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PII: S1568-9972(19)30115-6
DOI: https://doi.org/10.1016/j.autrev.2019.05.012
Reference: AUTREV 2335

To appear in: *Autoimmunity Reviews*

Received date: 12 January 2019
Accepted date: 18 January 2019

Please cite this article as: K. Rahimi, A. Ahmadi, K. Hassanzadeh, et al., Targeting the balance of T helper cell responses by curcumin in inflammatory and autoimmune states, Autoimmunity Reviews, https://doi.org/10.1016/j.autrev.2019.05.012

Targeting the balance of T helper cell responses by curcumin in inflammatory and autoimmune states

Kaveh Rahimi[1], Abbas Ahmadi[1], Kambiz Hassanzadeh[1], Zahra Soleimani[2], Thozhukat Sathyapalan[3], Asadollah Mohammadi[1**], Amirhossein Sahebkar[4,5,6*] sahebkara@mums.ac.ir

[1]Cellular and Molecular Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran.

[2]Immunology Research Center, Inflammation and Inflammatory Diseases Division, Department of Immunology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

[3]Department of Academic Diabetes, Endocrinology and Metabolism, Hull York Medical School, University of Hull, Hull HU3 2JZ, UK

[4]Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran.

[5]Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

[6]School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.

[*]Corresponding authors:

***Amirhossein Sahebkar:**
Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran. E-mail addresses:

****Asadollah Mohammadi:**
Cellular and Molecular Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Iran. Tel: +9866177-13446, Fax: +98-08733664654

Abstract

$CD4^+$ T helper (Th) cells are a crucial player in host defense but under certain conditions can contribute to the pathogenesis of inflammatory and autoimmune diseases. Beside the Th1/Th2 subset, several additional Th subsets have been identified, each with a distinctive transcription factor, functional properties, signature cytokine profile, and possible role in the pathophysiology of diseases. These newer Th subsets include Th17, regulatory Th cells (Tregs), and more

recently, Th9, Th22, and follicular T helper cells. Interestingly, imbalance of Th subsets contributes to the immunopathology of several disease states. Therefore, targeting the imbalance of Th subsets and their signature cytokine profiles by a safe, effective and inexpensive nutraceutical agent such as curcumin could be helpful to treat autoimmune and inflammatory diseases. In this study different Th subsets and how the imbalance of these subsets could promote pathology of several diseases has been reviewed. Furthermore, the role of curcumin in this process will be discussed and the impact of targeting Th subsets by curcumin.

Keywords:

T cell; Curcumin; Inflammation; Autoimmunity

Introduction

Immune system mounts an effective and appropriate response towards several pathogens such as viruses, bacteria, fungi, parasites, tumors, allergens, and other immune stimulants [1]. T cells, the cellular base of cell-mediated immunity (CMI), are the main subtypes of lymphocytes [2]. The 2 main subtypes of T lymphocytes are $CD4^+$ and $CD8^+$ T [2]. T helper (Th) cells are the subpopulations of $CD4^+$ T lymphocytes that is crucial in adaptive immune responses [2]. They exert distinct biological functions such as recruiting neutrophils, eosinophils, basophils, and mast cells to sites of stimulations, inducing macrophages to enhanced anti-microbial activity, helping B cells to makes antibodies, and production of chemokines and cytokines for shaping and orchestrating of various immune responses [2]. Activated $CD4^+$ Th lymphocytes based on their function, transcription factors and signature cytokines are differentiated and classified into various distinct subsets such as Th1, Th2, Th9, Th17, Th22, T-regulatory (Tregs), and follicular T helper (Tfh) cells [2].

Undoubtedly, the balance between Th cytokine secretion and their responses are necessary for orchestrating the normal immune responses against intracellular and extracellular pathogens, tumor cells, tolerance to autoantigens and alteration in Th1-Th2 and Th17-Treg balance results in several diseases such as allergic and atopic disease, tumors and autoimmune and inflammatory states such as Parkinson's disease, Alzheimer's disease, inflammatory bowel disease (IBD), and

rheumatoid arthritis (RA) [2]. Therefore, tending to rebalance Th imbalance may be a therapeutic way for manipulating immune responses.

Nowadays, 25% of current drugs are made from herbal medicine and also 10% of all medications are produced from microbial sources [3, 4]. Several herbal medications such as curcumin act as an immunomodulator, thus, could be a benefit for changing the immune response [5-8]. Curcumin is used since time immemorial as a dietary spice for the management of inflammatory conditions [9]. Curcumin has shown various biological and pharmacological actions including immunomodulatory, anti-oxidant and anti-inflammatory properties [9]. Based on various in-vitro and in-vivo studies curcumin has shown therapeutic potential in several Th cells-mediated conditions [9].

Therefore, here we review the different Th subsets and how the imbalance of these subsets could promote the pathology of diseases and the potential role of curcumin in modulating these imbalances.

The role of CD4 Th lymphocyte subsets

$CD4^+$ T cells have a central role in defending the body against pathogens, however, they could also be pathogenic and driving inflammation. Activated $CD4^+$ Th lymphocytes were classified into different subsets including Th1, Th2, Th9, Th17, Th22, Tfh and Tregs cells [10-12]. Th1 cells produce mainly interleukin (IL)-2 and interferon-gamma (IFN-γ). It also secretes a number of cytokines such as granulocyte-macrophage-colony-stimulating factor (GM-CSF), tumor necrosis factor-beta (TNF-β) and lymphotoxin as well as various factors which trigger Th1 differentiation [10-12].

IFN-γ-secreting Th1 cells increases toll-like receptors (TLRs) expression [13], promotes class switching of immunoglobulin G (IgG) and pathogenic autoantibody production [14], increases antigen presentation through major histocompatibility complex (MHC) [15], as well as suppression and induction of over 200 genes whose functional significance remains unknown [15]. Th1 cells also stimulate the bactericidal activity of phagocytes, activate macrophages, increased phagocytosis, and responsible for cell-mediated immunity [15]. IFN-γ, the signature cytokine of the Th1 subset, is a potent pro-inflammatory cytokine which plays crucial roles in

immunopathology [16]. IFN-γ is associated with the immunopathology of different autoimmune states [16].

By contrast, Th2 cells subset produce IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, IL-25, and Amphiregulin [2]. Th2 cells cause antibody production, eosinophil activation and recruitment, and inhibition of various macrophage functions [2, 17]. They also defense host against extracellular parasites including helminths as well as involves in the induction and persistence of various allergic and atopic diseases [2, 17].

The dichotomy of the Th1/Th2 cells axis was broken down after the identification of Th17 and Tregs cells [2]. Th17 cells are characterized by expression of the transcription factor retinoid-related orphan receptor-γt (RORγt) and secrete potent pro-inflammatory cytokines [18]. TGF-β and inflammatory cytokines have pivotal roles in the production of Th17 cells [19]. However, under certain states, these cells are responsible for the central nervous system (CNS) inflammatory demyelination and several inflammatory and autoimmune diseases, including asthma and allergy, RA, SLE, MS, IBD and psoriasis. [19].

The other subset of $CD4^+$ T lymphocytes is Tregs cells which is characterized by a $CD4^+$, $CD25^+$, and Forkhead box P3 ($FoxP3^+$) transcription factor ($CD4^+CD25^+FoxP3^+$) expression [20-22]. Treg cells suppress inflammation and autoimmunity by inhibiting immune responses and autoreactive effector T cells. A reduction in function and/or frequency of these cells contributes to conditions such as enteropathy, polyendocrinopathy, immune-dysregulation and X-linked syndrome (IPEX) [23-25]. Treg and Th17 cells are potentially associated with protection, pathogenesis, and progression of autoimmunity [26, 27]. Tregs have a protective role in autoimmune conditions, whereas Th17 cells enhance the progression of autoimmune diseases [26-28]. The Th cells subpopulation balance is critical for modulation of the immune system. Targeting the Th cells imbalance by safe and effective nutraceuticals may provide clinical efficacy in the conditions such as autoimmune diseases, asthma and allergy, inflammation, and organ transplantation.

An overview of the immunomodulatory properties of curcumin

Interest in the use of nutraceuticals and phytochemicals are growing nowadays so that 25% of current drugs are made from herbal medicines [29, 30]. Curcumin is a polyphenolic compound

which first described in 1910 [29, 30]. Multiple studies have demonstrated that curcumin is safe and effective in humans [30-34]. Curcumin possesses diverse pharmacological functions such as immunomodulatory and anti-inflammatory activities [30-34]. The immunomodulatory activities of curcumin which protect against immune-mediated diseases are due to its interaction with immune system cells [35-44]. Curcumin also interacts with several transcription factors and signal transducers [44, 45]. Curcumin reduces the numbers of neutrophils and eosinophils and increases the lymphocyte and NK cells count [35-44]. Curcumin also increases macrophage migration and infiltration as well as inhibits the activation of NF-κB [44, 45]. Moreover, curcumin reduces M1 macrophage polarization and induces M2 macrophage polarization [44, 45]. The functional properties and multiple pharmacological activities of curcumin on the immune system originate from NF-κB suppression and preventing the nuclear translocation of NF-κB p65 subunit [44, 45]. NF-κB has a crucial role in producing proinflammatory cytokines [44-46]. Therefore, curcumin and other NF-κB inhibitor agents are able to modulate and decreases the production of pro-inflammatory mediators. [45-47]. Curcumin also modulates immune responses by modulating IgG, IgM, and sIgA production.

Therefore, curcumin modulates the immune system by interacting with immune cells and potentially might have a therapeutic role in various inflammatory and autoimmune conditions. We have reviewed the therapeutic effect of curcumin by restoring the balance between various Th subsets.

Effects of curcumin on Th subset balance

There is growing evidence that curcumin regulates the function and proliferation of immune cells **(Fig.1)**. Investigation of curcumin on modulating the immune response [37] showed that the development of CTLs and the proliferation of splenic lymphocytes is significantly reduced by curcumin [37]. Curcumin inhibits the activation of NF-kB irreversibly, thereby impairing the expression/production of TNF-α and IL-12 by peritoneal macrophages and IFN-γ and IL-2 by splenic T lymphocytes [37]. Curcumin significantly reduced IL-12 production by heat-killed Listeria monocytogenes (HKL)-stimulated macrophages or lipopolysaccharide (LPS). Curcumin administration inhibited IL-12 production by HKL or LPS mediated macrophages stimulation which leads to Th1 cytokine profile inhibition [48]. This suggests that curcumin suppresses Th1

cytokine production by inhibiting IL-12 production thereby demonstrating its potential in the Th1-mediated disease states.

It is also a powerful inhibitor of T-lymphocytes proliferation **(Fig.1)**. Curcumin inhibited IL-2-dependent DNA synthesis by mouse $CD4^+$ T-lymphocytes, IL-2 and CD25 expression, demonstrating a suppressive effect on the IL-2 receptor (IL-2R) signaling. In addition, $CD4^+CD25^+$ regulatory T-cells treatment with curcumin down-regulated FoxP3 expression as well as Treg cells suppressor function [49].

Evidence suggests that curcumin shifts the Th1/Th2 balance towards Th2-type response in human peripheral mononuclear cells (PBMCs) [50]. Curcumin supplementation impairs Th1/Th17 cells differentiation during encephalomyelitis whilst induces Th2 cells differentiation. Feeding with 2% curcumin produced an anti-inflammatory phenotype in DCs [51]. These findings demonstrate that curcumin silences Th17/IL-23-mediated immunopathology through enhancing STAT-3 interaction in DCs.

When human $CD4^+$ T cells were stimulated with anti-CD2/CD3/CD28 and treated with curcumin, it inhibited cell proliferation, differentiation, and cytokine production suppressed $CD4^+$ T cell activation **(Fig.1)**. In addition, curcumin increased CCR7, L-selectin, and TGF-β expression at the late phase of T cell activation. Moreover, TGF-β is involved in curcumin-mediated late-phase Treg cells generation and the regulation of T cell activation **(Fig.1)**. Curcumin trough augmenting CCR7, CD69, TGF-β and L-selectin expression followed by Treg cells generation not only blocks but regulates $CD4^+$ T cell activation [52] **(Fig.1)**.

$CD4^+CD25^+$ Treg cells have a pivotal role in regulating the immune responses and critical to the maintenance of immunological tolerance to peripheral self-antigens and suppressing deleterious immune responses to the host [27], whereas Th17-cells contribute to the development, induction and progression of auto-inflammatory disorders [53]. Breaking the balance between Treg cells and Th17-cells was favoring the pro-inflammatory Th17 responses and recently implicated in several autoimmune diseases [53] raising the possibility of discovering orally available small molecules which can modulate the function of Th17 cells or the downstream signaling of the IL-17 receptor [54]. Therefore, inhibiting the master regulator of Th17 cells, RORγt, is a potential therapeutic target for the treatment of inflammatory and autoimmune disorders [54]. The role of Th17 cells in the immunopathology of neuroinflammatory disorders such as MS, AD, PD, and

schizophrenia has been clarified recently [55]. The expression of the IL-17A and RORγt, a Th17 cell related cytokine profiles, was significantly reduced in curcumin-treated groups. These findings showed that curcumin inhibited the induction, differentiation, development, and progression of Th17 cells in Th17-related disorders [56] **(Fig.1)**.

Curcumin supplementation inhibits the suppression of $CD4^+CD25^+$ Treg cells [57]. According to the role of curcumin in modulating Treg cells populations and function, it may be feasible in some cases to use curcumin as an immunotherapeutic agent for Treg-mediated diseases, such as sepsis and tumors. These results collectively indicate that curcumin is an immunomodulatory and immunosuppressive agent which inhibits cell-mediated cytotoxicity (CMC), cell proliferation, and pro-inflammatory cytokines production through inhibiting NF-kB activation and its nuclear translocation **(Fig.1)**.

Curcumin on Th balance in autoimmune disease

Autoimmune diseases are mainly caused by the immunological intolerance to self-antigens [27]. Myasthenia gravis (MG) is mainly caused by loss of self-tolerance, which allows the development of autoreactive lymphocytes [58]. The exact mechanisms involved in the failure of self-tolerance in autoimmune diseases have not been fully elucidated, one possible mechanism is deficits in numerical, functional, and migratory properties of Tregs cells [58]. When the safety and efficacy of curcumin in experimental autoimmune myasthenia gravis (EAMG) were investigated, curcumin administration ameliorated the clinical manifestation of EAMG, down-regulated the expression of MHC class II and CD80 and CD86 co-stimulatory molecules, suppressed the levels of pro-inflammatory cytokines and up-regulated the levels of anti-inflammatory cytokines [59]. Curcumin administration shifted the balance of Th1/Th17 toward Th2/Treg and promoted the differentiation of B cells into a subset of B10 cells [59]. Therefore, curcumin effectively ameliorates the clinical score of EAMG and is a potential management option for the treatment of MG.

IPEX syndrome is an autoimmune disease in boys which is lethal and is caused by mutations in the FoxP3 gene scurfin (scurfy) [60, 61]. The product of the Scurfin gene is required for the development of $CD4^+CD25^+$ Treg cells [61]. Currently, there are no effective therapies for IPEX and immunosuppressive therapy in patients is generally ineffective and causes several side effects [60, 61]. Curcumin administration via suppressing the Th1/Th2/Th17 responses in mice

attenuated the scurfy-induced immune disorder, a model of IPEX syndrome [62]. Curcumin administration reduced all of the Th1/Th2/Th17 cell populations and attenuated clinical symptoms of scurfy mice.

A good animal model for MS is an experimental autoimmune encephalomyelitis (EAE). It is a Th1 cell-mediated autoimmune demyelinating disease of the nervous system [63]. IL-12 trough inducing Ag-specific Th1 cells has a crucial role in the pathogenesis of CNS demyelination in EAE model and MS patients. Curcumin exhibits an inhibitory effect on the generation of pro-inflammatory cytokines by human macrophages and monocytes ages and has inhibited the STAT-4 activation and IL-12 production in the EAE model [44]. Curcumin by reducing the IL-12 production from macrophage/microglial cells and suppressing the neural Ag-specific Th1 cells differentiation significantly reduced the clinical severity and duration of EAE [44]. The EAE mice express higher levels of IFN-γ, IL-12, IL-17, and IL-23 in the CNS and lymphoid organs which significantly decreased following curcumin treatment. Curcumin treatment resulted in a decrease in the secretion of IFN-γ, IL-12, IL-17, and IL-23 in-vitro and in-vivo [64] **(Table.1. and .2).** Curcumin also up-regulates the $CD4^{+}CD25^{+}$ $FoxP3^{+}$ Treg cells populations, peroxisome proliferator-activated receptor γ (PPARγ) and IL-10 expression in the lymphoid and CNS organs of EAE mice [64] **(Fig.1)**. The Janus kinase-STAT pathway inhibition by curcumin markedly decreased Th1 differentiation and T cell proliferation by inhibition of IL-12 [65-67] **(Fig.1)**.

Effects of nanocurcumin supplementation on Th17 cells frequency, transcription factor expression, and Th17-related cytokines expression in healthy controls and patients with relapsing-remitting multiple sclerosis (RRMS) and also from patients whose received placebo at baseline and after 6 months of treatment were investigated [68]. Results showed that Th17 cells population in MS patients when compared with the healthy control group significantly increased. The nanocurcumin group showed a significant reduction in Th17 associated parameters such as Th17 proportions, RORγt, and IL-17 expression and also IL-17 secretion, but mRNA expression and protein levels of IL-23 were not significantly changed. While, in the placebo group, there are no significant changes in these parameters. Results imply that the increase in Th17 cells proportion might contribute to the pathogenesis of RRMS and nanocurcumin is able to restore these Th17 cells dysregulated populations in MS patients [68]. These findings showed that

curcumin differentially regulates $CD4^+$ T helper cell responses, reduced the duration and clinical severity of EAE by inhibiting IL-12 signaling in T cells and suggest its use in the treatment of MS and other Th1 and Th17-mediated autoimmune conditions [67-70]. Therefore, curcumin by influencing the Th1 and Th17 balance and secretion of pro-inflammatory mediators is a novel potential natural therapeutic agent for MS treatment.

Curcumin as a natural immunosuppressant agent has a bright prospect for preventing periodontitis and RA [71]. Periodontitis is a rising public health problem as well as a risk factor for the development of RA. It is mainly triggered by *Porphyromonas gingivalis* [72]. *P. gingivalis* in humans and animal models is able to induce experimental autoimmune arthritis through its unique bacterial peptidyl arginine deiminase [73, 74]. Curcumin appears to be an effective anti-bacterial agent against *P. gingivalis* biofilm formation and infection [71]. Curcumin also exerts unique immunosuppressant properties through the promotion of Treg cells population and inhibition of Th17 pro-inflammatory responses suppressing autoimmunity [71] **(Fig.1)**. Results affirmed that curcumin as a natural product is a potent protective compound for the management of both periodontitis and also RA.

Curcumin has been shown to ameliorate various nicotine-induced chronic inflammatory disorders [75]. The cytokines profile of Th1 and Th2, mRNA and protein expression of cytokines, transcription factors (AP-1), regulatory molecule (P53), growth factors (GM-CSF; TGF-β) in female Wister rats were determined to understand the mechanisms of curcumin action in this area. Data showed that the nicotine through up-regulation and down-regulation of different factors induces Th1/Th2 balance disruption. The study demonstrated that this Th1/Th2 imbalance was safely and effectively restored by curcumin administration [76].

The Th subsets imbalance is implicated in the pathogenesis of SLE [12]. Curcumin was added after stimulating $CD4^+$ T cells from untreated SLE patients and healthy volunteers with Th17 differentiating factors. After curcumin administration Th17 percentages decreased, IL-17A productions reduced, Treg cells populations and subsequently TGF-β1 productions increased. These findings were not observed in $CD4^+$ T cells cultures of individuals without SLE [77]. This shows that curcumin could rebalance Th17/Treg imbalance of SLE patients.

Effects of curcumin on Th subset balance in psoriasis

Psoriasis is an inflammatory disease of the skin which is characterized by keratinocytes hyper-proliferation and leukocytes infiltration [78, 79]. Recent evidence showed that several cytokines are involved in their pathogenesis [78-81]. It was suggested that the IL-17A/IL-23 cytokine axis have an important role in the pathophysiology of psoriasis [80, 81]. Curcumin besides its anti-bacterial and antioxidant activity is also able to decrease the expression of pro-inflammatory cytokines in keratinocytes [82-84]. Results showed that the curcumin gel formulation when used topically effectively suppressed imiquimod (IMQ), -induced psoriasis-like inflammation[83, 84]. In addition, curcumin by inhibiting IL-1β/IL-6 production indirectly down-regulated IL-17A and IL-23 expression [83, 84]. Thus, curcumin is able to ameliorate inflammation induced in the IMQ-induced psoriasis-like mice model by directly down-regulating pro-inflammatory cytokines production.

Effects of curcumin on Th1/Th2 and Th17/Treg balance in IBD

IBD is a disease of the gastrointestinal tract which mainly divided into two major subgroups: Ulcerative Colitis and Crohn's disease [85, 86]. Ulcerative colitis is an inflammatory disorder of the mucosa of the colon that affects millions of people worldwide and impairs their quality of life. While the etiology of IBD is not completely determined, it appears to be induced by pro-inflammatory cytokines such as TNF-α [85, 86]. Emerging evidence shows intriguing pharmacological effects of curcumin [44, 45, 47]. These include inhibitory effects on inducible nitric oxide synthase (iNOS), Cyclo-oxygenase (COX)-1 and-2, lipoxygenase (LOX), TNF-α, IFN-γ, and the NF-kB [44]. NF-kB is an essential factor for up-regulation of pro-inflammatory cytokines that increase in inflammatory diseases [44]. Recently, the safety and therapeutic effects of curcumin have been evaluated in various experimental models of IBD [44]. Curcumin changes the cytokine profiles of Th1 cells toward the anti-inflammatory Th2 type [87]. The safety profile and inhibitory effects of curcumin on major pro-inflammatory mediators suggest that it has a promising future for the treatment of patients with IBD [87]. Mitogen-activated protein kinases (MAPKs) and the c-Jun N-terminal kinase (JNK) modulate the transcription and expression of several genes that are involved in the inflammatory process of various chronic inflammatory diseases such as ulcerative colitis [85, 86]. Trinitrobenzene sulphonic acid (TNBS)-induced colitis, an animal model of IBD, has been described as Th1-mediated inflammation. The TNBS-induced colonic injury was also characterized by an increase of the TNF-α and reduction of the

IL-10. Curcumin decreased the expression of Th1-related cytokines and increased the expression of Th2-related cytokines in the mucosa of the colon [88]. Curcumin exerted therapeutic effects on colitis by modulating the Th1/Th2 balance and regulating the shift from Th1 to Th2 responses in TNBS-induced colitis [88]. Curcumin reduced the p38 MAPK activation and decreased COX-2 and iNOS expression. Also, the levels of TNF-α were significantly decreased and the IL-10 production was significantly increased in curcumin-treated rats [89, 90]. $CD4^+$ T lymphocytes proliferation was induced and secretion of Th2-related cytokines such as IL-4 and IL-5 were significantly increased by ConA and reduced by curcumin [91] **(Fig.1)**.

In colitis mice, curcumin notably increased $CD4^+CD25^+FoxP3^+$ Treg cells, while the secretion of TNF-α, IL-2, IL-6, IL-12 p40, IL-17 and IL-21 and the expression of co-stimulatory molecules such as TLR4, CD54, CD205, CD252, CD254, and CD256 on DCs were significantly decreased **(Fig.1)**. Curcumin potentially suppresses DCs maturation, induce tolerogenic option, and modulates DCs activation to enhance the inhibitory functions of Treg cells in colonic mucosa of the IBD model [92]. Also, curcumin Nanoparticle administration increased $CD4^+CD25^+FoxP3^+$ Treg cells expansion in the colonic mucosa of experimental colitis [93]. In conclusion, the inhibition of NF-κB expression and p38MAPK signaling by curcumin could explain the reduced COX-2, iNOS, and inflammatory cytokines (TNF-α, IL-2, IL-6, IL-12 p40, IL-17 and IL-21) expression in colonic mucosa and reducing the development of chronic experimental colitis. Therefore, in animal models of IBD and in humans, curcumin has demonstrated therapeutic potential.

Effects of curcumin on Th1/Th2 and Th17/Treg balance in asthma and allergy

Asthma and allergy worldwide increased particularly in industrially developed countries over the last few decades. Thus, recent progress has been made to explore novel alternative therapies includes herbal medicines. Curcumin has traditionally been used and recently has been shown to be effective in a treat and ameliorating inflammatory and immune-mediated disorders such as fever, pain, asthma, bronchitis, arthritis, dermatitis, and allergic inflammation [94]. A murine model of latex allergy showed an increase in the Th2 type of immune responses [95]. Latex-sensitized mice showed an increased in serum IgE, latex specific IgG1, IL-4, IL-5, IL-13, eosinophils count, and lungs inflammation [95]. Treatment of Latex-sensitized mice with curcumin showed a significant reduces in Th2-related responses with a simultaneous reduction in

eosinophils count. Inflammation of lung in curcumin-treated mice was markedly reduced and expression of co-stimulatory molecules on macrophages and DCs were significantly decreased [95]. Further, the anti-asthmatic properties of curcumin, through the intranasal route in an ovalbumin (OVA)-challenged asthma mouse model has been evaluated. Exposure to LPS by increasing IgE level, Th2-related cytokine IL-4, and IL-5 expression, and histamine release, exacerbates airway inflammation. administration of curcumin through the intranasal route reduced airway inflammation and exacerbation, whereas dexamethasone, was not as good as curcumin [96].

The effect of curcumin on the lymphocytes of atopic asthmatic patients was investigated. Lymphocytes stimulated with Dermatophagoides farinea in the absence or presence of curcumin. The protein levels of IL-4, IL-5, and GM-CSF in the culture supernatants were determined. Curcumin inhibited Dermatophagoides farinea-induced lymphocyte proliferation and IL-2 production **(Fig.1)**. IL-2 administration in the presence of curcumin restored the proliferative capacity of lymphocytes to Dermatophagoides farinea. Moreover, curcumin in a dose-dependent manner inhibited IL-4, IL-5, and GM-CSF production [97].

The protective effects of curcumin on food allergies in OVA and alum immunized mice were investigated. Results showed that curcumin significantly attenuated increased levels of IgE, IgG1, and MCP-1 in OVA-immunized mice. Furthermore, curcumin as an anti-allergic agent showed an immunosuppressive and immunoregulatory effect through modulating Th1/Th2 balance [98]. Also, curcumin strongly suppressed Th17 cells expansion and increased Treg cells populations **(Fig.1)**. Curcumin substantially decreased IL-17A level and increased IL-10 level, blocked OVA-induced increases in eosinophils and significantly rebalanced Treg/Th17 imbalance in bronchoalveolar lavage fluid and in the lung [99]. Curcumin administration significantly attenuated the inflammatory conditions in the asthma model by regulating Treg/Th17 balance [99]. These results suggest that curcumin administration as a therapeutic drug may be useful for controlling amelioration of Th2-mediated allergic diseases.

Effects of curcumin on Th1/Th2 and Th17/Treg balance in organ transplantation

DCs and Treg cells are essential factors in the development of organ transplant tolerance. Curcumin arrests DCs maturation and differentiation and induces a tolerogenic phenotype which increases $CD4^{+}CD25^{+}FoxP3^{+}$ Tregs cells populations and suppressive functions in-vitro and in-

vivo [100] **(Table.1. and .2)**. Curcumin-treated DCs demonstrated a significant reduction in co-stimulatory molecules expressions. Curcumin-treated DCs also decreased their IL-12 mRNA expression and protein secretion. Functionally, the allostimulatory capacity of DCs and intracellular IFN-γ expression in response to T cells stimulation significantly decreased. Hypo-responsiveness of T cell was arising from the generation of $CD4^{+}CD25^{hi}CD127^{low}$ $FoxP3^{+}$ Treg cells phenotype that put on suppressive effects on naïve $CD4^{+}$ T cells, although the effect was not specific to the antigen. DCs treated with curcumin promoted the development of $CD4^{+}CD25^{+}FoxP3^{+}$ Tregs and reduced subsequent alloproliferative capacity in mice [100].

The effect of curcumin in the prevention or progression of acute graft-versus-host disease (GVHD) in a murine model were investigated [101] **(Table.1. and .2)**. When treated with curcumin the acute GVHD mice showed a reduction in the severity of acute GVHD. While flow cytometric analysis showed that in the curcumin-treated acute GVHD mice the number of $CD4^{+}CD25^{+}FoxP3^{+}$ Tregs cells populations, as well as the CD8+ Treg cells, were notably increased [101]. Therefore, these results collectively revealed that curcumin by up-regulation of Treg populations percentage and functions has protective effects on acute GVHD.

Curcumin on Th1/Th2 and Th17/Treg balance in cancers

Tumor cells escaping from the immune system are mostly targeted and inhibited by effector and memory T cells function [102-104]. Curcumin, by targeting several molecular molecules and transcription factors, has shown great antitumor activity. Several pieces of evidence have shown the immune-protective potential of this natural polyphenol against tumor cells [105, 106]. Effect of curcumin on prevention of tumor-induced immune dysfunction was examined and results showed that in tumor-bearing hosts, curcumin inhibited loss of T-cell populations, expanded central and effector memory T cell percentage, reversed the Th2-related immune responses and prevented T-cell proliferation inhibition [107]. Moreover, tumors up-regulated Treg cell populations and induce the production of the immunosuppressive cytokines such as TGF-β and IL-10 [108]. Curcumin also enhances $CD8^{+}$ T cells cytotoxicity against tumors by changes in the tumor microenvironment. Moreover, results showed that the accumulation and function of T-cells were increased through the inhibition of different immunosuppressors agents [109]. In patients with colon cancer after curcumin therapy, there was a suppression of the FoxP3 gene expression showing a reversal of bounding of FoxP3 to T-bet which prevented IFN-γ expression

[110]. Collectively, in contrast to other conditions which curcumin increased Treg cells population and suppressed Th1 responses, in cancer microenvironment, curcumin treatment convert Tregs to Th1 cells by increasing IFN-γ production and suppressing FoxP3 expression. Due to the various properties of curcumin in cancer, asthma, allergy, transplantation, and autoimmune disease, understanding the mechanisms of action of curcumin is an intriguing challenge. Collectively, these findings indicate that curcumin could be exploited for the prevention and management of tumor-induced immune system suppression and may have the potential for clinical application.

Conclusion and future perspectives

In brief, curcumin has potent immunosuppressive properties both *in vitro and in-vivo*. Curcumin has the potency to selectively enhance the function and number Tregs as well as suppress macrophage and DC-mediated differentiation of Th1 and Th17. The effects of curcumin on Th9 and Th22 are unclear and need further investigations. Emerging evidence points towards curcumin having a therapeutic potential in Th1-, Th2- and Th17-driven inflammatory as well as autoimmune diseases. However, confirmatory clinical data from randomized controlled trials would be integral to introduce curcumin to the armamentarium of drugs for these diseases.

Conflict of interests: None.

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Table 1. In-vitro studies that have evaluated the effects of curcumin on Th balance.

Cell lines	Curcumin dose	Duration	Effects	Reference
T cells	50 mg/kg (low-dose group) or 100 mg/kg curcumin	11 to 45day	Down-regulated the levels of pro-inflammatory cytokines (IL-17, IFN- α and TNF- α) and up-regulated the levels of the anti-inflammatory cytokine IL-10	[1]

	(high-dose group)			
Human chondrocytes	50 μM curcumin	4 & 24 hrs	Resveratrol suppressed NF-κB-regulated gene products involved in inflammation (cyclooxygenase-2, matrix metalloproteinase (MMP)-3, MMP-9, vascular endothelial growth factor), inhibited apoptosis (Bcl-2, Bcl-xL, and TNF-α receptor-associated factor 1) and prevented activation of caspase-3. IL-1β-induced NF-κB activation	[2]
T cell	2.5, 5 and 10 μm	0 to 4 days	Regulation of T helper 1 (Th1) and Treg	[3]
Raw264.7 cells	200 mg/kg		Inhibition of NF-kb activation in the asthmatic lung tissue	[4]
T cells	1% curcumin	92.5 days	Decreased all of the Th1/Th2/Th17 cell populations	[5]
Intestinal epithelial cells	(0–150 mm)	45 min	Inhibited IL-1b-mediated ICAM-1 and IL-8 gene expression in IEC-6, HT-29, and Caco-2 cells. Cytokine-induced NF-kb DNA binding activity	[6]
T-lymphocyte	5, 10 and 20 μm	120 h	Inhibits IL-2 signaling by reducing available IL-2 and high-affinity IL-2R, as well as interfering with IL-2R signaling	[7]
Stromal cells isolated from women with endometriosis	1, 10, 30 or 50 mm	24 hrs	Inhibited TNF-a-induced secretion of IL-6, IL-8 and MCP-1.	[8]
Human peripheral blood mononuclear cells	1.5 and 13.6 mm		Modulates the expression profile of Th1 cells	[9]
T cells	0, 5, 10 and 20 μm	0 to 6 hours	Expression of the anti-apoptotic protein Bcl-2.	[10]
T cells	0, 2.5, 5, 10, and 25 μg/ml	30 min	Induced a dose-dependent decrease in JAK and STAT phosphorylation	[11]
Lymphocytes	Cr, 10 PM	3 days	Curcumin inhibited IL-5, GM-CSF, and IL-4 production in a concentration-dependent manner.	[12]
Monocytes and alveolar macrophages	0.5m 5 m 1 and 10 μm	24 hrs	The inhibitory effect on the production of IL-8, MIP-1a, MCP-1, IL-1b, and TNF-a by PMA- or LPS-stimulated monocytes and alveolar macrophages	[13]
γδ T cells	1 μm 10 μm 30 and 75 μm	16, 24 hrs	Inhibited isopentenyl pyrophosphate-induced release of the chemokines macrophage inflammatory protein- 1α and -1β and RANTES. Curcumin also blocked isopentenyl pyrophosphate-induced activation of NF-kb and AP-1.	[14]
Neutrophilic	25, 50 and 75 μm	6 hrs	Curcumin was found to inhibit LPS-induced cytokine production, includingmip-1α, MIP-1β, IL-6, IL-8 (CXCL-8) and GRO-α.	[15]
Myeloma cells	10 μm and 100 μm	30 min, 8 hrs	Curcumin was a potent inhibitor of STAT3 phosphorylation, and this plays a role in the suppression of MM proliferation	[16]
Human mantle cell lymphoma	10, 25, 50 and 100 μm	8 hrs.	Downregulated constitutive active NF-kb and inhibited the constitutively active IkB kinase (IKK), and phosphorylation of IkB and p65. Curcumin also	[17]

			inhibited constitutive activation of Akt, needed for IKK activation.	
Dendritic cells	0, 1, 5 10 and 25 µm	45 min	Induction of Th1 responses and a normal cell-mediated immune response.	[18]
SUIT-2	0 µm, 10 µm, 50 µm, and 100 µm	2 hrs	*IL-8* was inhibited NF-kb activity was reduced	[19]
EAC cell lines, OE33, and OE19	50mm nano-curcumin	48 hrs	Decreased the secretion of pro-inflammatory cytokines from *in vitro* activated T cells	[20]
CD4+ T cells	0.5, 1.0, 2.5, 5.0 mg	48 hrs	Inhibition of IL-12 production by macrophages stimulated in vitro with either LPS or HKL, leading to the inhibition of Th1 cytokine profile (decreased IFN-γ and increased IL-4 production) in CD4+ T cells. These findings suggest that curcumin may inhibit Th1 cytokine profile in CD4+ T cells by suppressing IL-12	[21]
T cells	20 µg	18 hrs	Decreases IL-12-induced STAT4 phosphorylation, IFN-γ production, and IL-12 Rβ1 and β2 expressions.	[22]
CD 4+ monocytes	20µm or 30µm		Cytokine and chemokine expression and reducing both migration and endocytosis	[23]
CD8 cytotoxic T lymphocytes Mice	10 mm	24 hrs	Inhibited the suppressive activity of Treg cells by downregulating the production of TGF-b and IL-10 in these cells	[24]
T-cell lymphoma cell lines	5–20 mm	48 hours	Curcumin selectively induces apoptosis in association with the downregulation of STAT-3 and NF-kb signaling pathways in CTCL cells	[25]
Human peripheral blood mononuclear Cells	With dose of 0.01 0.1, 1, 5 & 10 µm for 48 hours	48 hrs.	Shift the Th1–Th2-type immune balance towards Th2-type immunity	[26]
BV2 cell line	5 and 10 µm		Inhibited the phosphorylation of STAT1 and 3 as well as JAK1 and 2 in microglia activated with gangliosides, LPS, or IFN-γ.	[27]
Colonic myofibroblasts	5, 10 and 20 µm	30 min, 24 hrs	Reduced p38 MAPK activation in curcumin-treated mucosal biopsies enhanced IL-10 and reduced IL-1b. We demonstrate dose-dependent suppression of MMP-3 in CMF with curcumin.	[28]
T cell	2.5, 5 & 10 µm	24 hrs.	Curcumin suppresses NF-κB activation.	[29]
Murine macrophage-like cells RAW264.7	1, 25, 50 µm	12 hr [30]s.	Inhibited the production of pro-inflammatory cytokine IL-18 in E. Coli LPS stimulated murine macrophage-like cells RAW264.7	[30, 31]
Carcinoma cell lines of the Pancreas (bxpc-3, Hs-700T and Hs-766T, aspc-1, PANC-1, Capan-1 and Capan-2)	0.1, 1, 10 and 100 µm		Curcumin (diferuloylmethane), NF-κB inhibitor	[32]
Murine spleen lymphocytes	0, 3. 125, 6. 25, 12.5, 25, 50, 100, 200/µmol/L	24 hrs	Suppress the expression of NF~B p65	[33]

Human monocytes	1.5-12.5µm	72 hrs	Suppressed NF-κB binding and cytokine Release in THP-1 cells	[34]
Cytotoxic T lymphocytes	12.5–30 mmol/L	8 hrs	Interleukin-2 (IL-2) or alloantigen-induced proliferation of splenic lymphocytes, and development of cytotoxic T lymphocytes is significantly suppressed	[35]
Mouse RAW264.7 macrophages	1–100µm	1 hrs	Inhibition of NF-κB nuclear translocation as well as the induction of downstream inflammatory mediators including pro-inflammatory cytokine mrna and protein (tumor necrosis factor-α, interleukin-1β, and interleukin-6).	[36]
Human monocytic macrophage cell line	0.3, 2.5 and 5 µm	30-6-min	Inhibited lipopolysaccharide (LPS)-induced production of TNF and IL-l by a human monocytic macrophage cell line, Mono Mac 6.	[37]
Human keratinocyte cell line HACAT	20 µm	24 hrs	Inhibited the expression of TNF-α-induced IL-1ß, IL-6, and TNF-α, but not IL-8, in TNF-α-treated HACAT cells as well as the TNF-α-induced cyclin E expression. In addition, curcumin inhibited the activation of MAPKS (JNK, p38 MAPK, and ERK) and NF-κB in TNF-α-treated HACAT cells.	[38]
Dendritic cells	25 µm	24 hrs	Reduced IL-6 and IL-23	[39]
CD4+ T cell cultures of SLE patients	0.1 and 1 µg/ml	72 hrs	Reduce IL-17A	[40]
Dendritic cells	25 mm		Development of foxp3+ Tregs and reduced subsequent alloproliferative capacity	[41]
Dendritic cells	10 or 50 mm	24 hrs	Curcumin-treated DC induced differentiation of native CD41 T cells into Treg resembling Treg in the intestine, including both CD41CD251 Foxp31 Treg and IL-10- producing Tr1 cells. Such Treg induction required IL-10, TGF-b and retinoic acid produced by curcumin-modulated DC.	[42]
Human CD4+ T cells	0.2 or 2 mg/ml of Curcumin	3 days	Curcumin not merely blocks, but regulates CD2/CD3/CD28-initiated CD4+ T cell activation by augmenting CD69, CCR7, L-selectin and TGF-b1 expression followed by regulatory T cell generation	[43]
CD4+CD25+ T cells	5, 10, 20 µM	36 hours	Suppress IL-2 production Foxp3 expression was also reduced On Tregs after curcumin stimulation	[44]
T-cell	60 mmol/L	24 hrs	CD8 T-cell activation was significantly Increased when cocultured with curcumin-pretreated	[45]

Table 2. In vivo and clinical studies that have evaluated the effects of curcumin on Th balance.

Animal	**Curcumin dose**	**Duration**	**Route**	**Th1 Th2 Th17 Treg**	**Reference**
Rat	(30 mg·kg-1·d-1, ip) for 15 days	15 days	i.p	Decreased the expression of Th1 cytokines increase the expression of Th1 cytokines	(46)
Rat	200 mg/kg	2, 4 & 6 hrs	i.p	Increase in messenger RNA levels and protein content of tumor necrosis factor-α,	(47)

				interleukin-6, and matrix metalloproteinase-9	
Rat	50 mg/kg (low-dose group) or 100 mg/kg curcumin (high-dose group)	45 days	i.p	Lowering circulating TNF-α concentration	(48)
Mouse	300 µg curcumin (Sigma) in 1% carboxymethyl cellulose		oral	Inhibited the phosphorylation of the p65 subunit of NF-κB in BMMCs	(49)
Rat	50 or 100 µg	days 0 to 25		Inhibits EAE by blocking IL-12 signaling in T cells and suggest its use in the treatment of MS and other Th1 cell-mediated inflammatory diseases	(50)
Mouse	Curcumin gel (curcumin 1 g, HPC 3 g, azone 1 g, ethanol (96%) 17 g, and distilled water q.s. to 100 g.	10 days		Was capable of impacting the IL-23/IL-17A axis by inhibiting IL-1b/IL-6 and then indirectly down-regulating IL-17A/IL-22 production.	(51)
Mouse	curcumin (0.1–1%)	Diet		Curcumin demonstrates limited effectiveness on Th-1 mediated colitis in IL-10-/- mice,	(52)
Rat	100 mg/kg	6 days	intragastric	Reduce serum TNF-α and IL-6 levels	(53)
Rat	80 mg/kg body weight/day	21 days	oral	Th1/Th2 balance through upregulation and downregulation of different factors	(54)
Rat	30 mg	15 days	i.p	Increased proportion of IFN-γ/IL-4 in splenocytes and circulation. Dex and Cur+Dex decreased the expression of Th1 cytokines but could not increase the expression of Th2 cytokines and the proportion of IFN-γ/IL-4. Cur exerted therapeutic effects on colitis by regulating the shift from Th1 to Th2	(46)
Mouse	curcumin gel	12 days		Relieving TPA-induced inflammation by directly down-regulating IFNγ production	(55)
Human	10 µm	30 days		After the curcumin therapy, the Forkhead box protein (Foxp) 3 positive Treg frequency was markedly reduced, the frequency of Th1 cells was significantly increased in Cca patients.	(30)
Rat	50–100 mg/kg/day	2 week	Oral	Curcumin significantly attenuated the damage and caused substantial reductions of the rise in MPO activity and tumor necrosis factor alpha (TNF)-α. Also, curcumin was able to reduce nitrites colonic levels and induced downregulation of COX-2 and iNOS expression, and a reduction in the activation of p38 MAPK;	(56)

Mouse	50, 100 and 300 mg/kg	10 days		Curcumin also reduced the levels of nitric oxide (NO) and O2-associated with the favorable expression of Th1 and Th2 cytokines and inducible NO synthase. These findings suggest that curcumin or diferuloylmethane, a major component of the food flavor turmeric, exerts beneficial effects in experimental colitis and may, therefore, be useful in the treatment of IBD.	(57)
Murine	360mg/dose	3 or 4 times/day for three months		The inhibitory effects of curcumin on major inflammatory mechanisms like COX-2, LOX, TNF-α, IFN-γ, NF-kB and its unrivaled safety profile suggest that it has bright prospects in the treatment of IBD	(58)
Rat	20 mg	20 days	i.p	downregulation of Th1 cytokine response and NO production by macrophages, and their upregulation in NK cells	(59)
Rat	1% Cur or 0.02%	2 week	diet	suppressed (P , 0.05) NF-kB p65 nuclear translocation in activated CD41 T-cells.	(60)
Muse	10 mM; 100 µl/mouse	28 days	IP	up-regulated activities of the antioxidant enzymes, and suppressed serum levels of TNF-α and IL-1β.	(61)
Mouse	250 µg		intragastric	suppression of Th2 responses as evidenced by reduced IL-4 and IL-13 production and depletion of eosinophils in the lungs, and attenuation of lung inflammation through expression of molecules such as TSLP, MMP-9, and OAT.	(62)
Mouse	5 and 10 mg/kg	9th to 14th day	i.n	Th2 cytokine, IL-5 is responsible for eosinophil and neutrophil recruitments to the lungs and TNF-a release.	(63)
male BALB/c and SJL/J mice	2 %	7 days	diet	Secretion of IL-4 and IL-5 by CD4+ lymphocytes of BALB/c mice but not SJL/J mice was significantly augmented	(64)
Mice	3 mg/ kg or 30 mg/kg	16 days	oral	maintaining Th1/Th2 balance	(65)
Rat	(50–100 mg/kg/day)	2 week	Oral gavage	downregulation of COX-2 and iNOS expression, and a reduction in the activation of p38 MAPK	(56)
Mouse	(50 mg/kg, 100 mg/kg, 200 mg/kg).	28 days	ip	Th17 cells and significantly increased Treg cells.	(66)
Mouse	100 µg	14 days		IL-12 and IL-23 that decreased after treatment with curcumin.	(67)
Mouse	2%	22 days	diet	enhanced STAT3 phosphorylation and suppressed expression of *Il12b* and *Il23a*.	(68)
Mouse	1%	18 and 32 week age	diet	decreased the proteinuria level and serum levels of IgG1, IgG2a and anti-dsDNA IgG antibodies in NZB/W F1 female mice	(69)
Rat	40 mg/kg	7 days	gavage	Curcumin pretreatment significantly inhibited the expression of IL-1β, IL-2, and	(70)

				IL-6.	
Mouse	7mg/mL	5 days	ip	CD8 T-cell activation was significantly increased when co-cultured with curcumin pretreated	(45)
Mouse	Nanoparticle curcumin	7 days		suppressed mucosal mRNA expression of TNF-α, IL-1β, IL-6, CXCL1 and CXCL2 in colonic epithelial tissues.	(71)

Figure 1. Effect of curcumin on T helper cells differentiation, survival, proliferation, polarization, and functions. Curcumin has potent immunosuppressive and immunomodulatory effects on T helper cells in-vitro and in-vivo. Curcumin has the potency to selectively enhance Tregs percentage and function and suppress macrophages and DCs maturation-mediated Th1 and Th17 differentiation. Therefore, curcumin may be an effective therapeutic agent for Th1-, Th2-, and Th17-driven inflammatory and autoimmune diseases and its use may thus be useful as a good strategy to treat inflammatory and autoimmune diseases. The effects of curcumin on Th9 and Th22 in unclear and need investigations.