have shown that PPARγ can act as a nuclear receptor for curcumin in different cell types [147]. PPARγ agonists inhibit EAE by modulating Th1/Th17 responses [147]. In vivo treatment with curcumin has been shown to elevate the expression of PPARγ in the CNS and lymphoid organs in mice with EAE, suggesting its association with the regulation of Th1/Th17 responses in EAE [147].

Furthermore, in MS, curcumin inhibits the differentiation and development of Th17 cells by down-regulating the expression of IL-6, IL-21, and RORγt signaling and inhibition of STAT3-phosphorylation. Curcumin can also suppress IL-17 mRNA expression and T cell levels of INF-γ in patients experiencing MS [98].

hKv1.3 (a voltage-gated channel) increases proliferation and activation of effector memory T cells (TEM, CCR7-CD45RO+ T lymphocyte) when the plasma membrane is depolarized. This channel has a key role in the severity of some autoimmune diseases, such as MS and RA [148, 149]. Curcumin can suppress the proliferation and the production of proinflammatory cytokines of TEM cells by inhibiting hKv1.3 channels, which contributes to the efficacy of curcumin in the treatment of autoimmune diseases [150].
3.10. Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is classified as an autoimmune disease resulting from progressive destruction of insulin-producing β cells by self-reactive T lymphocyte responses [151]. High levels glucose can stimulate NF-κB activation and subsequent overexpression of pro-inflammatory cytokines [152]. TLRs sense high glucose and underlie an inflammatory cascade that leads to disease progression [153]. Activation of caveolin-1 (cav-1), a signaling protein associated with caveolae, confers anti-inflammatory effects through direct binding to TLR4 and blocking TLR4 interaction with MyD88 and TRIF, as well as downstream activation of the NF-κB pathway [154]. Curcumin was found to inhibit TLR4 activation by regulating caveolin-1 phosphorylation at Tyr14 in diabetic patients [155]. Curcumin ameliorates diabetes in rats by reducing vascular and renal inflammation through regulation of the gene expression of IL 6, TNFα, IL-1b, and NO at the level of both transcription and translation [156]. In LPS-stimulated DCs, curcumin inhibits IL 6, TNFα, IL-1b, and NO production [155-157]. T-helper type 1 (Th1) lymphocytes and their hallmark cytokine, IFN-γ, are central in the pathogenesis of TIDM [156]. APC from curcumin-treated mice was also found to reduce Th1 cell proliferation and the cytokine IFN-γ [156].

3.11. Chronic serum sickness

Curcumin can inhibit both classical and alternate pathways of complement activation [158]. The complement system includes a number of small proteins in the blood that serve as inactive precursors (pro-proteins) that could be triggered, cleaved and activated by several factors such as microbial products or antigen-antibody complexes [159]. The complement cascade is activated with the formation of C5b–9. Complement components are implicated in the chemotaxis of immune cells to the site of inflammation and subsequent release of proinflammatory cytokines.
Serum sickness is a hypersensitivity (type III) immune reaction that can be described by deposition of immune complexes (antigen-IgG binding) in the micro-vasculature, which leads to complement activation and results in inflammation [158].

It has been reported that curcumin pretreatment in complement factor H-deficient mice with chronic serum sickness (CSS) leads to decreased severity of kidney disease in immune complex glomerulonephritis by reducing splenic B cells. This, in turn, leads to a reduction in IgG deposits similar to the reduction in C9 deposits in the circulation. This study also indicated that curcumin can prevent the reduction of alternative macrophages, M2c, which participate in immune suppression and tissue repair and matrix remodeling in CSS. Curcumin was also found to diminish the expression of pro-inflammatory mRNAs (KC, MIP-2) in CSS. Consequently, these modulations are accompanied with efficient repair of injured tissue, and also protection of kidney function [160].

In summary, curcumin reduces type III hypersensitivity reactions in CSS by inhibiting pro-inflammatory chemokines, preventing the reduction of alternative macrophages, diminishing B cell numbers and responses (such as the inhibition of IgG production), and reducing the levels of C9 in deposits and in the circulation. Thus, curcumin has several beneficial effects and may represent a potential adjunct therapy in CSS.

### 3.12. Systemic lupus erythematosus and Sjogren's Syndrome

It has been reported that heat-solubilized curcumin or turmeric can prevent autoantibody formation against cognate autoantigens in patients with Sjogren’s syndrome (SS) – an autoimmune disease of salivary and tear glands – and systemic lupus erythematosus (SLE) – an autoimmune disease affecting multiple organs – [161]. Anti-Ro 60/anti-La autoantibodies are present in up to 90% of patients with SS and anti-Ro autoantibodies are present in up to 50% of
SLE patients [162]. Heat-solubilized curcumin/turmeric has been demonstrated to significantly decrease the binding of autoantibodies to autoantigens in patients with SS and SLE [162].

Lupus nephritis (LN) is a hallmark complication of systemic lupus erythematosus. Curcumin has been shown to have protective effects on LN that can be attributed to its interaction with Treg cells [163]. Mechanistically, curcumin was found to up-regulate the expression of Foxp3 in CD4+CD25+ Treg cells. FOXP3 is a master regulator in Treg cells, which controls the expression of multiple genes that mediate the characteristics of these immune cells [163].

Both the production of autoantibodies against the nucleus and the formation of glomerular immune deposits are implicated in the pathogenesis of LN [163]. Deposition of IgG immune complexes in the glomeruli was shown to be reduced in curcumin-treated mice. Curcumin has also been reported to decrease proteinuria and serum levels of IgG1, IgG2a, and anti-dsDNA IgG antibodies in female NZB/W F1 mice [163].

In conclusion, curcumin can ameliorate autoimmune disorders such as SS, SLE, and LN by inhibition of antibody–antigen interactions, decreasing autoantigen-autoantibody deposition in tissues and various microvasculature beds, preventing humoral-mediated immunity through suppression of antibody production [particularly antibodies, which contribute to complement activation (such as IgG)], and by enhancement of regulatory responses involving T reg cells.

3.13. Allergic diseases

Production of Th2 cytokines (L-4, IL-5, IL-13), eosinophilia, and IgE play a central role in allergic responses, such as asthma [164]. Curcumin can be considered a potential treatment for allergic inflammatory diseases by suppressing the production of Th2 cytokines that affect recruitment and function of eosinophils, as well as IgE synthesis [165].
The effects of curcumin against allergic diseases were examined in terms of the production of IL-5, granulocyte macrophage-colony stimulating factor (GM-CSF), and IL-4 by lymphocytes from bronchial asthmatics in response to house dust mites (Dermatophagoides farinae) [166]. The results showed that curcumin (10 µM) can reduce the aforementioned cytokines and can inhibit the expression of Th2 cytokines, IL-4 and IL-5, which leads to the suppression of Th2 responses [166]. As previously described, it has been found that curcumin (30 mg/kg) can inhibit Th1, but enhance Th2 cytokine synthesis [127]. These contradictory results can be attributed to a dose-dependent effect of curcumin.

Intragastric administration of curcumin (250 µg/mouse) in latex sensitized-BALB/c mice attenuated Th2 response and inflammation in the lung tissue [167]. Furthermore, some findings indicated that eosinophilia in curcumin-treated mice is substantially reduced [167]. Co-stimulatory molecules, such as CD80, CD86, and OX40L, all showed increased expression in latex-sensitized mice as compared to normal mice [167]. It was also shown that curcumin can reduce the expression of co-stimulatory molecules (CD80, CD86, and OX40L) on APCs. In addition, curcumin has been shown to reduce the gene expression of MMP-9 and thymic stromal lymphopoietin (TSLP), which leads to a reduced inflammatory response [167].

NO may stimulate eosinophilic infiltration to the airway and alter Th1/Th2 balance in favor of the latter, thereby contributing to airway inflammation. Curcumin treatment has been shown to decrease the production of iNOS (which produces high amounts of NO) in lung tissue [168]. Allergic conjunctivitis is a prevalent eye disease manifested by conjunctival congestion, itchiness, increased Ag-specific IgE, mast cell activation, and local eosinophilic infiltration [169]. The immunopathogenesis of allergic conjunctivitis involves a combination of IgE-mediated and Th2 cell-mediated responses [169]. It was reported that curcumin (20 mg/kg/day)
can mitigate infiltration of IL-4- and IL-5-producing cells in the spleens and cervical lymph nodes (CLN) of mice in an allergic conjunctivitis model induced by ovalbumin [168].

It has also been reported that oral administration of curcumin in a mouse model of IgE/Ag-mediated passive systemic anaphylaxis significantly attenuates serum Leukotriene C4 (LTC₄), prostaglandin D2 (PGD₂), and histamine levels that are crucial mediators in the development of inflammation and allergic diseases such as asthma [170]. It is well known that Ca²⁺ is essential for arachidonic acid release from phospholipids and degranulation in IgE/Ag-induced mast cells. Likewise, curcumin was found to inhibit intracellular Ca²⁺ influx via phospholipase Cγ₁ (PLCγ₁) activation, the NF-κB pathway, and the phosphorylation of mitogen-activated protein kinases (MAPKs) [171]. Notch plays a pivotal role in the regulation and preservation of the balance among cellular proliferation, differentiation, and apoptosis [172, 173]. Notch1 has been reported to be up-regulated in mice with experimentally-induced asthma, suggesting its role in the pathogenesis of asthma through regulation of Th1/Th2 differentiation [174]. Curcumin (200 mg/kg) administration to mice can reduce airway inflammation by inhibiting the Notch1–GATA3 (a key transcription factor in Th2 cell development) signaling pathway [175].

Tregs can mitigate inflammatory and allergic responses [176]. Th17 cells and their cytokines, such as IL-17A and IL-17F, are implicated in antigen-induced neutrophil recruitment and the enhancement of eosinophilic infiltration to the airways mediated by Th2 cells [177]. The balance between Th17 and Treg cells is a key determinant in inflammatory and allergic diseases such as asthma [178]. Some experimental studies have indicated that airway inflammation and bronchial hyper-responsiveness are mitigated after curcumin treatment in ovalbumin-inducedtic mice; an effect that is mediated by regulation of the Tregs/Th17. Curcumin has been demonstrated to
suppress IL-17A production by Th17 cells and increase IL-10 production by Treg cells, which result in the inhibition of eosinophilic infiltration and mucus hypersecretion [178].

In summary, curcumin attenuates allergic disease by affecting various contributing cells (decreasing activation of Th2, Th17, and increasing activation of Treg cells) and their cytokine production (downregulation of IL-4, IL-5, IL-13, IL-17 and upregulation of IL-10). Curcumin also influences signaling pathways (NF-κB and MAPK) and transcription factors (GATA3). Finally, curcumin decreases inflammation mediated by arachidonic acid metabolites (LTC4 and PGD2). Therefore, the potential efficacy of curcumin as an adjunctive therapy for allergic diseases is conceivable.


The immunosuppressive potential of curcumin on Th1 cytokines that are frequently overexpressed in patients with graft rejection after renal transplant has been evaluated. The results to date have demonstrated that curcumin has an inhibitory effect on Th1 cytokine induction after renal transplant. Likewise, curcumin was shown to be an efficient immunosuppressant adjuvant when used with cyclosporine [179]. Importantly, in an experimental study, it was found that curcumin (100 mg/d) can strengthen the immunosuppressive efficacy of cyclosporine in rat cardiac allografts and in attenuating mixed lymphocyte reactions [180]. The anti-proliferative effect of sirolimus or rapamycin, which have the immunosuppressant functions to prevent organ transplant rejection and inhibits IL-2 production, is primarily mediated by inhibition of mTOR (mammalian target of rapamycin). The immunosuppressive effects of low concentrations of curcumin (1.25–2.5 μM) and sirolimus (5ng/ml) were found to be synergistic in activated peripheral blood mononuclear cells (PBMCs) [63]. One potential benefit
of this synergistic effect is the possibility of reducing the administered doses of sirolimus, which can subsequently result in the reduction of adverse effects (e.g. hypercholesterolemia, hypertriglyceridemia, thrombopenia, leukopenia, and anemia) in patients with autoimmune diseases or those receiving an organ transplant [63].

An important adverse effect of allogenic hematopoietic stem cell transplantation (HSCT) is GVHD (Graft-versus-Host Disease), which can occur after bone marrow transplantation (BMT) [100]. Acute GVHD is an immune response driven mainly by Th1 and Th17 cells [100]. Curcumin is known to inhibit allo reactive T cell responses, IFN-γ (secreted by Th1 cells), IL-17 (secreted by Th17 cells), and AP-1 activity production in vitro [100]. In addition, pretreatment of mice with curcumin (100 µg/mouse) resulted in increased populations of CD4+ Treg cells, as well as CD8+ Treg cells, in recipient mice with acute GVHD. The protective effect of curcumin in preventing acute GVHD might be attributed to the impact of this phytochemical on B cell homeostasis and antibody production [181].

4. Concluding remarks

Accumulating in vitro, experimental, and clinical studies suggest that new agents, including traditional herbal medicines, such as curcumin, can be used in the treatment of inflammatory and immune-mediated diseases. The studies presented in this review support this notion that curcumin not only enhances anti-tumor immunity, but also ameliorates various inflammatory and immune-mediated diseases including RA, OA, IBD, ICH, CLD, periodontal disease, obesity, acute pancreatitis, immune-mediated liver injury, obesity-induced inflammation, MS, EAE, SS, SLE, T1DM, CSS, allergic inflammatory disease, GVHG, and grafts surveillance. This is due to the interaction of curcumin with a diverse set of cellular and molecular targets, including transcription factors, various inflammatory mediators (including pro-inflammatory cytokines),
chemokines, CRP, ESR, PG-E2, immune complexes, surface markers of cells, and cell adhesion molecules. To sum up, the most important target of curcumin is the NF-κB pathway, which represents the master switch in the regulation of the inflammatory response. In conclusion, curcumin may influence various features of the immune system in various diseases with immunological etiology. With regard to clinical-based studies, curcumin administration has demonstrated a potential adjuvant effect in the treatment of immune-mediated diseases. Immunosuppressant drugs show a variation in their efficacy from one patient to another. These drugs are very expensive and inevitably have the potential to induce adverse side effects, so it is strongly recommended that clinical applications be undertaken to use the immunomodulatory effects of curcumin in the treatment of patients with immune-mediated diseases.

Conflict or interest

The authors have no direct conflict of interests related to the content of this review.
References


140. Liu, W., et al., **Curcumin reduces brain-infiltrating T lymphocytes after intracerebral hemorrhage in mice.** Neuroscience letters, 2016. 620: p. 74-82.


183. Jain, S.K., et al., Curcumin supplementation lowers TNF-α, IL-6, IL-8, and MCP-1 secretion in high glucose-treated cultured monocytes and blood levels of TNF-α, IL-6, MCP-1, glucose, and glycosylated hemoglobin in diabetic rats. Antioxidants & redox signaling, 2009. 11(2): p. 241-249.


Figure legends

Figure 1. Isolation of curcumin from *Curcuma longa* rhizomes (turmeric).

Figure 2. Molecular targets of curcumin.
Table 1. The effects of curcumin on the key cytokines and chemokines.

<table>
<thead>
<tr>
<th>Cytokine/chemokine</th>
<th>Function</th>
<th>Effect</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1</td>
<td>Major pro-inflammatory cytokine</td>
<td>Decrease</td>
<td>[59, 182]</td>
</tr>
<tr>
<td>TNFα</td>
<td>Major pro-inflammatory cytokine</td>
<td>Decrease</td>
<td>[182, 183]</td>
</tr>
<tr>
<td>IL-2</td>
<td>T-Cell lymphocyte proliferation</td>
<td>Decrease</td>
<td>[35]</td>
</tr>
<tr>
<td>IL-4</td>
<td>B-Cell proliferation</td>
<td>Decrease/increase</td>
<td>[141]</td>
</tr>
<tr>
<td>IL-5</td>
<td>Immunoglobulin secretion, eosinophil function, allergy</td>
<td>Decrease/increase</td>
<td>[166]</td>
</tr>
<tr>
<td>IL-6</td>
<td>Major pro-inflammatory cytokine, B-cell differentiation, nerve cell</td>
<td>Decrease</td>
<td>[183, 184]</td>
</tr>
<tr>
<td>IL-8</td>
<td>Neutrophil chemotaxis, angiogenesis</td>
<td>Decrease</td>
<td>[182, 183, 185, 186]</td>
</tr>
<tr>
<td>IL-10</td>
<td>Anti-inflammatory cytokine, also has T-cell stimulatory effects</td>
<td>Increase</td>
<td>[187]</td>
</tr>
<tr>
<td>IL-12</td>
<td>Promoting cellular immunity against intracellular bacterial</td>
<td>Decrease</td>
<td>[35, 187]</td>
</tr>
<tr>
<td>Interferon-γ</td>
<td>Macrophage activation, T- and B-cell activation and differentiation</td>
<td>Decrease</td>
<td>[35, 187]</td>
</tr>
<tr>
<td>IL-13</td>
<td>Induces matrix metalloproteinases, induces IgE (Th2 cytokine)</td>
<td>Decrease</td>
<td>[188]</td>
</tr>
<tr>
<td>IL-17</td>
<td>Pro-inflammatory cytokine (Th17 cytokine)</td>
<td>Decrease</td>
<td>[189]</td>
</tr>
<tr>
<td>MCP1 (CCL2)</td>
<td>Neuroinflammation, monocyte and basophil chemoattractant</td>
<td>Decrease</td>
<td>[182, 183]</td>
</tr>
<tr>
<td>MIP1α (CCL3)</td>
<td>Activates granulocytes, induces synthesis of pro-inflammatory cytokines</td>
<td>Decrease</td>
<td>[183]</td>
</tr>
<tr>
<td>GROα (CXCL1)</td>
<td>Neutrophil chemoattractant, wound healing</td>
<td>Decrease</td>
<td>[190]</td>
</tr>
<tr>
<td>GROβ (CXCL2)</td>
<td>Neutrophil and monocyte chemoattractant</td>
<td>Decrease</td>
<td>[190]</td>
</tr>
<tr>
<td>IP10 (CXCL10)</td>
<td>NK cell, monocyte and macrophage chemoattractant,</td>
<td>Decrease</td>
<td>[191]</td>
</tr>
<tr>
<td>SDF1 (CXCL12)</td>
<td>Lymphocyte chemoattractant</td>
<td>Decrease</td>
<td>[192]</td>
</tr>
<tr>
<td>Dose of curcumin</td>
<td>Experimental model</td>
<td>Type of disease</td>
<td>Findings</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------</td>
<td>----------------</td>
<td>----------</td>
</tr>
<tr>
<td>5mg/ml</td>
<td>Mouse model of SS</td>
<td>SS</td>
<td>decreased binding of Anti Ro 60 and Anti Ro 273 to related autoantigens</td>
</tr>
<tr>
<td>25 µM</td>
<td>Human monocyte derived DC and mice DC</td>
<td>-</td>
<td>Decreased expression of CD83,CD80, CD86 ,MHC class II and CD40, increased function of FoxP3+ Tregs</td>
</tr>
<tr>
<td>0–25 µM</td>
<td>DC derived from murine BM</td>
<td>-</td>
<td>Decreased expression of CD80, CD86 and MHC class II, decreased level of IL-12, IL-1,IL-6, TNFα, increased mannose receptor-mediated endocytosis, inhibited MAPK activation and the translocation of NF-KB p65.</td>
</tr>
<tr>
<td>20 mg</td>
<td>macrophages and NK cells from Mice bearing AK-5 tumor</td>
<td>AK-5 tumor</td>
<td>Decreased of Th1 cytokine response , decreased of NO production by macrophages, increased NO production by NKs</td>
</tr>
<tr>
<td>50µm</td>
<td>Cultured YAMC and peritoneal Macrophag, and Bone marrow-derived neutrophils from Human and mouse</td>
<td>IBD</td>
<td>Decreased secretion of MIP-2, IL-1b, KC, and MIP-1a CECs and in macrophages, inhibition of PMN motility down regulation of PI3K activity, AKT phosphorylation,</td>
</tr>
<tr>
<td>10,20 µm</td>
<td>Ba/F3 cells (murine pro-B cell line)</td>
<td>-</td>
<td>Inhibition of TLR4 ligand-induced activations of NF-kB, IRF3, inhibition of COX-2 expression</td>
</tr>
<tr>
<td>1 µM</td>
<td>TS/A breast cancer cells and NK cells isolated from BALB/c mice</td>
<td>-</td>
<td>Reversion tumor exosome-mediated inhibition of natural killer cell activation, prevention of</td>
</tr>
<tr>
<td>Concentration</td>
<td>Cell Type and Source</td>
<td>Disease/Clinical Setting</td>
<td>Effects</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------</td>
<td>-------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>0, 0.5 and 20 uM</td>
<td>Lung inflammatory cells from preterm newborns</td>
<td>Chronic Lung Disease (CLD)</td>
<td>Significant inhibition of IL-1b and IL-8 but minimal inhibition of TNFα expression</td>
</tr>
<tr>
<td>(1.5–12.5 μM)</td>
<td>Human monocytic (THP-1) cells</td>
<td>Diabetes</td>
<td>Suppressed NF-κB and TNFα Inhibition of releasing MCP-1</td>
</tr>
<tr>
<td>10 μM</td>
<td>Cultured RAW 264.7 cells derived from murine macrophages</td>
<td>-</td>
<td>Inhibition of NFκB, IKK1, IKK2 activation and iNOS induction</td>
</tr>
<tr>
<td>0-30μM</td>
<td>A375 and Hs294T human metastatic melanoma cell lines</td>
<td>-</td>
<td>Inhibition the phosphorylation of STAT1 protein, production of IFN-α and IFN-γ and Signal Transduction</td>
</tr>
<tr>
<td>50μm</td>
<td>Human multiple myeloma cell lines</td>
<td>-</td>
<td>Down-regulation of the constitutive activation of NF-KB, suppression of proliferation and induction of apoptosis</td>
</tr>
<tr>
<td>0-20μm</td>
<td>Human B lymphocyte cell lines (Namalwa and Daudi) and HepG2 cell line</td>
<td>-</td>
<td>Inhibition the expression of BLyS and a DNA-binding site for the transcriptional factor NF-κB in the BLyS promoter region Supersession nuclear translocation of p65</td>
</tr>
<tr>
<td>0-250ng/ml</td>
<td>Macrophage from rat</td>
<td>Adjuvant-induced chronic RA</td>
<td>Reduction of interferon-1b, TNFα, IL-6, NO</td>
</tr>
<tr>
<td>12.5–30 mmol/L</td>
<td>Splenic lymphocyte and peritoneal macrophages C57BL/6J mice</td>
<td>-</td>
<td>Inhibited the expression/production of IL-2 and IFN-γ by splenic T lymphocytes and IL-12 and TNF-α by peritoneal macrophages</td>
</tr>
<tr>
<td>Concentration</td>
<td>Cell Type/Organization</td>
<td>Condition</td>
<td>Effect</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------</td>
<td>-----------</td>
<td>--------</td>
</tr>
<tr>
<td>20 ng/ml</td>
<td>Human keratinocyte cell line (HaCaT cells)</td>
<td>-</td>
<td>expression of IL-1β, IL-6, and TNF-α as well as cyclin E</td>
</tr>
<tr>
<td>1-100µm</td>
<td>mouse 3T3-L1 fibroblasts</td>
<td>Obesity</td>
<td>Inhibition of activation of NF-κB signaling reduction of TNF-α, IL-1β, IL-6, and COX-2 gene expression and a reduction of secreted IL-6 and PGE2</td>
</tr>
<tr>
<td>10µM</td>
<td>Human Effector Memory T Lymphocyte</td>
<td>RA MS</td>
<td>inhibition of hKv1.3 expression Inhibitory effect inhibition of TEM cell proliferation, decreased INFγ secretion</td>
</tr>
<tr>
<td>0-6 µg/ml</td>
<td>mouse splenic macrophages</td>
<td>-</td>
<td>Inhibition of IL-12 production, inhibition of Th1 cytokine profile in CD4+ T cells.</td>
</tr>
</tbody>
</table>

SS, Sjogren's Syndrome; DC, Dendritic cells; T reg cell, T regulatory cell; BM, Bone Marrow; MHC, Major Histocompatibility; NF-KB, Nuclear factor-kappa-B; PI3K, phosphoinositide 3-kinase; IBD, Inflammatory Bowel Disease; Conditionally immortalized mouse colonic epithelial cells (YAMC); MIP-2, macrophage inflammatory protein; KC, keratinocyte chemoattractant; CECs, colonic epithelial cells IKK1, IkB kinase 1; IKK2, IkB kinase; IRF3, interferon regulatory transcription factor 3; MS, multiple sclerosis; RA, rheumatoid arthritis
<table>
<thead>
<tr>
<th>Dose of curcumin</th>
<th>Experimental model</th>
<th>Findings</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg/kg</td>
<td>brain-infiltrating T lymphocytes from C57BL/6 mice with hemorrhage</td>
<td>Reduced the number of cerebral T lymphocytes, reduced the expression of VCAM-1, INF-γ and IL-17 in the mouse brain</td>
<td>[140]</td>
</tr>
<tr>
<td>1% Cur + 0.02% Limonin mice</td>
<td>Suppression of NF-kB p65 modulate CD4+ T-cell–mediated inflammation.</td>
<td></td>
<td>[197]</td>
</tr>
<tr>
<td>0- 100 μg curcumin in 25 μl DMSO female C57BL/6 mice with EAE</td>
<td>decreased the secretion of IFNγ, IL-17, IL-12 and IL-23 up-regulation of IL-10, peroxisome proliferator activated receptor γ and CD4+CD25+Foxp3+</td>
<td></td>
<td>[98]</td>
</tr>
<tr>
<td>25, 50 or 100 mg/kg/day C57BL/6 mice</td>
<td>Increased proliferation and cytotoxicity of CD8+ T cells and IFN-γ secretion against 3LL tumor cells</td>
<td></td>
<td>[114]</td>
</tr>
<tr>
<td>250 μg curcumin in 250 μl PBS BALB/c mice</td>
<td>Reduced Th2 response Eosinophilia and lung inflammation. Decreased co-stimulatory molecule expression (CD80, CD86, and OX40L) on APCs decreased expression of MMP-9, OAT, and TSLP genes</td>
<td></td>
<td>[167]</td>
</tr>
<tr>
<td>20 mg, 100 mg, and 20 mg / kg C57BL/10ScSn (wildtype) mice</td>
<td>increased numbers of regulatory T cells decreased mucosal T lymphocyte and neutrophils numbers increased levels of the anti-inflammatory cytokine IL-10 in ileum, mesenteric lymph nodes and spleen decreased IL-23p19,IFN-γ, TNF-α, IL-6, MCP-1 in the ileum</td>
<td></td>
<td>[198]</td>
</tr>
<tr>
<td>30 and 100 mg/kg rats</td>
<td>Decreased expression of IL--6, TNF-α and prostaglandin E2 synthase in the gingival tissues. Modulation of p38 MAPK and NF-KB activation</td>
<td></td>
<td>[138]</td>
</tr>
<tr>
<td>30 , 100 mg/kg (Cfh)</td>
<td>reduction in the number of splenic CD19+ B cells and the ratio of</td>
<td></td>
<td>[160]</td>
</tr>
<tr>
<td>body weight</td>
<td>CD19 : CD3 cells</td>
<td>reduced macrophages in the kidney reduced mRNA expression of MCP-1 , TGF-B,matrix proteins, fibronectin, laminin and collagen</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>------------------</td>
<td>------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>100mg/kg</td>
<td>Rat diabetic nephropathy</td>
<td>Decreased IL-6,TNFα,IL-1β</td>
<td></td>
</tr>
</tbody>
</table>

Vascular cell adhesion molecule-1 (VCAM-1); APC, Antigen Presenting Cell
Table 4. effects of curcumin on immune cells and diseases related to immune system in human studies.

<table>
<thead>
<tr>
<th>Population size (n)</th>
<th>Dose of curcumin</th>
<th>Type of disease</th>
<th>Findings</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>2 grams/day</td>
<td>CLL</td>
<td>Increased of CD4, CD8 and NK cells</td>
<td>[92]</td>
</tr>
<tr>
<td>61</td>
<td>8 g/day</td>
<td>SS</td>
<td>heat-solubilized curcumin decreased binding of Anti-Ro 60</td>
<td>[162]</td>
</tr>
<tr>
<td>74</td>
<td>8 g/day</td>
<td>SLE</td>
<td>heat-solubilized curcumin decreased binding of Anti-Ro 60</td>
<td>[162]</td>
</tr>
<tr>
<td>46</td>
<td>1 g/d</td>
<td>SM exposed patients</td>
<td>Decreased Serum IL-8 and hs-CRP</td>
<td>[102]</td>
</tr>
<tr>
<td>30</td>
<td>1 g/d</td>
<td>obesity</td>
<td>Decreased serum levels of IL-1β, VEGF, and IL-4, No impact on the concentrations of IL-2, IL-6, IL-8, IL-10, IFNγ, EGF, and MCP-1.</td>
<td>[141]</td>
</tr>
<tr>
<td>40</td>
<td>1500 mg/day</td>
<td>OA</td>
<td>Reduced serum concentrations of IL-4, IL-6 and hs-CRP No impact on serum levels of TNF-α and TGF-β and ESR</td>
<td>[119]</td>
</tr>
</tbody>
</table>

CLL, Chronic Lymphocytic Leukemia; SS, Sjogren's syndrome; SLE, Systemic Lupus Erythematosus; SM, sulphur mustard; hs-CRP, high-sensitivity C-reactive protein; OA, Osteo Arthritis
Figure 1: The transformation of Curcuma longa L. into turmeric powder.