Curcumin: a modulator of inflammatory signaling pathways in the immune system

Kolsoum Rezaie Kahkhaie[a,b], Ali Mirhosseini[c], Ali Aliabadi[d], Asadollah Mohammadi[e], Mohammad Javad mosavi[f,g], Saeed Mohammadian Haftcheshmeh[h*], Thozhukat Sathyapalan[i], Amirhossein Sahebkar[j,k,l*]

[a]Department of Medical Biochemistry, Faculty of Medicine, Zabol University of medical Sciences, Zabol, Iran
[b]Medicinal Plants Research Center, Faculty of Medicine, Zabol University of medical Sciences, Zabol, Iran
[c]Immunology Research Center, Inflammation and Inflammatory Diseases Division, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[d]Department of Medicinal Chemistry, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[e]Cellular and Molecular Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran.
[f]Department of Immunology and Allergy, Faculty of Medicine, Bushehr University of Medical Sciences, Bushehr, Iran
[g]Immunology Department, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[h]Department of Medical Immunology, Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[i]Department of Academic Diabetes, Endocrinology and Metabolism, Hull York Medical School, University of Hull, Hull HU3 2JZ, UK
[j]Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran.
[k]Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
[l]School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.

#Corresponding Authors:

Saeed Mohammadian Haftcheshmeh, Department of Medical Immunology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; Postal code: 91766-99199; Fax: 05138012762.

Amirhossein Sahebkar, PharmD, PhD, Department of Medical Biotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, P.O. Box: 91779-48564, Iran. Tel: 985118002288; Fax: 985118002287; E-mail: sahebkara@mums.ac.ir; amir_saheb2000@yahoo.com

Running title: Curcumin, immune system and inflammation

Abstract

Curcumin is a natural compound derived from the spice, turmeric, that has been extensively reported for its efficacy in controlling or treatment of several inflammatory diseases. There is a growing body of literature that recognizes the anti-inflammatory effects of curcumin in the immune system. On the other hand, the role of inflammatory signaling pathways has been highlighted in the pathogenesis of several inflammatory diseases and signaling molecules involved in these pathways are considered as valuable targets for new treatment approaches. We aimed to provide a comprehensive overview of the modulatory effects of curcumin on inflammatory signaling pathways which leads to inhibition of inflammation in different types of immune cells and animal models. In this comprehensive review, we elaborate on how curcumin can effectively inhibit multiple signaling molecules involved in inflammation including NF-κB, JAKs/STATs, MAPKs, β-catenin, and Notch-1.

Keywords: Curcumin, Inflammation, Inflammatory signaling pathway, Inflammatory diseases

Abbreviations

HSPs	Heat shock proteins
LPS	Lipopolysaccharide
DCs	Dendritic cells
TNF-α	Tumor necrosis factor-α
IL	Interleukin
IFN	Interferon
NF-κB	Nuclear factor-κB
JAK/STAT	Janus kinase/Signal transducer and activator of transcription
MAPK	Mitogen-activated protein kinase
IBD	Inflammatory bowel disease
RA	Rheumatoid arthritis
SLE	Systemic Lupus Erythematosus
MS	Multiple sclerosis
T1DM	Type 1 diabetes mellitus
IκB	Inhibitors of NF-κB
IKK	IκB kinase
BMECs	Brain microvascular endothelial cells
HUVECs	Human umbilical vein endothelial cells
ICAM-1	Intercellular adhesion molecule 1
VCAM-1	Vascular cell adhesion molecule 1
MCP-1	Monocyte chemoattractant protein-1
PPARγ	Peroxisome proliferator-activated receptor-gamma
iNOS	Inducible nitric oxide synthase
COX-2	Cyclooxygenase-2
SHP2	Src homology 2 domain-containing protein tyrosine phosphatase
OSM	Oncostatin M
MMP	Matrix metalloproteinase
EAE	Experimental allergic encephalomyelitis
RORγt	RAR-related orphan receptor gamma
TGF-β	Transforming growth factor β
SOCS	Suppressor of cytokine signaling
PIAS	Protein inhibitor of activated STAT
ERK	Extracellular receptor-activated kinase
JNK	C-Jun N-terminal kinase
PGE2	Prostaglandin E2
MPO	Myeloperoxidase
CMF	Colonic myofibroblasts
ROS	Reactive oxygen species
BBB	Blood-brain barrier
FLS	Fibroblast-like synoviocyte
LDH	Lactate dehydrogenase
OGD	Oxygen-glucose deprivation
GSK3	Glycogen synthase kinase 3

GATA3	Transcription factor GATA binding protein 3
TAK1	Transforming growth factor (TGF)-activated kinase 1
PMA	Phorbol 12-myristate 13-acetate
DLN	Draining lymph node
CRP	C-reactive protein
VEGF	Vascular endothelial growth factor

Inflammation and inflammatory signaling pathways

Inflammation is one of the major types of immune responses. It has an important role in both innate and adaptive immunity and has a crucial role in the defense against many harmful stimuli, of both endogenous and exogenous origin [1,2]. During the inflammatory process, several immune cells (such as leucocytes) and plasma proteins (such as cytokines, complement proteins) are brought into the site of infection or damage in tissues and subsequently activated [3]. These blood-derived components of the immune system mediate inflammation to eliminate invading pathogens (such as bacteria, viruses, and fungi) and also promote tissue repair [4,5]. The immune system has evolved to recognize the molecular structures of both foreign and endogenous molecules [such as lipopolysaccharide (LPS), heat shock proteins (HSPs)] by receptors expressed by cells of the immune system such as macrophages, dendritic cells (DCs), endothelial cells, B cells, and T cells [1,6,7]. As a consequence of binding of these receptors to their ligands, intracellular signal transduction pathways are activated to initiate and promote inflammatory responses in immune cells against the above-mentioned agents [8,9,7]. During the inflammatory response, several inflammatory mediators such as pro-inflammatory cytokines and chemokines are produced by immune cells [3,10,7]. The most important pro-inflammatory cytokines in the immune responses are tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, IL-12, interferon-γ (IFN-γ) and IL-8 [3,7]. In addition, the interaction of the aforementioned cytokines with their receptors on the surface of immune cells also activates inflammatory signaling cascades in a positive feedback loop. The three main signaling pathways that mediate the inflammatory response in immune cells include nuclear factor-κB (NF-κB) signaling pathway, Janus kinase/Signal transducer and activator of transcription (JAK/STAT) signaling pathway, and

mitogen-activated protein kinase (MAPK) signaling pathway [11-13]. Inflammation is a protective biological response of the host immune system and is carefully controlled by several mechanisms [4,14,15]. However, failure in these mechanisms which tightly regulate inflammatory signaling pathways leads to unabated inflammation and generation of immune-mediated inflammatory diseases such as inflammatory bowel disease (IBD), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), atherosclerosis and multiple sclerosis (MS)][16-19]. Therefore, modulation of these signaling molecules in the inflammatory signaling pathways can effectively induce anti-inflammatory effects and could potentially be a valuable approach for the management of inflammatory diseases.

One of the natural compounds that have shown potential anti-inflammatory properties and promise in the management or control of several inflammatory diseases is curcumin. Herein, provide a comprehensive overview of the modulatory effects of curcumin on the inflammatory signaling pathways which leads to inhibition of inflammation in different types of immune cells and animal models.

Curcumin and its immunomodulatory effects

Curcumin is a natural compound derived from *Curcuma longa* L. (also called turmeric, a member of Zingiberacea family) that is being used extensively for the management of several diseases. Research supports the critical roles played by curcumin and its analogs such as antibacterial, antiviral, antifungal, antioxidant, anti-inflammatory, hepatoprotective and anti-tumor activities [20-30]. In addition, it is well established that curcumin is considered to be a safe natural compound [31,20]. In recent years, there has been an increasing interest in using curcumin as an

immunomodulatory agent in the immune system. The immunomodulatory effect of curcumin arises from its interaction with a wide range of immune cells such as macrophages, DCs, B and T cells [32,33]. The anti-inflammatory properties of curcumin have been demonstrated in the human and animal models of several inflammatory disorders such as RA, SLE, MS, type 1 diabetes mellitus (T1DM), atherosclerosis, metabolic syndrome, periodontal disease, colitis, and Alzheimer's disease [34,33,35,36]. Interestingly, recent evidence suggests that curcumin can reduce the pro-inflammatory cytokines such as IFN-γ, TNF-α, IL-1 and IL-8 via interaction with several signaling and transcription molecules such as NF-κB, JAKs/STASs, MAPKs and β-catenin [34,37-41]. In this narrative review, we demonstrate that curcumin interacts with various signaling molecules in the inflammatory signaling pathways, thereby acting as an anti-inflammatory agent.

Effect of Curcumin on the NF-κB signaling pathway

NF-κB was first identified in the B cells as a nuclear protein that binds specifically to kappa enhancer motif sequences in the NF-kB target genes [42]. This master transcription factor plays an essential role in the inducible expression of many genes associated with the inflammatory responses in the immune system including antimicrobial peptides, chemokines and cytokines [43,44]. NF-κB proteins are located in the cytoplasm of the cells and repressed by their inhibitory proteins that are known as the inhibitors of NF-κB (IκBs) [42]. In response to various stimuli, the IκB becomes phosphorylated by an active IκB kinase (IKK), which results in the dissociation of IκB from NF-κB [44]. Subsequently, NF-κB is released, translocated to the nucleus and bind their DNA binding sites to regulate the transcription of a large number of genes [43,44].

There is increasing evidence that the mode of action of curcumin involves modulating the NF-κB pathway, which may be considered as one of the key targets of curcumin (Figure 1) [45-50]. The NF-κB network could be modulated at two stages: the inhibition of the NF-κB activation process, and by direct inhibition of NF-κB. In this regard, Brennan *et al*. reported that curcumin could inhibit NF-κB activation by inhibiting the degradation of IκB-α and reacting with the NF-kB itself in TNF-activated Jurkat T lymphoma cells [51]. Curcumin may also interfere with the binding activity of NF-κB to the κB site in the IL-12p40 promoter, which significantly inhibits IL-12 production in LPS-activated macrophages [52,53]. In addition, curcumin treatment inhibited the NF-kB activation induced by oxygen-glucose deprivation in injured brain microvascular endothelial cells (BMECs) [54]. Kim *et al*. reported that curcumin negatively regulates the production of pro-inflammatory cytokines (IL-1, IL-6, and TNF-α) from maturing DCs [55]. In addition, the curcumin-treated DCs manifested an impaired induction of T_H1 responses and a normal cell-mediated immune response [55]. This indicates that the inhibitory effect of curcumin on DCs maturation, at least in part, could be derived from its actions on the NF-κB activation as a potential target [55].

Further studies suggest that curcumin inhibits NF-κB signaling pathway by promoting the expression of IκB-α in activated human macrophages by influenza virus infection [56]. In addition, curcumin derivative BDMC33-treated macrophages showed an interrupted degradation of IκB, resulting in attenuation of NF-κB nuclear translocation [57]. As a consequence of this event, the production of several pro-inflammatory mediators including NO, TNF-α, and IL-1β was suppressed by curcumin [57]. Kumar and colleagues studied the effects of curcumin on the adhesion of monocytes to human umbilical vein endothelial cells (HUVECs) [58]. They

demonstrated that the anti-inflammatory activity of curcumin may be due, in part, to the inhibition of leukocyte recruitment [58]. Curcumin blocked the TNF-induced adhesion of monocytes to HUVECs by inhibiting the expression of adhesion molecules and TNF-mediated activation of NF-κB [58]. Cho *et al*. reported that curcumin has an inhibitory effect on the expression of IL-1β and IL-6 expression induced in TNF-α-treated HaCaT cells [59]. They suggested that curcumin exerts it's anti-inflammatory and growth inhibitory effects by negative regulation of the NF-κB pathway [59]. Bisdemethoxycurcumin, the active component of turmeric, suppresses the production of inflammatory cytokines including TNF-α, IL-8, and IL-6 by inhibiting the NF-κB activation and IκB degradation in pharmacologically-induced inflammation in the human mast cells [60].

Pan *et al*. reported that a new synthetic curcumin analog (C66) decreased high glucose-induced over-expressions of intercellular adhesion molecule 1 (ICAM-1) or CD54 (an important ligand for β2 integrins), vascular cell adhesion molecule 1 (VCAM-1) and monocyte chemoattractant protein-1 (MCP-1). It also reduced renal macrophage infiltration and injury by suppressing NF-κB activation in diabetic mice [61].

Curcumin decreases the NF-κB activation in TCR-stimulated non-obese diabetic lymphocytes [62]. Moreover, Soetikno *et al*. observed that the administration of curcumin protects against the development of diabetic nephropathy [37]. Diabetic nephropathy is a major complication of diabetes and can be considered as an inflammatory disease [63]. Monocytes/macrophages as the main source of pro-inflammatory mediators including TNF-α, IL-1β, MCP-1 and are the key inflammatory cells involved in the pathogenesis of the diabetic nephropathy [64,65]. Macrophages infiltrating into the glomerulus are implicated in the development of glomerular

injury [64]. It has been indicated that curcumin could reduce macrophage infiltration by suppressing the activation of the NF-κB pathway in diabetic rat models [37]. In accord with this finding, Ghosh *et al*. demonstrated that curcumin treatment improves renal function in the animal models with chronic renal failure by antagonizing the effect of TNF-α in peroxisome proliferator-activated receptor-gamma (PPARγ) [66]. It also blocked transactivation of NF-κB [66].

Effect of Curcumin on JAK/STAT signaling pathway

The JAK/STAT signaling pathway is one of the most important pathways that regulate inflammation in immune cells by transducing the signal of types 1 and 2 cytokines receptors in response to various pro-inflammatory cytokines [67,13]. This pathway includes the four known Janus kinases (JAK1-3 and TYK2), which are associated with the aforementioned receptors, and seven STATs (STAT1-4, 5a, 5b, and 6) [67,13].

In innate immunity, these intracellular molecules mediate signaling cascades induced by type I and type II interferon (i.e., IFN-α/β and IFN-γ). They can effectively induce the activation, maturation, and function of DCs and macrophages [68]. In acquired immunity, JAK/STAT signaling regulates the activation and differentiation of different subtype of T cells including T_H1 (JAK2, TYK2, STAT1, and STAT4), T_H2 (JAK1, JAK3, and STAT6), and T_H17 (STAT3) from naïve $CD4^+$ T cells [13,67,69]. Despite the physiologic roles played by JAK/STAT signaling, this pathway is also involved in the pathogenesis of several inflammatory diseases such as RA, IBD, MS, T1DM, SLE, and periodontitis, hence could be considered as a valuable target for the regulation of inflammation [70-74].

The inhibitory action of curcumin on JAK/STAT signaling pathway has been confirmed in a study conducted by Kim *et al*., where it was shown that curcumin suppresses phosphorylation of JAK1, JAK2 and their downstream molecules such as STAT1 and STAT3 in IFN-γ, gangliosides or LPS–activated microglial cells. As a result, the expression of several pro-inflammatory mediators including inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), MCP-1 and ICAM-1 were impaired in activated microglial cells [75]. In this regard, the activation of Src homology 2 domain-containing protein tyrosine phosphatases (SHP)-2, a key negative regulator of JAK activity, is one of the several molecular mechanisms by which curcumin mediates suppression of JAK activation [75]. Oncostatin M (OSM) is an important member of IL-6 cytokine superfamily that is involved in the pathogenesis of several inflammatory diseases, such as RA, by inducing several matrix metalloproteinases (MMPs). In line with previous findings, it has been reported that curcumin treatment suppressed the OSM-induced phosphorylation and DNA binding activity of STAT1 (but not JAK1, JAK2, and JAK3) in bovine and human primary articular chondrocyte [76]. By its inhibitory action on STAT1, curcumin suppresses the OSM-induced production of MMP1, MMP3, and MMP13 in chondrocytes [76]. Another in vitro study assessing the mechanisms underlying curcumin-regulated JAK/STAT signaling showed that curcumin potently inhibits the expression of LPS-induced IL-6, TNF-α, and COX-2 in macrophage cell line RAW264.7 via its modulatory effect on suppressor of cytokine signaling (SOCS)1 and SOCS3 [77]. SOCS proteins negatively regulate the overactivation of the JAK/STAT signaling in responses to inflammatory cytokines through interaction with both JAKs and STATs [78,79]. This evidence provides a novel molecular mechanism by which curcumin regulates the JAK-STAT-mediated inflammatory responses in macrophages. Another in vitro study suggested that curcumin reduced the

expression of several inflammatory mediators including ICAM-1, MCP-1, and IL-8 at both mRNA and protein levels by suppressing the STAT3-phosphorylation in TNF-α-stimulated HUVECs [80].

In experimental allergic encephalomyelitis (EAE), characterized by the predominance of auto-reactive T_H1 and T_H17 cells responses, curcumin blocks the IL-12-induced phosphorylation of JAK2, TYK2 and their downstream molecules, i.e. STAT3 and SATA4 in T cells [81]. Curcumin also inhibits the production of IL-12 by macrophages and DCs [81-83]. With regard to the essential role of IL-12 in the differentiation of T_H1 cells [84], curcumin can strongly suppress the proliferation and differentiation of auto-reactive T_H1 cells in several autoimmune diseases such as MS via inhibition of IL-12 production and its signaling cascade. Similar to effects on T_H1 cells, curcumin also effectively suppresses proliferation and differentiation of auto-reactive T_H17 cells, another important subtype of T $CD4^+$ cells involved in the pathogenesis of EAE [85]. This is mediated by both suppressing IL-6, IL-21, and IL-17 production, and by inhibiting STAT3-phosphorylation and RAR-related orphan receptor gamma (RORγt) activation in response to the aforementioned cytokines [85]. It is interesting to note that IL-6 and IL-21 are required for the differentiation of T_H17 cells from naïve $CD4^+$ T cells by activating STAT3 signaling and its downstream transcription factor of RORγt [86,87]. Curcumin treatment attenuated CNS inflammation, demyelination and severity of clinical paralysis in animal models of EAE owing to its modulatory effects on JAK/STAT signaling [81,85]. This evidence is further supported by other studies which showed curcumin could exert its beneficial anti-inflammatory effects in an animal model of colitis and intestinal inflammation by inhibiting the phosphorylation of JAK2, STAT3 and STAT6 [88,40,89]. This is followed by downregulated protein expression of TNF-α, IL-1β, IFN-γ, IL-

23, IL-12p70 and up-regulated expression of anti-inflammatory cytokines including IL-4, IL-10, IL-13 and transforming growth factor β (TGF-β) [88,40,89]. In addition, curcumin also inhibits the activation of $CD4^+CD7^-$ T cells by downregulation of the STAT-3 signaling pathway [90,91]. $CD4^+CD7^-$ T cells are a distinct subset of $CD4^+$ T cells which produce T_H2-like cytokine profiles including IL-4 and IL-10. They are involved in the pathogenesis of several inflammatory skin diseases [92].

DCs are key cells crucial for the initiation of pro-inflammatory responses in autoimmune and inflammatory diseases such as colitis and are one of the main targets of curcumin [93,94]. It has been documented that curcumin suppress activation and maturation of DCs in colitis mice by targeting JAK/STAT signaling and also by up-regulation of three important negative regulators of this pathway including SOCS 1 and 3 and protein inhibitor of activated STAT3 (PIAS3) [40,89]. Taken together, this growing evidence provides a better understanding of the mechanism of anti-inflammatory action for curcumin via modulating of JAK/STAT inflammatory signaling.

Effect of Curcumin on MAPKs signaling pathway

MAPKs are a group of serine-threonine protein kinases that contribute to gene induction, proliferation, cellular differentiation, and inflammatory responses [95]. There are three main groups of MAPKs which include extracellular receptor-activated kinase (ERK), P38 and C-Jun N-terminal kinase (JNK) [96]. MAPKs play major roles in the production of pro-inflammatory cytokines and can be considered as valuable targets for the treatment of inflammatory diseases [95,97].

In order to study the effect of curcumin on inflammation related to MAPKs signaling pathway, Morgana *et al*. investigated its effects on LPS-stimulated raw 264.7 murine macrophages and found that curcumin remarkably reduced prostaglandin E2 (PGE2) level and the expression of TNF-α and IL-6 by inhibiting phosphorylation and activation of p38 MAPK [77]. In addition, another in vitro study indicated that pretreatment of murine microglia cell line N9 with curcumin and demethoxycurcumin (DMC) could reduce LPS-induced phosphorylation of p38, JNK and ERK1/2 MAPKs pathways, resulting in inhibition of the production of ROS by microglial cells [98]. Consistent with previous studies, Kim *et al*., demonstrated that pretreatment of immature DCs cells with curcumin suppressed the LPS-induced maturation function of DCs by inhibiting phosphorylation of all three main MAPKs (JNK, p38, and ERK)[55]. Moreover, curcumin effectively inhibited COX-2 expressions (both in mRNA and protein levels) in UVB-irradiated HaCaT cells by an inhibitory action on activation of p38 MAPK and JNK [99].

RA is a chronic inflammatory disease characterized by the infiltration of several immune cells such as macrophage, DCs, T and B lymphocytes in the inflamed joints to produce pro-inflammatory cytokines including IL-1β, IL-6, TNF-α, IFN-γ, IL-17, and IL-12 [100]. In response to these pro-inflammatory cytokines, resident synovial fibroblast cells also produce large amounts of IL-6, IL-8, COX-2, and MMPs which results in the progressive joint destruction, deformity, and disability [101,102]. Treatment of human synovial fibroblast cell line MH7A and fibroblast-like synoviocytes (FLS) of RA patients with curcumin decreased PMA or IL-1β-induced phosphorylation of ERK1/2, but not p38, which led to reduced expression of IL-6 [103].

Dry eye disorder is a common inflammatory eye disease where hyperosmosis followed by the inflammation of the ocular surface is involved [104]. In addition, high expression of pro-

inflammatory cytokines such as IL-1β and IL-6 has been observed in patients with dry eye disorder [105,106]. In a study by Min Chen et al., pretreatment of hyperosmotic-stimulated human corneal epithelial cells with curcumin prevented an increase in the IL-1β, IL-6 and TNF-α production. Interestingly, p38 inhibitor (SB 203580), but not JNK inhibitor (600125), has been able to completely inhibit the IL-1β production, suggesting that the potential anti-inflammatory effects of curcumin are mediated by its suppressive effect on p38 pathway. Importantly, p38 inhibitor also reduced the activation of NF-κB, which proves that activation of the NF-κB occurs after the activation of p38 [107]. These findings provide evidence that curcumin is able to suppress NF-κB signaling cascade both through its direct interaction with NF-κB and by inhibition of its upstream activator (i.e. p38 MAPK).

After brain ischemia, brain microvascular endothelial cells (BMECs), the principal cells in the blood-brain barrier (BBB), can cause inflammation by producing several inflammatory cytokines such as IL-1β [108]. Hence preventing inflammatory processes in BMECs can potentially reduce brain damage. In a study by Zhan *et al*., curcumin was able to significantly reduce the lactate dehydrogenase (LDH) release and IL-1β production in oxygen-glucose deprivation (OGD)-stimulated BMECs via inhibition of p38 and JNK phosphorylation. In line with the Min Chen *et al* study, P38 inhibitor (SB203580) suppresses activation of NF-κB, suggesting that curcumin can potentially inhibit these two pathways simultaneously [54].

In an animal model of colitis, curcumin treatment effectively reduced both myeloperoxidase (MPO) activity and production of TNF-α, COX-2 and iNOS by suppressing p38 phosphorylation. Moreover, the production of anti-inflammatory cytokine IL-10 was up-regulated [109]. These findings are in accord with a recent study suggesting that treatment of colonic mucosal biopsies

and colonic myofibroblasts (CMF) of IBD patients with curcumin resulted in reduced p38 phosphorylation which was followed by a decrease in the IL-1β and MMP-3 production [110].

Asthma is a long-term chronic inflammatory disease characterized by the production of pro-inflammatory cytokines such as TNF-α, and IL-1β in the airways [111,112]. MAPKs are one of the important factors in the production of these pro-inflammatory proteins, hence inhibiting this pathway can be a valuable treatment option for this disease [113]. In this regard, in a study by Singh *et al*., in an animal model of chronic asthma intranasal curcumin was able to inhibit all of the three main pathways of MAPKs (p38, JNK, and ERK) [114]. As a result, the levels of nitrite, COX-2 and reactive oxygen species (ROS) were significantly reduced [114].

Other Targets of Curcumin

Curcumin has also shown immunomodulatory effects on different signaling molecules in the immune cells. Yang *et al*. demonstrated that treatment with curcumin down-regulated the expression of glycogen synthase kinase 3 (GSK-3), a negative regulator of Wnt/β-catenin signaling pathway and up-regulated the expression of β-catenin, a chief downstream transcription factor of the canonical Wnt signaling pathway, in LPS-stimulated BMDC [41]. As a result, Wnt/β-catenin signaling was activated in curcumin-treated BMDC that led to the inhibition of DCs activation and maturation [41]. In addition, in a mouse model of allergic asthma, administration of curcumin for 9 days attenuated asthma symptoms and inflammatory responses in the airway by activating the Wnt/β-catenin signaling pathway, especially in DCs [41].

While investigating further molecular targets of curcumin and its anti-inflammatory effects, Cheong *et al*. found that treatment of mouse model of acute asthma with curcumin (200 mg/kg) decreased both mRNA and protein levels of Notch 1 receptor and it's downstream transcription factor GATA binding protein 3 (GATA3), a master regulator of T_H2 cells differentiation, in lung tissues [115]. Notch 1-GATA3 signaling pathway plays a crucial role in the pathogenesis of allergic asthma by promoting the differentiation of T_H2 cells [116-119]. Therefore, curcumin attenuated the allergic airway inflammation by inhibiting the Notch 1-GATA3 signaling pathway and subsequent suppression of T_H2 cells differentiation [115,120]. Recently, another in vivo study has shown that curcumin can also inhibit the phosphorylation of transforming growth factor (TGF)-activated kinase 1 (TAK1) in inflamed spinal cord cells which suppress production of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6 in a mouse model of acute spinal injury [121]. TAK1 is one of the MAPKKK family members and a major upstream modulator for the activation of NF-κB and P38 in microglial cells [122]. Therefore, curcumin can effectively suppress activation of these important pro-inflammatory transcription factors not only through direct interaction on NF-κB, P38 but also through their upstream molecules, especially TAK1,.

Anti-inflammatory effects of curcumin in clinical trials

Over the past decade, a large number of clinical studies has investigated the anti-inflammatory effects of curcumin in several diseases. In a randomized clinical trial conducted by Alizadeh *et al*., administration of 80 mg curcumin nanomicelle daily for 10 weeks significantly reduced plasma levels of inflammatory mediators including TNF-α and C-reactive protein (CRP) in infertile men

[123]. Another randomized clinical trial evaluating the anti-inflammatory effects of curcumin supplementation found that oral administration of 500 mg turmeric (containing 22.1 mg the active ingredient curcumin) for 2 months significantly reduced the serum levels of IL-8, but not TNF-α, in patients with type 2 diabetic nephropathy [124]. The anti-inflammatory effects of curcumin were further supported by a randomized clinical trial conducted by Panahi *et al*., which found that curcumin treatment (1 g/day) effectively reduced serum levels of TNF-α, IL-6, and MCP-1 in patients with metabolic syndrome [125]. In addition, a decrease in the plasma levels of IL-4 and IL-6 were observed after treatment of patients with knee osteoarthritis with pure curcuminoids (1500 mg/day) for 6 weeks [126]. Another clinical study found that oral administration of curcuminoids (comprising curcumin, demethoxycurcumin, and bisdemethoxycurcumin) at a daily dose of 1 g for 4 weeks significantly reduced serum concentration of IL-1β, IL-4 and vascular endothelial growth factor (VEGF), but not TNF-α, IL-6, IL-8, IFN-γ, and MCP-1 in obese individuals [127]. Moreover, by reducing TNF-α, IL-8, IL-6, MCP-1, and hs-CRP, curcumin effectively mediated its anti-inflammatory effects in sulfur mustard-intoxicated patients with chronic pulmonary or cutaneous complications. This disease is characterized by the overproduction of several pro-inflammatory cytokines [128,129]. In line with the findings of previous studies, anti-inflammatory effects of curcumin were also reported in a clinical study where it has been shown that administration of curcumin (180 mg/day) for 8 weeks resulted in a reduction of serum levels of pro-inflammatory mediators including TNF-α, IL-8, IL-6, MCP-1, and hs-CRP in patients with solid tumors. As a consequence, systemic inflammation in these patients was suppressed by curcumin supplementation [130]. All of the studies reviewed here have demonstrated the anti-inflammatory effects of curcumin in several

diseases by its modulatory effects on inflammatory signaling pathway as the main targets of curcumin. Table 2 summaries anti-inflammatory effects of curcumin in recently completed clinical trials.

Concluding remarks

There is growing evidence that curcumin through interaction with a diverse set of cellular and molecular targets, has an anti-inflammatory role and therefore can be considered as a valuable natural compound for managing various inflammatory diseases. Curcumin can inhibit the inflammatory process in different types of immune cells and animal models (Table 1, Figure 1). Curcumin has been found to suppress several inflammatory cascades in immune cells which result in 1) inhibition of activation, maturation and cytokines production of two important cells of innate *immunity i.e.* macrophages and DCs, and (2) inhibition of activation, proliferation, maturation and cytokines production of T cell subsets such as T_H1, T_H2 and T_H17. Interestingly, curcumin as a pleiotropic molecule can simultaneously target multiple signaling molecules such as NF-κB, JAKs/STATs, MAPKs and Wnt/β catenin, suggesting its potential as a signaling molecule-targeted therapeutic agent for inflammatory and immune-related diseases.

Compliance with ethical standards

Funding: None.

Conflict of interest: The authors declare that they have no conflict of interest in this study.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Bianchi ME (2007) DAMPs, PAMPs and alarmins: all we need to know about danger. J Leukocyte Biol 81 (1):1-5. doi:https://doi.org/10.1189/jlb.0306164
2. Grivennikov SI, Greten FR, Karin M (2010) Immunity, inflammation, and cancer. Cell 140 (6):883-899. doi:https://doi.org/10.1016/j.cell.2010.01.025
3. Dinarello CA (2000) Proinflammatory cytokines. Chest 118 (2):503-508. doi:https://doi.org/10.1378/chest.118.2.503
4. Medzhitov R (2008) Origin and physiological roles of inflammation. Nature 454 (7203):428. doi:https://doi.org/10.1038/nature07201
5. Medzhitov R (2010) Inflammation 2010: new adventures of an old flame. Cell 140 (6):771-776. doi:https://doi.org/10.1016/j.cell.2010.03.006
6. Takeuchi O, Akira S (2010) Pattern recognition receptors and inflammation. Cell 140 (6):805-820. doi:https://doi.org/10.1016/j.cell.2010.01.022
7. Mohammadi A, Sharifi A, Pourpaknia R, Mohammadian S, Sahebkar A (2018) Manipulating macrophage polarization and function using classical HDAC inhibitors: Implications for autoimmunity and inflammation. Critical reviews in oncology/hematology 128:1-18. doi:https://doi.org/10.1016/j.critrevonc.2018.05.009
8. Gordon S (2002) Pattern recognition receptors: doubling up for the innate immune response. Cell 111 (7):927-930. doi:https://doi.org/10.1016/S0092-8674(02)01201-1
9. Palm NW, Medzhitov R (2009) Pattern recognition receptors and control of adaptive immunity. Immunological reviews 227 (1):221-233. doi:https://doi.org/10.1111/j.1600-065X.2008.00731.x
10. Keyel PA (2014) How is inflammation initiated? Individual influences of IL-1, IL-18 and HMGB1. Cytokine 69 (1):136-145. doi:https://doi.org/10.1016/j.cyto.2014.03.007
11. Lawrence T (2009) The nuclear factor NF-κB pathway in inflammation. Cold Spring Harbor perspectives in biology:a001651. doi:https://doi.org/10.1101/cshperspect.a001651
12. Kyriakis JM, Avruch J (1996) Sounding the alarm: protein kinase cascades activated by stress and inflammation. Journal of Biological Chemistry 271 (40):24313-24316. doi:https://doi.org/10.1074/jbc.271.40.24313
13. O'shea JJ, Holland SM, Staudt LM (2013) JAKs and STATs in immunity, immunodeficiency, and cancer. New England Journal of Medicine 368 (2):161-170. doi:https://doi.org/10.1056/NEJMra1202117
14. Hanada T, Yoshimura A (2002) Regulation of cytokine signaling and inflammation. Cytokine & growth factor reviews 13 (4-5):413-421. doi:https://doi.org/10.1016/S1359-6101(02)00026-6
15. MacDonald TT, Monteleone I, Fantini MC, Monteleone G (2011) Regulation of homeostasis and inflammation in the intestine. Gastroenterology 140 (6):1768-1775. doi:https://doi.org/10.1053/j.gastro.2011.02.047
16. Barnes PJ, Karin M (1997) Nuclear factor-κB—a pivotal transcription factor in chronic inflammatory diseases. New England journal of medicine 336 (15):1066-1071. doi:https://doi.org/10.1056/NEJM199704103361506
17. Martinon F, Tschopp J (2004) Inflammatory caspases: linking an intracellular innate immune system to autoinflammatory diseases. Cell 117 (5):561-574. doi:https://doi.org/10.1016/j.cell.2004.05.004
18. Brydges S, Kastner D (2006) The systemic autoinflammatory diseases: inborn errors of the innate immune system. In: Current Concepts in Autoimmunity and Chronic Inflammation. Springer, pp 127-160. doi:https://doi.org/10.1007/3-540-29714-6_7
19. Abou-Raya A, Abou-Raya S (2006) Inflammation: a pivotal link between autoimmune diseases and atherosclerosis. Autoimmunity reviews 5 (5):331-337. doi:https://doi.org/10.1016/j.autrev.2005.12.006
20. Aggarwal BB, Harikumar KB (2009) Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic

diseases. The international journal of biochemistry & cell biology 41 (1):40-59. doi:https://doi.org/10.1016/j.biocel.2008.06.010
21. Mohammadi A, Fazeli B, Taheri M, Sahebkar A, Poursina Z, Vakili V, Yazdi SZ, Keramati Z, Boostani R, Hampson I, Rafatpanah H (2017) Modulatory effects of curcumin on apoptosis and cytotoxicity-related molecules in HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) patients. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 85:457-462. doi:https://doi.org/10.1016/j.biopha.2016.11.050
22. Jalili-Nik M, Soltani A, Moussavi S, Ghayour-Mobarhan M, Ferns GA, Hassanian SM, Avan A (2018) Current status and future prospective of Curcumin as a potential therapeutic agent in the treatment of colorectal cancer. Journal of cellular physiology 233 (9):6337-6345. doi:https://doi.org/10.1002/jcp.26368
23. Mohammadi A, Blesso CN, Barreto GE, Banach M, Majeed M, Sahebkar A (2018) Macrophage plasticity, polarization and function in response to curcumin, a diet-derived polyphenol, as an immunomodulatory agent. The Journal of nutritional biochemistry 66:1-16. doi:https://doi.org/10.1016/j.jnutbio.2018.12.005
24. Momtazi AA, Sahebkar A (2016) Difluorinated curcumin: A promising curcumin analogue with improved anti-tumor activity and pharmacokinetic profile. Current Pharmaceutical Design 22 (28):4386-4397. doi:10.2174/1381612822666160527113501
25. Momtazi AA, Shahabipour F, Khatibi S, Johnston TP, Pirro M, Sahebkar A (2016) Curcumin as a MicroRNA regulator in cancer: A review. Reviews of Physiology, Biochemistry and Pharmacology 171:1-38. doi:10.1007/112_2016_3
26. Panahi Y, Khalili N, Sahebi E, Namazi S, Karimian MS, Majeed M, Sahebkar A (2017) Antioxidant effects of curcuminoids in patients with type 2 diabetes mellitus: a randomized controlled trial. Inflammopharmacology 25 (1):25-31. doi:10.1007/s10787-016-0301-4
27. Panahi Y, Kianpour P, Mohtashami R, Jafari R, Simental-Mendiá LE, Sahebkar A (2016) Curcumin Lowers Serum Lipids and Uric Acid in Subjects with Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial. Journal of Cardiovascular Pharmacology 68 (3):223-229. doi:10.1097/FJC.0000000000000406
28. Panahi Y, Kianpour P, Mohtashami R, Jafari R, Simental-Mendía LE, Sahebkar A (2017) Efficacy and Safety of Phytosomal Curcumin in Non-Alcoholic Fatty Liver Disease: A Randomized Controlled Trial. Drug Research 67 (4):244-251. doi:10.1055/s-0043-100019
29. Sahebkar A (2013) Why it is necessary to translate curcumin into clinical practice for the prevention and treatment of metabolic syndrome? BioFactors 39 (2):197-208. doi:10.1002/biof.1062
30. Teymouri M, Pirro M, Johnston TP, Sahebkar A (2017) Curcumin as a multifaceted compound against human papilloma virus infection and cervical cancers: A review of chemistry, cellular, molecular, and preclinical features. BioFactors 43 (3):331-346. doi:10.1002/biof.1344
31. Jurenka JS (2009) Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. Alternative medicine review 14 (2)
32. Gao X, Kuo J, Jiang H, Deeb D, Liu Y, Divine G, Chapman RA, Dulchavsky SA, Gautam SC (2004) Immunomodulatory activity of curcumin: suppression of lymphocyte proliferation, development of cell-mediated cytotoxicity, and cytokine production in vitro. Biochemical pharmacology 68 (1):51-61. doi:https://doi.org/10.1016/j.bcp.2004.03.015
33. Abdollahi E, Momtazi AA, Johnston TP, Sahebkar A (2018) Therapeutic effects of curcumin in inflammatory and immune-mediated diseases: A nature-made jack-of-all-trades? Journal of cellular physiology 233 (2):830-848. doi:https://doi.org/10.1002/jcp.25778
34. Momtazi-Borojeni AA, Haftcheshmeh SM, Esmaeili S-A, Johnston TP, Abdollahi E, Sahebkar A (2017) Curcumin: A natural modulator of immune cells in systemic lupus erythematosus. Autoimmunity reviews. doi:https://doi.org/10.1016/j.autrev.2017.11.016

35. Soltani A, Salmaninejad A, Jalili-Nik M, Soleimani A, Javid H, Hashemy SI, Sahebkar A (2019) 5'-Adenosine monophosphate-activated protein kinase: A potential target for disease prevention by curcumin. Journal of cellular physiology 234 (3):2241-2251. doi:https://doi.org/10.1002/jcp.27192
36. Sahebkar A, Cicero AFG, Simental-Mendía LE, Aggarwal BB, Gupta SC (2016) Curcumin downregulates human tumor necrosis factor-α levels: A systematic review and meta-analysis ofrandomized controlled trials. Pharmacological Research 107:234-242. doi:10.1016/j.phrs.2016.03.026
37. Soetikno V, Sari FR, Veeraveedu PT, Thandavarayan RA, Harima M, Sukumaran V, Lakshmanan AP, Suzuki K, Kawachi H, Watanabe K (2011) Curcumin ameliorates macrophage infiltration by inhibiting NF-κB activation and proinflammatory cytokines in streptozotocin induced-diabetic nephropathy. Nutrition & metabolism 8 (1):35. doi:https://doi.org/10.1186/1743-7075-8-35
38. Gonzales AM, Orlando RA (2008) Curcumin and resveratrol inhibit nuclear factor-kappaB-mediated cytokine expression in adipocytes. Nutrition & metabolism 5 (1):17. doi:https://doi.org/10.1186/1743-7075-5-17
39. Han S-S, Keum Y-S, Seo H-J, Surh Y-J (2002) Curcumin suppresses activation of NF-κB and AP-1 induced by phorbol ester in cultured human promyelocytic leukemia cells. BMB Reports 35 (3):337-342. doi:https://doi.org/10.5483/BMBRep.2002.35.3.337
40. Zhao H-M, Xu R, Huang X-Y, Cheng S-M, Huang M-F, Yue H-Y, Wang X, Zou Y, Lu A-P, Liu D-Y (2016) Curcumin suppressed activation of dendritic cells via JAK/STAT/SOCS signal in mice with experimental colitis. Frontiers in pharmacology 7:455. doi:https://doi.org/10.3389/fphar.2016.00455
41. Yang X, Lv J-N, Li H, Jiao B, Zhang Q-H, Zhang Y, Zhang J, Liu Y-Q, Zhang M, Shan H (2017) Curcumin reduces lung inflammation via Wnt/β-catenin signaling in mouse model of asthma. Journal of Asthma 54 (4):335-340. doi:https://doi.org/10.1080/02770903.2016.1218018
42. Sen R, Baltimore D (1986) Inducibility of κ immunoglobulin enhancer-binding protein NF-κB by a posttranslational mechanism. Cell 47 (6):921-928. doi:https://doi.org/10.1016/0092-8674(86)90807-X
43. Sha WC, Liou H-C, Tuomanen EI, Baltimore D (1995) Targeted disruption of the p50 subunit of NF-κB leads to multifocal defects in immune responses. Cell 80 (2):321-330. doi:https://doi.org/10.1016/0092-8674(95)90415-8
44. Xiao C, Ghosh S (2005) NF-kappaB, an evolutionarily conserved mediator of immune and inflammatory responses. Advances in experimental medicine and biology 560:41-45. doi:https://doi.org/10.1007/0-387-24180-9_5
45. Kunnumakkara AB, Guha S, Krishnan S, Diagaradjane P, Gelovani J, Aggarwal BB (2007) Curcumin potentiates antitumor activity of gemcitabine in an orthotopic model of pancreatic cancer through suppression of proliferation, angiogenesis, and inhibition of nuclear factor-kappaB-regulated gene products. Cancer research 67 (8):3853-3861. doi:https://doi.org/10.1158/0008-5472.CAN-06-4257
46. Shakibaei M, John T, Schulze-Tanzil G, Lehmann I, Mobasheri A (2007) Suppression of NF-kappaB activation by curcumin leads to inhibition of expression of cyclo-oxygenase-2 and matrix metalloproteinase-9 in human articular chondrocytes: Implications for the treatment of osteoarthritis. Biochem Pharmacol 73 (9):1434-1445. doi:https://doi.org/10.1016/j.bcp.2007.01.005
47. Yekollu SK, Thomas R, O'Sullivan B (2011) Targeting curcusomes to inflammatory dendritic cells inhibits NF-kappaB and improves insulin resistance in obese mice. Diabetes 60 (11):2928-2938. doi:https://doi.org/10.2337/db11-0275
48. Liu JL, Pan YY, Chen O, Luan Y, Xue X, Zhao JJ, Liu L, Jia HY (2017) Curcumin inhibits MCF-7 cells by modulating the NF-kappaB signaling pathway. Oncol Lett 14 (5):5581-5584. doi:https://doi.org/10.3892/ol.2017.6860
49. Jin CY, Lee JD, Park C, Choi YH, Kim GY (2007) Curcumin attenuates the release of pro-inflammatory cytokines in lipopolysaccharide-stimulated BV2 microglia. Acta pharmacologica Sinica 28 (10):1645-1651. doi:https://doi.org/10.1111/j.1745-7254.2007.00651.x

50. Suresh S, Sankar P, Telang AG, Kesavan M, Sarkar SN (2018) Nanocurcumin ameliorates Staphylococcus aureus-induced mastitis in mouse by suppressing NF‑κB signaling and inflammation. Int Immunopharmacol 65:408-412. doi:https://doi.org/10.1016/j.intimp.2018.10.034
51. Brennan P, O'Neill LA (1998) Inhibition of nuclear factor kappaB by direct modification in whole cells--mechanism of action of nordihydroguaiaritic acid, curcumin and thiol modifiers. Biochem Pharmacol 55 (7):965-973. doi:https://doi.org/10.1016/S0006-2952(97)00535-2
52. Kang BY, Chung SW, Chung W, Im S, Hwang SY, Kim TS (1999) Inhibition of interleukin-12 production in lipopolysaccharide-activated macrophages by curcumin. European journal of pharmacology 384 (2-3):191-195. doi:https://doi.org/10.1016/S0014-2999(99)00690-1
53. Kang BY, Song YJ, Kim KM, Choe YK, Hwang SY, Kim TS (1999) Curcumin inhibits Th1 cytokine profile in CD4+ T cells by suppressing interleukin-12 production in macrophages. Br J Pharmacol 128 (2):380-384. doi:https://doi.org/10.1038/sj.bjp.0702803
54. Dong HJ, Shang CZ, Peng DW, Xu J, Xu PX, Zhan L, Wang P (2014) Curcumin attenuates ischemia-like injury induced IL-1beta elevation in brain microvascular endothelial cells via inhibiting MAPK pathways and nuclear factor-kappaB activation. Neurol Sci 35 (9):1387-1392. doi:https://doi.org/10.1007/s10072-014-1718-4
55. Kim G-Y, Kim K-H, Lee S-H, Yoon M-S, Lee H-J, Moon D-O, Lee C-M, Ahn S-C, Park YC, Park Y-M (2005) Curcumin inhibits immunostimulatory function of dendritic cells: MAPKs and translocation of NF-κB as potential targets. The Journal of Immunology 174 (12):8116-8124. doi:https://doi.org/10.4049/jimmunol.174.12.8116
56. Xu Y, Liu L (2017) Curcumin alleviates macrophage activation and lung inflammation induced by influenza virus infection through inhibiting the NF-kappaB signaling pathway. Influenza Other Respir Viruses 11 (5):457-463. doi:https://doi.org/10.1111/irv.12459
57. Lee KH, Chow YL, Sharmili V, Abas F, Alitheen NB, Shaari K, Israf DA, Lajis NH, Syahida A (2012) BDMC33, A curcumin derivative suppresses inflammatory responses in macrophage-like cellular system: role of inhibition in NF-kappaB and MAPK signaling pathways. Int J Mol Sci 13 (3):2985-3008. doi:https://doi.org/10.3390/ijms13032985
58. Kumar A, Dhawan S, Hardegen NJ, Aggarwal BB (1998) Curcumin (Diferuloylmethane) Inhibition of Tumor Necrosis Factor (TNF)-Mediated Adhesion of Monocytes to Endothelial Cells by Suppression of Cell Surface Expression of Adhesion Molecules and of Nuclear Factor-κB Activation. Biochemical Pharmacology 55 (6):775-783. doi:https://doi.org/10.1016/S0006-2952(97)00557-1
59. Cho JW, Lee KS, Kim CW (2007) Curcumin attenuates the expression of IL-1beta, IL-6, and TNF-alpha as well as cyclin E in TNF-alpha-treated HaCaT cells; NF-kappaB and MAPKs as potential upstream targets. International journal of molecular medicine 19 (3):469-474. doi:https://doi.org/10.3892/ijmm.19.3.469
60. Kong R, Kang OH, Seo YS, Zhou T, Kim SA, Shin DW, Kwon DY (2018) MAPKs and NFkappaB pathway inhibitory effect of bisdemethoxycurcumin on phorbol12myristate13acetate and A23187induced inflammation in human mast cells. Molecular medicine reports 17 (1):630-635. doi:https://doi.org/10.3892/mmr.2017.7852
61. Pan Y, Zhang X, Wang Y, Cai L, Ren L, Tang L, Wang J, Zhao Y, Wang Y, Liu Q, Li X, Liang G (2013) Targeting JNK by a New Curcumin Analog to Inhibit NF-kB-Mediated Expression of Cell Adhesion Molecules Attenuates Renal Macrophage Infiltration and Injury in Diabetic Mice. PLoS ONE 8 (11):e79084. doi:https://doi.org/10.1371/journal.pone.0079084
62. Castro CN, Barcala Tabarrozzi AE, Winnewisser J, Gimeno ML, Antunica Noguerol M, Liberman AC, Paz DA, Dewey RA, Perone MJ (2014) Curcumin ameliorates autoimmune diabetes. Evidence in accelerated murine models of type 1 diabetes. Clinical and experimental immunology 177 (1):149-160. doi:https://doi.org/10.1111/cei.12322

63. Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T (2005) Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes care 28 (1):164-176. doi:https://doi.org/10.2337/diacare.28.1.164
64. Duran-Salgado MB, Rubio-Guerra AF (2014) Diabetic nephropathy and inflammation. World journal of diabetes 5 (3):393-398. doi:https://doi.org/10.4239/wjd.v5.i3.393
65. Moreno JA, Gomez-Guerrero C, Mas S, Sanz AB, Lorenzo O, Ruiz-Ortega M, Opazo L, Mezzano S, Egido J (2018) Targeting inflammation in diabetic nephropathy: a tale of hope. Expert opinion on investigational drugs 27 (11):917-930. doi:https://doi.org/10.1080/13543784.2018.1538352
66. Ghosh SS, Massey HD, Krieg R, Fazelbhoy ZA, Ghosh S, Sica DA, Fakhry I, Gehr TW (2009) Curcumin ameliorates renal failure in 5/6 nephrectomized rats: role of inflammation. American journal of physiology Renal physiology 296 (5):F1146-1157. doi:https://doi.org/10.1152/ajprenal.90732.2008
67. Leonard WJ, O'Shea JJ (1998) Jaks and STATs: biological implications. Annu Rev Immunol 16 (1):293-322. doi:https://doi.org/10.1146/annurev.immunol.16.1.293
68. Schindler C, Levy DE, Decker T (2007) JAK-STAT signaling: from interferons to cytokines. Journal of Biological Chemistry 282 (28):20059-20063. doi:https://doi.org/10.1074/jbc.R700016200
69. Tamiya T, Kashiwagi I, Takahashi R, Yasukawa H, Yoshimura A (2011) Suppressors of cytokine signaling (SOCS) proteins and JAK/STAT pathways: regulation of T-cell inflammation by SOCS1 and SOCS3. Arteriosclerosis, thrombosis, and vascular biology 31 (5):980-985. doi:https://doi.org/10.1161/ATVBAHA.110.207464
70. O'Shea JJ, Schwartz DM, Villarino AV, Gadina M, McInnes IB, Laurence A (2015) The JAK-STAT pathway: impact on human disease and therapeutic intervention. Annual review of medicine 66:311-328. doi:https://doi.org/10.1146/annurev-med-051113-024537
71. Coskun M, Salem M, Pedersen J, Nielsen OH (2013) Involvement of JAK/STAT signaling in the pathogenesis of inflammatory bowel disease. Pharmacological research 76:1-8. doi:https://doi.org/10.1016/j.phrs.2013.06.007
72. O'shea JJ, Plenge R (2012) JAK and STAT signaling molecules in immunoregulation and immune-mediated disease. Immunity 36 (4):542-550. doi:https://doi.org/10.1016/j.immuni.2012.03.014
73. STAT CJK, EGF P (2005) The Jak-STAT pathway in rheumatoid arthritis. The Journal of rheumatology 32 (9):1650-1653
74. Haftcheshmeh SM, Mohammadi A, Soltani A, Momtazi-Borojeni AA, Sattari M (2018) Evaluation of STAT1 and Wnt5a gene expression in gingival tissues of patients with periodontal disease. J Cell Biochem 0 (0). doi:https://doi.org/10.1002/jcb.27487
75. Kim HY, Park EJ, Joe E-h, Jou I (2003) Curcumin suppresses Janus kinase-STAT inflammatory signaling through activation of Src homology 2 domain-containing tyrosine phosphatase 2 in brain microglia. The Journal of Immunology 171 (11):6072-6079. doi:https://doi.org/10.4049/jimmunol.171.11.6072
76. Li WQ, Dehnade F, Zafarullah M (2001) Oncostatin M-induced matrix metalloproteinase and tissue inhibitor of metalloproteinase-3 genes expression in chondrocytes requires Janus kinase/STAT signaling pathway. The Journal of Immunology 166 (5):3491-3498. doi:https://doi.org/10.4049/jimmunol.166.5.3491
77. Guimarães MR, Leite FRM, Spolidorio LC, Kirkwood KL, Rossa Jr C (2013) Curcumin abrogates LPS-induced pro-inflammatory cytokines in RAW 264.7 macrophages. Evidence for novel mechanisms involving SOCS-1,-3 and p38 MAPK. Archives of oral biology 58 (10):1309-1317. doi:https://doi.org/10.1016/j.archoralbio.2013.07.005
78. Starr R, Willson TA, Viney EM, Murray LJ, Rayner JR, Jenkins BJ, Gonda TJ, Alexander WS, Metcalf D, Nicola NA (1997) A family of cytokine-inducible inhibitors of signalling. Nature 387 (6636):917. doi:https://doi.org/10.1038/43206

79. Endo TA, Masuhara M, Yokouchi M, Suzuki R, Sakamoto H, Mitsui K, Matsumoto A, Tanimura S, Ohtsubo M, Misawa H (1997) A new protein containing an SH2 domain that inhibits JAK kinases. Nature 387 (6636):921. doi:https://doi.org/10.1038/43213
80. Kim YS, Ahn Y, Hong MH, Joo SY, Kim KH, Sohn IS, Park HW, Hong YJ, Kim JH, Kim W (2007) Curcumin attenuates inflammatory responses of TNF-α-stimulated human endothelial cells. Journal of cardiovascular pharmacology 50 (1):41-49. doi:https://doi.org/10.1097/FJC.0b013e31805559b9
81. Natarajan C, Bright JJ (2002) Curcumin inhibits experimental allergic encephalomyelitis by blocking IL-12 signaling through Janus kinase-STAT pathway in T lymphocytes. The Journal of Immunology 168 (12):6506-6513. doi:https://doi.org/10.4049/jimmunol.168.12.6506
82. Kang BY, Chung SW, Chung W-J, Im S-Y, Hwang SY, Kim TS (1999) Inhibition of interleukin-12 production in lipopolysaccharide-activated macrophages by curcumin. European journal of pharmacology 384 (2-3):191-195
83. Kang B, Song Y, Kim KM, Choe Y, Hwang S, Kim TS (1999) Curcumin inhibits Th1 cytokine profile in CD4+ T cells by suppressing interleukin-12 production in macrophages. British journal of pharmacology 128 (2):380-384. doi:https://doi.org/10.1038/sj.bjp.0702803
84. Zhu J, Yamane H, Paul WE (2010) Differentiation of effector CD4 T cell populations (*). Annu Rev Immunol 28:445-489. doi:https://doi.org/10.1146/annurev-immunol-030409-101212
85. Xie L, Li X-K, Funeshima-Fuji N, Kimura H, Matsumoto Y, Isaka Y, Takahara S (2009) Amelioration of experimental autoimmune encephalomyelitis by curcumin treatment through inhibition of IL-17 production. International immunopharmacology 9 (5):575-581. doi:https://doi.org/10.1016/j.intimp.2009.01.025
86. Zhou L, Ivanov II, Spolski R, Min R, Shenderov K, Egawa T, Levy DE, Leonard WJ, Littman DR (2007) IL-6 programs T H-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. Nature immunology 8 (9):967. doi:https://doi.org/10.1038/ni1488
87. Wei L, Laurence A, Elias KM, O'Shea JJ (2007) IL-21 is produced by Th17 cells and drives IL-17 production in a STAT3-dependent manner. Journal of biological chemistry 282 (48):34605-34610. doi:https://doi.org/10.1074/jbc.M705100200
88. Liu L, Liu YL, Liu GX, Chen X, Yang K, Yang YX, Xie Q, Gan HK, Huang XL, Gan HT (2013) Curcumin ameliorates dextran sulfate sodium-induced experimental colitis by blocking STAT3 signaling pathway. International immunopharmacology 17 (2):314-320. doi:https://doi.org/10.1016/j.intimp.2013.06.020
89. Zhang X, Wu J, Ye B, Wang Q, Xie X, Shen H (2016) Protective effect of curcumin on TNBS-induced intestinal inflammation is mediated through the JAK/STAT pathway. BMC complementary and alternative medicine 16 (1):299. doi:https://doi.org/10.1186/s12906-016-1273-z
90. Haftcheshmeh SM, Tajbakhsh A, Kazemi M, Esmaeili SA, Mardani F, Fazeli M, Sahebkar A (2018) The clinical importance of CD4+ CD7− in human diseases. Journal of cellular physiology
91. Zhang C, Li B, Zhang X, Hazarika P, Aggarwal BB, Duvic M (2010) Curcumin selectively induces apoptosis in cutaneous T-cell lymphoma cell lines and patients' PBMCs: potential role for STAT-3 and NF-kappaB signaling. The Journal of investigative dermatology 130 (8):2110-2119. doi:https://doi.org/10.1038/jid.2010.86
92. Haftcheshmeh SM, Tajbakhsh A, Kazemi M, Esmaeili SA, Mardani F, Fazeli M, Sahebkar A (2019) The clinical importance of CD4(+) CD7(-) in human diseases. Journal of cellular physiology 234 (2):1179-1189. doi:https://doi.org/10.1002/jcp.27099
93. Hart AL, Al-Hassi HO, Rigby RJ, Bell SJ, Emmanuel AV, Knight SC, Kamm MA, Stagg AJ (2005) Characteristics of intestinal dendritic cells in inflammatory bowel diseases. Gastroenterology 129 (1):50-65. doi:https://doi.org/10.1053/j.gastro.2005.05.013
94. Blanco P, Palucka AK, Pascual V, Banchereau J (2008) Dendritic cells and cytokines in human inflammatory and autoimmune diseases. Cytokine & growth factor reviews 19 (1):41-52. doi:https://doi.org/10.1016/j.cytogfr.2007.10.004

95. Dong C, Davis RJ, Flavell RA (2002) MAP kinases in the immune response. Annual review of immunology 20 (1):55-72. doi:https://doi.org/10.1146/annurev.immunol.20.091301.131133
96. Seger R, Krebs EG (1995) The MAPK signaling cascade. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 9 (9):726-735
97. Johnson GL, Lapadat R (2002) Mitogen-activated protein kinase pathways mediated by ERK, JNK, and p38 protein kinases. Science 298 (5600):1911-1912. doi:https://doi.org/10.1126/science.1072682
98. Zhang L, Wu C, Zhao S, Yuan D, Lian G, Wang X, Wang L, Yang J (2010) Demethoxycurcumin, a natural derivative of curcumin attenuates LPS-induced pro-inflammatory responses through down-regulation of intracellular ROS-related MAPK/NF-κB signaling pathways in N9 microglia induced by lipopolysaccharide. International Immunopharmacology 10 (3):331-338. doi:https://doi.org/10.1016/j.intimp.2009.12.004
99. Cho JW, Park K, Kweon GR, Jang BC, Baek WK, Suh MH, Kim CW, Lee KS, Suh SI (2005) Curcumin inhibits the expression of COX-2 in UVB-irradiated human keratinocytes (HaCaT) by inhibiting activation of AP-1: p38 MAP kinase and JNK as potential upstream targets. Experimental & molecular medicine 37 (3):186-192. doi:https://doi.org/10.1038/emm.2005.25
100. Firestein GS, McInnes IB (2017) Immunopathogenesis of rheumatoid arthritis. Immunity 46 (2):183-196. doi:https://doi.org/10.1016/j.immuni.2017.02.006
101. Huber L, Distler O, Tarner I, Gay R, Gay S, Pap T (2006) Synovial fibroblasts: key players in rheumatoid arthritis. Rheumatology 45 (6):669-675. doi:https://doi.org/10.1093/rheumatology/kel065
102. Meinecke I, Rutkauskaite E, Gay S, Pap T (2005) The role of synovial fibroblasts in mediating joint destruction in rheumatoid arthritis. Current pharmaceutical design 11 (5):563-568. doi:https://doi.org/10.2174/1381612053381945
103. Kloesch B, Becker T, Dietersdorfer E, Kiener H, Steiner G (2013) Anti-inflammatory and apoptotic effects of the polyphenol curcumin on human fibroblast-like synoviocytes. International Immunopharmacology 15 (2):400-405. doi:https://doi.org/10.1016/j.intimp.2013.01.003
104. Stevenson W, Chauhan SK, Dana R (2012) Dry eye disease: an immune-mediated ocular surface disorder. Archives of ophthalmology (Chicago, Ill : 1960) 130 (1):90-100. doi:https://doi.org/10.1001/archophthalmol.2011.364
105. Calonge M, Enríquez-de-Salamanca A, Diebold Y, González-García MJ, Reinoso R, Herreras JM, Corell A (2010) Dry eye disease as an inflammatory disorder. Ocular immunology and inflammation 18 (4):244-253. doi:https://doi.org/10.3109/09273941003721926
106. Brignole F, Pisella P-J, Goldschild M, De Saint Jean M, Goguel A, Baudouin C (2000) Flow cytometric analysis of inflammatory markers in conjunctival epithelial cells of patients with dry eyes. Investigative ophthalmology & visual science 41 (6):1356-1363. doi:https://doi.org/10.1016/s0002-9394(00)00701-7
107. Chen M, Hu D-N, Pan Z, Lu C-W, Xue C-Y, Aass I (2010) Curcumin protects against hyperosmoticity-induced IL-1β elevation in human corneal epithelial cell via MAPK pathways. Experimental eye research 90 (3):437-443. doi:https://doi.org/10.1016/j.exer.2009.12.004
108. Stanimirovic D, Satoh K (2000) Inflammatory mediators of cerebral endothelium: a role in ischemic brain inflammation. Brain Pathology 10 (1):113-126. doi:https://doi.org/10.1111/j.1750-3639.2000.tb00248.x
109. Camacho-Barquero L, Villegas I, Sánchez-Calvo JM, Talero E, Sánchez-Fidalgo S, Motilva V, Alarcón de la Lastra C (2007) Curcumin, a Curcuma longa constituent, acts on MAPK p38 pathway modulating COX-2 and iNOS expression in chronic experimental colitis. International Immunopharmacology 7 (3):333-342. doi:https://doi.org/10.1016/j.intimp.2006.11.006
110. Epstein J, Docena G, MacDonald TT, Sanderson IR (2010) Curcumin suppresses p38 mitogen-activated protein kinase activation, reduces IL-1β and matrix metalloproteinase-3 and enhances IL-10 in the mucosa of children and adults with inflammatory bowel disease. British Journal of Nutrition 103 (6):824-832. doi:https://doi.org/10.1017/S0007114509992510

111. Barnes PJ (2008) The cytokine network in asthma and chronic obstructive pulmonary disease. The Journal of clinical investigation 118 (11):3546-3556. doi:https://doi.org/10.1172/JCI36130
112. Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM (2000) Asthma: from bronchoconstriction to airways inflammation and remodeling. American journal of respiratory and critical care medicine 161 (5):1720-1745. doi:https://doi.org/10.1164/ajrccm.161.5.9903102
113. Duan W, Wong WS (2006) Targeting mitogen-activated protein kinases for asthma. Curr Drug Targets 7 (6):691-698. doi:https://doi.org/10.2174/138945006777435353
114. Chauhan PS, Singh D, Dash D, Singh R (2018) Intranasal curcumin regulates chronic asthma in mice by modulating NF-κB activation and MAPK signaling. Phytomedicine. doi:https://doi.org/10.1016/j.phymed.2018.06.022
115. Chong L, Zhang W, Nie Y, Yu G, Liu L, Lin L, Wen S, Zhu L, Li C (2014) Protective effect of curcumin on acute airway inflammation of allergic asthma in mice through Notch1–GATA3 signaling pathway. Inflammation 37 (5):1476-1485. doi:https://doi.org/10.1007/s10753-014-9873-6
116. Guo X-j, Zhou M, Ren L-p, Yang M, Huang S-g, Xu W-g (2009) Small interfering RNA-mediated knockdown of Notch1 in lung. Chinese medical journal 122 (21):2647-2651. doi:https://doi.org/10.3760/cma.j.issn.0366-6999.2009.21.023
117. Park C-S (2010) Eosinophilic bronchitis, eosinophilia associated genetic variants, and notch signaling in asthma. Allergy, asthma & immunology research 2 (3):188-194. doi:https://doi.org/10.4168/aair.2010.2.3.188
118. Fang TC, Yashiro-Ohtani Y, Del Bianco C, Knoblock DM, Blacklow SC, Pear WS (2007) Notch directly regulates Gata3 expression during T helper 2 cell differentiation. Immunity 27 (1):100-110. doi:https://doi.org/10.1016/j.immuni.2007.04.018
119. Hozumi K, Negishi N, Tsuchiya I, Abe N, Hirano Ki, Suzuki D, Yamamoto M, Engel JD, Habu S (2008) Notch signaling is necessary for GATA3 function in the initiation of T cell development. European journal of immunology 38 (4):977-985. doi:https://doi.org/10.1002/eji.200737688
120. Osborne BA, Minter LM (2007) Notch signalling during peripheral T-cell activation and differentiation. Nature Reviews Immunology 7 (1):64. doi:https://doi.org/10.1038/nri1998
121. Zhang N, Wei G, Ye J, Yang L, Hong Y, Liu G, Zhong H, Cai X (2017) Effect of curcumin on acute spinal cord injury in mice via inhibition of inflammation and TAK1 pathway. Pharmacological Reports 69 (5):1001-1006. doi:https://doi.org/10.1016/j.pharep.2017.02.012
122. Landström M (2010) The TAK1–TRAF6 signalling pathway. The international journal of biochemistry & cell biology 42 (5):585-589. doi:https://doi.org/10.1016/j.biocel.2009.12.023
123. Alizadeh F, Javadi M, Karami AA, Gholaminejad F, Kavianpour M, Haghighian HK (2018) Curcumin nanomicelle improves semen parameters, oxidative stress, inflammatory biomarkers, and reproductive hormones in infertile men: A randomized clinical trial. Phytotherapy Research 32 (3):514-521. doi:https://doi.org/10.1002/ptr.5998
124. Khajehdehi P, Pakfetrat M, Javidnia K, Azad F, Malekmakan L, Nasab MH, Dehghanzadeh G (2011) Oral supplementation of turmeric attenuates proteinuria, transforming growth factor-β and interleukin-8 levels in patients with overt type 2 diabetic nephropathy: a randomized, double-blind and placebo-controlled study. Scandinavian journal of urology and nephrology 45 (5):365-370. doi:https://doi.org/10.3109/00365599.2011.585622
125. Panahi Y, Hosseini MS, Khalili N, Naimi E, Simental-Mendía LE, Majeed M, Sahebkar A (2016) Effects of curcumin on serum cytokine concentrations in subjects with metabolic syndrome: A post-hoc analysis of a randomized controlled trial. Biomedicine & pharmacotherapy 82:578-582. doi:https://doi.org/10.1016/j.biopha.2016.05.037
126. Rahimnia A-R, Panahi Y, Alishiri G, Sharafi M, Sahebkar A (2015) Impact of supplementation with curcuminoids on systemic inflammation in patients with knee osteoarthritis: findings from a randomized

double-blind placebo-controlled trial. Drug research 65 (10):521-525. doi:https://doi.org/10.1055/s-0034-1384536
127. Ganjali S, Sahebkar A, Mahdipour E, Jamialahmadi K, Torabi S, Akhlaghi S, Ferns G, Parizadeh SMR, Ghayour-Mobarhan M (2014) Investigation of the effects of curcumin on serum cytokines in obese individuals: a randomized controlled trial. The Scientific World Journal 2014. doi:http://dx.doi.org/10.1155/2014/898361
128. Panahi Y, Ghanei M, Bashiri S, Hajihashemi A, Sahebkar A (2015) Short-term curcuminoid supplementation for chronic pulmonary complications due to sulfur mustard intoxication: positive results of a randomized double-blind placebo-controlled trial. Drug research 65 (11):567-573. doi:https://doi.org/10.1055/s-0034-1389986
129. Panahi Y, Sahebkar A, Parvin S, Saadat A (2012) A randomized controlled trial on the anti-inflammatory effects of curcumin in patients with chronic sulphur mustard-induced cutaneous complications. Annals of clinical biochemistry 49 (6):580-588. doi:https://doi.org/10.1258/acb.2012.012040
130. Panahi Y, Saadat A, Beiraghdar F, Sahebkar A (2014) Adjuvant therapy with bioavailability-boosted curcuminoids suppresses systemic inflammation and improves quality of life in patients with solid tumors: a randomized double-blind placebo-controlled trial. Phytotherapy research 28 (10):1461-1467. doi:https://doi.org/10.1002/ptr.5149
131. Belcaro G, Cesarone MR, Dugall M, Pellegrini L, Ledda A, Grossi MG, Togni S, Appendino G (2010) Product-evaluation registry of Meriva(R), a curcumin-phosphatidylcholine complex, for the complementary management of osteoarthritis. Panminerva medica 52 (2 Suppl 1):55-62
132. Belcaro G, Cesarone MR, Dugall M, Pellegrini L, Ledda A, Grossi MG, Togni S, Appendino G (2010) Efficacy and safety of Meriva(R), a curcumin-phosphatidylcholine complex, during extended administration in osteoarthritis patients. Alternative medicine review : a journal of clinical therapeutic 15 (4):337-344
133. Moreillon JJ, Bowden RG, Deike E, Griggs J, Wilson R, Shelmadine B, Cooke M, Beaujean A (2013) The use of an anti-inflammatory supplement in patients with chronic kidney disease. Journal of complementary & integrative medicine 10. doi:https://doi.org/10.1515/jcim-2012-0011
134. Shelmadine BD, Bowden RG, Moreillon JJ, Cooke MB, Yang P, Deike E, Griggs JO, Wilson RL (2017) A Pilot Study to Examine the Effects of an Anti-inflammatory Supplement on Eicosanoid Derivatives in Patients with Chronic Kidney Disease. Journal of alternative and complementary medicine (New York, NY) 23 (8):632-638. doi:https://doi.org/10.1089/acm.2016.0007
135. Usharani P, Mateen AA, Naidu MU, Raju YS, Chandra N (2008) Effect of NCB-02, atorvastatin and placebo on endothelial function, oxidative stress and inflammatory markers in patients with type 2 diabetes mellitus: a randomized, parallel-group, placebo-controlled, 8-week study. Drugs in R&D 9 (4):243-250. doi:https://doi.org/10.2165/00126839-200809040-00004
136. Chuengsamarn S, Rattanamongkolgul S, Luechapudiporn R, Phisalaphong C, Jirawatnotai S (2012) Curcumin extract for prevention of type 2 diabetes. Diabetes care 35 (11):2121-2127. doi:https://doi.org/10.2337/dc12-0116
137. Samadian F, Dalili N, Poor-Reza Gholi F, Fattah M, Malih N, Nafar M, Firoozan A, Ahmadpoor P, Samavat S, Ziaie S (2017) Evaluation of Curcumin's effect on inflammation in hemodialysis patients. Clinical nutrition ESPEN 22:19-23. doi:https://doi.org/10.1016/j.clnesp.2017.09.006
138. Soveyd N, Abdolahi M, Djalali M, Hatami M, Tafakhori A, Sarraf P, Honarvar NM (2018) The Combined Effects of omega -3 Fatty Acids and Nano-Curcumin Supplementation on Intercellular Adhesion Molecule-1 (ICAM-1) Gene Expression and Serum Levels in Migraine Patients. CNS & neurological disorders drug targets 16 (10):1120-1126. doi:https://doi.org/10.2174/1871527317666171213154749

139. Abdolahi M, Sarraf P, Javanbakht MH, Honarvar NM, Hatami M, Soveyd N, Tafakhori A, Sedighiyan M, Djalali M, Jafarieh A, Masoudian Y, Djalali M (2018) A Novel Combination of omega-3 Fatty Acids and Nano-Curcumin Modulates Interleukin-6 Gene Expression and High Sensitivity C-reactive Protein Serum Levels in Patients with Migraine: A Randomized Clinical Trial Study. CNS & neurological disorders drug targets 17 (6):430-438. doi:https://doi.org/10.2174/1871527317666180625101643
140. Abdolahi M, Tafakhori A, Togha M, Okhovat AA, Siassi F, Eshraghian MR, Sedighiyan M, Djalali M, Mohammadzadeh Honarvar N, Djalali M (2017) The synergistic effects of omega-3 fatty acids and nano-curcumin supplementation on tumor necrosis factor (TNF)-alpha gene expression and serum level in migraine patients. Immunogenetics 69 (6):371-378. doi:https://doi.org/10.1007/s00251-017-0992-8
141. Abdolahi M, Jafarieh A, Sarraf P, Sedighiyan M, Yousefi A, Tafakhori A, Abdollahi H, Salehinia F, Djalali M (2019) The Neuromodulatory Effects of omega-3 Fatty Acids and Nano-Curcumin on the COX-2/ iNOS Network in Migraines: A Clinical Trial Study from Gene Expression to Clinical Symptoms. Endocrine, metabolic & immune disorders drug targets. doi:https://doi.org/10.2174/1871530319666190212170140
142. Holt PR, Katz S, Kirshoff R (2005) Curcumin therapy in inflammatory bowel disease: a pilot study. Digestive diseases and sciences 50 (11):2191-2193. doi:https://doi.org/10.1007/s10620-005-3032-8
143. Epstein J, Docena G, MacDonald TT, Sanderson IR (2010) Curcumin suppresses p38 mitogen-activated protein kinase activation, reduces IL-1beta and matrix metalloproteinase-3 and enhances IL-10 in the mucosa of children and adults with inflammatory bowel disease. The British journal of nutrition 103 (6):824-832. doi:https://doi.org/10.1017/s0007114509992510

Table 1. A brief overview of molecular targets of curcumin and its anti-inflammatory effects; (-) and (+) signs show negative and positive effects of curcumin on its target molecules respectively.

Type of study	Cells/animal models	Biologic effects	Targets	Ref.
- In vitro	TNF-α or IL-1β-stimulated Jurkat and thymoma cells	- Inhibit NF-κB activation by interfering with IκBα degradation - Reacting with p50 in the NF-κB complex	NF-κB (-) IκB (+)	[51]
- In vitro	LPS- stimulated splenic macrophages	- Inhibit interleukin-12 production	NF-κB (-) NF-κB binding to the κB site (-)	[52]
- In vitro	OGD- treated BMECs	- Reduce LDH release - Decrease IL-1β production	NF-κB p65 (-) p-IκB (-) p38 (-) JNK (-)	[54]
- In vitro	LPS-stimulated BMDCs	- Inhibit expression of co-stimulatory molecules including CD80, CD86, and MHC class II - Induce the immature state of DCs with high endocytic capacity - Inhibit the capacity of DC to induce T_H1 responses - Inhibit production of IL-12, IL-1β, IL-6, and TNF-α	NF-κB p65 (-) p38 (-) ERK (-) JNK (-)	[55]
- In vitro	IFN-γ/LPS-stimulated macrophage	- Inhibit secretion of NO, TNF-α, and IL-1β	NF-κB (-) JNK (-) ERK (-)	[57]
- In vitro	TNF-α-stimulated HUVECs	- Inhibit cell surface expression of ICAM-1, VCAM-1, and ELAM-1 -Blocked their adhesion to monocytes	NF-κB (-)	[58]
- In vitro	TNF-α-treated HaCaT cells	- Inhibit expression of IL-1β, IL-6, and TNF-α	NF-κB (-) p38 (-) ERK (-) JNK (-)	[59]
- In vitro	PMA and calcium ionophore A23187-treated human mast cells	- Suppresses production of TNF-α, IL-8, and IL-6	NF-κB (-) IκB (+) p38 (-) JNK (-)	[60]
- In vivo	Renal epithelial NRK-52E cells	- Inhibit high glucose-induced over-expressions of ICAM-1, VCAM-1, and MCP-1 - Reduce renal macrophage infiltration	NF-κB (-) JNK (-)	[61]
- Ex vivo	Splenocytes in an animal model of diabetes	- Inhibit pancreatic leucocyte infiltration - Impair proliferation and IFN-γ production	NF-κB p65 (-)	[62]
- In vitro	M-stimulated BDC2·5-splenocytes	- Decrease proliferation of $CD4^+$ T lymphocytes		

	LPS and IFN-γ-stimulated DCs	- Inhibit expression of co-stimulatory molecules including CD80, CD86, CD40, and MHC class II - Reduce production of IL-12p70, IL-6, and TNF-α - Inhibit NO release		
- In vivo	An animal model of diabetes	- Decrease TNF-α, IL-1β, ICAM-1, MCP-1 protein expression - Reduces macrophage infiltration	NF-κB (-) IκBα (+)	[37]
- In vivo	Animal models with chronic renal failure	-Antagonize effect of TNF-α in PPARγ	NF-κB (-)	[66]
- In vitro	DLN cells	- Decrease proliferation - Reduce mRNA expression of IL-17, TGF-β, IL-6, IL-21, and RORγt	STAT3 (-)	[85]
	Jurkat T cells			
- In vivo	Spinal cord cells of an animal model of EAE	- Reduce mRNA expression of IL-17, TGF-β, IL-6, IL-21, and RORγt		
- In vitro	Spleen cells in animal model of EAE	- Decrease proliferation and IL-12-induced responses - Decrease IL-12 and IFN-γ production	JAK2 (-) TYK2 (-) STAT3 (-) STAT4 (-)	[81]
	Peritoneal macrophage cells of an animal model of EAE	- Decrease IL-12 production		
	Mouse microglial cell line	- Decrease IL-12 production		
- In vitro	TNF-α-stimulated HUVECs	- Reduce the expression of ICAM1, MCP1, and IL-8	NF-κB (-) p38 (-) JNK (-) STAT3 (-)	[80]
- In vitro	Gangliosides, IFN-γ or LPS-stimulated Rat microglia cells	- Suppress induction of COX-2 and iNOS	JAK1 (-) JAK2 (-) STAT1 (-) STAT3 (-) SHP-2 (+)	[75]
	Gangliosides, IFN-γ or LPS-stimulated murine BV2 microglial cells			
- In vitro	LPS-stimulated RAW 264.7 murine macrophage	- Inhibit expression of IL-6, TNF-α, and COX-2	NF-κB (-) SOCS1 (+) SOCS3 (+) p38 (-)	[77]
- In vitro	OSM-stimulated bovine and human chondrocytes	- Reduce expression of MMP-1, MMP-3, and MMP-13	STAT1 (-) JNK (-)	[76]
- In vivo	Colonic tissue cells of an animal model of colitis	- Reduce expression of TNF-α and IL-1β - Inhibit activity of MPO	STAT3 (-)	[88]

- In vivo	Colonic tissue cells of an animal model of colitis	- Inhibit activity of MPO - Reduce production of TNF-α, IFN-γ - Increase production of IL-10, IL-13, and TGF-β - Inhibit expression of iNOs	STAT1 (-) SOCS1 (+)	[89]
- In vivo	Peyer's patches lymphocytes of an animal model of colitis	- Decrease the total number of DCs - Reduce expression of co-stimulatory molecules on DCs including MHC Ⅱ, CD40, CD83, CD273, and CD282	JAK2 (-) STAT3 (-) STAT6 (-) SOCS1 (+) SOCS3 (+) PIAS3 (+)	[40]
- In vitro	Human corneal epithelial cells	- Reduce mRNA expression of IL-6, TNF-α, and IL-1β	NF-κB p65 (-) p38 (-) JNK (-)	[107]
- In vivo	Colonic tissue cells of an animal model of colitis	- Inhibit activity of MPO - Reduce production of TNF-α - Increase production of IL-10 - Reduce expression of COX-2 and iNOS	p38 (-)	[109]
- Ex vivo	Mucosal biopsies and myofibroblasts of IBD patient	- Decrease IL-1β and MMP-3 production - Increase production of IL-10	p38 (-)	[110]
- In vivo	Animal model of Chronic asthma	- Reduce levels of nitrate COX-2 and ROS.	NF-κB (-) p38 (-) ERK (-) JNK (-)	[114]
- In vitro	LPS-stimulated murine microglia cell line N9	- Inhibit production of ROS	p38 (-) ERK (-) JNK (-)	[98]
- In vitro	MH7A cells and RA-FLS	- Reduce expression of IL-6	NF-κB (-) ERK (-)	[103]
- In vitro	DCs	- Inhibit maturation and function of BMDCs. - Reduce the ability of DCs to induce T cells responses	GSK-3 (-) β-catenin (+)	[41]
- In vivo	Lung tissues of a mouse model of asthma	- Reduce production of IL-4 and increase production of IFN-γ		
- In vivo	Lung tissues of a mouse model of asthma	- Inhibit differentiation of T_H2 cells	Notch 1 receptor (-) Notch 2 receptor (-) GATA3 (-)	[115]
- In vivo	Spinal cord cells of a mouse model of acute spinal cord injury	- Inhibit production of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and NO	TAK (-)	[121]

Table 2. Anti-inflammatory effects of curcumin in recently completed clinical trials.

Population size (N)	Type of disease	Dose of turmeric, curcumin, or curcuminoids	Duration of intervention	Findings	Ref.
60	Infertility	80 mg/day	10 weeks	Reduced plasma level of TNF-α and CRP	[123]
40	Type 2 diabetic nephropathy	66.3 mg/day	2 month	Decreased plasma and urinary level of IL-8	[124]
117	Metabolic syndrome	1 g/day	8 weeks	Reduced plasma level of TNF-α, IL-6, and MCP-1	[125]
40	Knee osteoarthritis	1500 mg/day	6 weeks	Reduced plasma level of IL-4 and IL-6	[126]
50	Osteoarthritis	200 mg/day	3 month	Reduced plasma level of CRP	[131]
100	Osteoarthritis	200 mg/day	8 month	plasma level of IL-1β, IL-6, sCD40-L, sVCAM-1, and ESR	[132]
30	Obesitiy	1 g/day	4 weeks	Reduced plasma level of IL-1β, IL-4, and VEGF	[127]
89	Sulfur mustard intoxication	1.5 g/day	4 weeks	Reduced plasma level of TNF-α, IL-8, IL-6, MCP-1, and hs-CRP	[128]
96	Sulfur mustard-induced cutaneous complications	1 g/day	4 weeks	Reduced plasma level of IL-8 and hs-CRP	[129]
80	Solid tumors	180 mg/day	8 weeks	Reduced plasma level of TNF-α, IL-8, IL-6, MCP-1, and hs-CRP	[130]
16	Chronic kidney disease	1.648 g/day	8 weeks	Reduced plasma level of CRP	[133]

16	Chronic kidney disease	1.648 g/day	8 weeks	Attenuated the increase in the plasma level of PGE2,	[134]
67	Type 2 diabetes mellitus.	1500 mg/day	8 weeks	Reduced plasma level of TNF-α and IL-6	[135]
237	Type 2 diabetes mellitus.	1500 mg/day	9 month	Increased plasma level of adiponectin	[136]
71	Hemodialysis	66.3 mg/day	12 weeks	Reduced plasma level of TNF-α, IL-6, and hs-CRP	[137]
72	Migraine	80 mg/day	2 month	Reduced plasma level of ICAM-1	[138]
80	Migraine	80 mg/day	2 month	Reduced plasma level of IL-6, and hs-CRP	[139]
74	Migraine	80 mg/day	2 month	Reduced plasma level of TNF-α	[140]
74	Migraine	80 mg/day	2 month	Reduced plasma level of COX-2/iNOS	[141]
5	Crohn's disease	1.08 g/day 1.44 g/day	1 month 2 month	Reduced plasma level of CRP and ESR	[142]
5	Ulcerative proctitis	1.1 g/day 1.65 g/day	1 month 2 month	Reduced plasma level of CRP and ESR	[142]
Ex vivo	Inflammatory bowel disease	5-50 µM	0.5-24 h	Reduced plasma level of IL-1 and MMP-3 Increased plasma level of IL-10	[143]

Figure legend

Figure 1. A schematic view of curcumin's modulatory effects on NF-κB, JAK/STAT, and MAPKs pathway. Curcumin suppresses activation and phosphorylation of JAKs and STATs proteins. Moreover, curcumin via both direct interactions with NF-κB and IκB suppresses activation of NF-κB. Finally, curcumin inhibits MAPK signaling pathway via its interaction with three main members of this pathway including JNK, p38, and ERK. As a result of curcumin's modulatory functions, the pro-inflammatory process including infiltration of leukocyte into the site of inflammation, activation, maturation and also the production of pro-inflammatory mediators by innate immune cells strongly was inhibited. On the other hand, curcumin suppresses acquired immune responses by its inhibitory effects on the activation, differentiation and cytokines production of T cells.