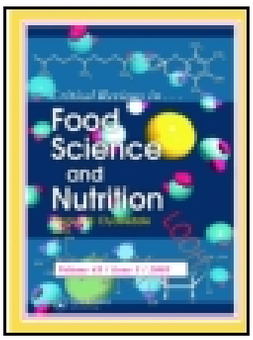

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Immune Modulation by Curcumin: The Role of Interleukin-10

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Abstract

Cytokines are small secreted proteins released by different types of cells with specific effects on cellular signaling and communication *via* binding to their receptors on the cell surface. IL-10 is known to be a pleiotropic and potent anti-inflammatory and immunosuppressive cytokine that is produced by both innate and adaptive immunity cells including dendritic cells, macrophages, mast cells, natural killer cells, eosinophils, neutrophils, B cells, $CD8^+$ T cells, and T_H1, T_H2, and T_H17 and regulatory T cells. Both direct and indirect activation of the stress axis promotes IL-10 secretion. IL-10 deregulation plays a role in the development of a large number of inflammatory diseases such as neuropathic pain, Parkinson's disease, Alzheimer's disease, osteoarthritis, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, type 1 diabetes, inflammatory bowel disease, and allergy. Curcumin is a natural anti-inflammatory compound able to induce the expression and production of IL-10 and enhancing its action on a large number of tissues. *In*

vitro and in pre-clinical models curcumin is able to modulate the disease pathophysiology of conditions such as pain and neurodegenerative diseases, bowel inflammation, and allergy, but also of infections and cancer through its effect on IL-10 secretion. In humans, at least one part of the positive effects of curcumin on health could be related to its ability to enhance IL-10 – mediated effects.

Key words

Chronic diseases; Curcumin; Human health; Inflammation; Interleukin-10

Turmeric

Turmeric, *Curcuma longa* L. (Zingiberaceae family), is a small tropical tree that originated and is cultivated extensively in southern Asia (e.g., India and Bangladesh) and in East Asia (e.g., Japan). The root and rhizome of the plant have been used in traditional medicine for centuries, dating back to 600 BC (Pari et al., 2008).

Chemical Composition

The dried rhizome of *Curcuma* spp. contain turmerin (a water-soluble peptide), essential oils (d-a-phellandrene, cineol, d-borneol, d-sabinene, valeric acid), and curcuminoids as main phenolic compounds, including curcumin (diferuloylmethane) [1,7-bis-(4-hydroxy-3 methoxyphenyl)-1,6-heptadiene-3, 5-dione], demethoxycurcumin, cyclocurcumin and bisdemethoxycurcumin. Curcumin makes up 2 to 5% of the spice. Curcuminoids, responsible for the yellow color of the plant, can be defined as phenolic compounds derived from the roots of *Curcuma* spp. (Zingiberaceae). In addition, important volatile components of *Curcuma longa* L. (turmeric) include turmerone, atlantone, and zingiberene. Other components include various sugars, fats, minerals, proteins, and resins (Krishnaswamy et al., 1998; Maheshwari et al., 2006). Curcumin was first isolated in 1815 by Vogel and Pelletier. The crystalline form of curcumin, as diferuloylmethane, was identified in 1870 by Daube and the feruloylmethane skeleton of curcumin was described in 1910 by Lampe. Curcumin forms an orange/yellow crystalline powder and has been used to confer health benefits to people for many decades (Pari et al., 2008).

Therapeutic Uses and Pharmacological Characteristics of Curcumin

Turmeric has been used in Asian medicine since around 2000 BC. Turmeric is a very popular culinary spice and is also used in Ayurvedic medicine as an aromatic, stimulant and coloring agent. In traditional medicine, curcumin has been used to treat indigestion, throat infections, rheumatism, sinusitis, common colds, and liver ailments, as well as topically to heal wounds or treat skin ulcers (Kunnumakkara et al., 2017).

Curcumin and curcuminoids have been shown by multiple lines of evidence to be effective therapeutic agents against several types of diseases such as cancer (Iranshahi et al., 2010;

Teymouri et al., 2016; Momtazi et al., 2016a; Momtazi & Sahebkar, 2016; Mirzaei et al., 2016; Ramezani et al., 2017; Rezaee et al., 2017), cardiometabolic diseases (Sahebkar, 2010; Sahebkar, 2013; Mohammadi et al., 2013; Sahebkar, 2014a; Panahi et al., 2014; Panahi et al., 2016a; Karimian et al., 2017; Ganjali et al., 2017), pulmonary diseases (Lelli et al., 2017), liver diseases (Momtazi et al., 2016b; Rahmani et al. 2016; Panahi et al., 2017a), and anxiety and depression (Esmaily et al., 2015; Panahi et al., 2015a). According to the recent studies, the antioxidant (Panahi et al., 2012a; Sahebkar et al., 2013; Panahi et al., 2015b; Sahebkar, 2015; Panahi et al., 2016b; Panahi et al., 2017b) and anti-inflammatory (Panahi et al., 2012b; Sahebkarb, 2014) effects are likely the most important medicinal properties of curcumin which have been shown in various pathophysiological conditions. Curcumin is in fact a potent free radical scavenger and inhibit COX2 and 5-lipooxygenase (5-LOX) expression and catalytic activity.

Curcumin is a potent immunomodulatory agent, as well. Curcumin can modify immune cell activity including T and B cells, macrophages, neutrophils, dendritic cells (DC) and natural killer cells (NKC). Curcumin down-regulates pro-inflammatory cytokines such as IL-1, IL-2, IL-6, IL-8, IFN-γ, as well as monocyte chemotactic protein 1-1 (MCP-1), iNOS and NO production in many pathological conditions (Ganjali et al., 2014; Ghandadi et al., 2016; Panahi et al., 2016c; Derosa et al., 2016; Abdollahi et al., 2017; Karimian et al., 2017). Curcumin inhibits the proliferation of lymphocytes and their ability to secrete IL-4, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF). On the other hand, curcumin can induce the expression and production of IL-10 to counteract inflammatory conditions. Some of the anti-inflammatory effects of curcumin include the inhibition of angiotensin-converting-enzyme (ACE) and a reduction in TNF-α, IL-12 activity and macrophage infiltration. Curcumin inhibits TGF-β and NF-κB signaling, as well as the expression of α-smooth muscle actin and Tenascin-C, an anti-adhesive protein (Kobayashi et al., 1997; Nanji et al., 2003; Sánchez-Calvo et al., 2009; Sunagawa et al., 2011).

The activity of matrix metalloproteinases (MMPs) and expression of adhesion molecules was suppressed by curcumin. Other important pharmacological properties of curcumin include anti-angiogenic, immunomodulatory, anti-diabetic, antiviral, antibacterial, anti-metastatic, anti-nociceptive cancer preventive, and potentially chemotherapeutic properties (Araujo & Leon,

2001; Chattopadhyay et al., 2004; Maheshwari et al., 2006; Singh & Khar, 2006; Aggarwal & Sung, 2009).

Given the chronic nature of the above reported diseases, the duration of treatment should be chronic as well. As it regards the daily dosage, it would be strongly variable depending of the largely different oral bioavailability of the different pharmaceutical forms available on the market.

Interleukin- 10

Cytokines are essential small secreted proteins released by different types of cells. They have specific effects on cellular signaling and communication *via* binding to their receptors on the cell surface (Borish & Steinke, 2003; Steinke & Borish, 2006; Commins et al. 2010). Cytokines play key roles in physiological and pathological processes in multicellular organisms through regulation of gene expression patterns, cytoskeleton organization, inflammation and immunomodulatory effects, and release of secretory vesicles (Borish & Steinke, 2003; Steinke & Borish, 2006; Commins et al. 2010).

Fiorentino first reported on the actions of IL-10 as an exquisite immune mediator in 1989 (Fiorentino et al., 1989). He demonstrated that T helper 2 (T_H2) cells are the main source of IL-10 production (Fiorentino et al., 1989). Now almost three decades later, IL-10 is known to be a pleiotropic and potent anti-inflammatory and immunosuppressive cytokine, that is produced by cells of both innate and adaptive immunity including dendritic cells (DC), macrophages, mast cells, natural killer (NK) cells, eosinophils, neutrophils, B cells and T cell subtypes especially the T_H2 and Treg cells (Moore et al., 2001). Astrocytes, microglia, and neurons are the major sources of IL- 10 production in the central nervous system (CNS). The major source of IL-10 in the periphery is macrophages (Kwilasz et al., 2015).

The expression of IL-10 is controlled on the transcriptional and post-transcriptional levels. Both direct (e.g., inflammation of the CNS through trauma, neurosurgery, or increased intra-brain pressure) and indirect (e.g., bacteremia) activation of the stress axis promotes IL-10 secretion. The IL10 gene is transactivated by the cAMP response element binding protein (CREB/ATF) in

monocytes and the signal transducer and activator of transcription molecules Stat1, Stat3, Stat4, Stat5, as well as Notch in T lymphocytes (Brenner et al., 2003; Chang et al., 2007). In addition to the above, activation of the p38 mitogen-activated protein kinase pathway results in IL-10 production (Sabat et al., 2010; Xu et al., 2013).

Physiological and pathological roles of IL-10

M2-like macrophages and regulatory T cells (Tregs) are two main anti-inflammatory leukocytes that produce IL-10 (Gabryšová et al., 2009). Monocyte/macrophage functions are suppressed by IL-10 action. IL-10 has been shown to inhibit the production of pro inflammatory cytokines IL-1β and TNF-α, as well as the expression of major histocompatibility complex (MHC) class II proteins, which are normally found on antigen-presenting cells. Co-stimulatory and adhesion molecules (CD86 and CD54) that stimulate a pro-inflammatory response in macrophages, were also inhibited by IL-10. Moreover, IL-10 inhibits the action of IL-12 and IL-23, known mediators of inflammatory immune response (McKinstry et al., 2009). Differentiation of Tregs is also increased by IL-10 (Heine et al., 2014).

T_H1/T_H2 balance is one of the most important aspects of the immunomodulatory action of IL-10. T_H1 and T_H2 play important roles in cell-mediated immunity and mucosal immunity, respectively. IL-10 enhances the activation and proliferation of B cells, which are important in the mucosal defense against bacterial toxins and intestinal parasites (Ng et al., 2013).

IL-10 stimulates multiple aspects of B cell function including differentiation, proliferation, survival, and antibody production. IL-10 also stimulates the proliferation of mast cells and thymocytes. In contrast, IL-10 can suppress IL-2 production and CD28 signaling and this inhibits the activation and proliferation of T cells (Chinen et al., 2016).

Finally, IL-10 potentially has anti-cancer effects through the inhibition of angiogenesis, and reductions in IL-1β, TNF-α, and IL-6 production that play important roles in neovascularization, as well as through down-regulation of vascular endothelial growth factor in tumor-associated macrophages (Huang et al., 1999).

Several factors alter IL-10 concentration and function. Altered IL-10 function is associated with the pathology of many diseases and immunodeficiency conditions, including infections (Cilfone et al., 2015), allergy (Akbari et al., 2001), autoimmune reactions (Batoulis et al., 2011), tumor

development (Yang & Lattime, 2003), and transplant tolerance (Sabat, 2010). In addition, IL-10 is involved in different physiological or non-immune pathological processes, including physical and psychological stressful events such as exercise, exposure to different kinds of pain, extreme thermal conditions, sleep deprivation, depression, hypoxia, etc. (Mingomataj & Bakiri, 2016). Increased IL-10 concentrations have been shown to protect against damage to tissues, including diabetic wounds, ischemic stroke, and myocardial remodeling (Kant et al., 2014; Kanazawa et al., 2015).

IL-10 has further beneficial effects in physiological conditions like learning and cognition (Zhao et al., 2015), pregnancy and breastfeeding (Hwang et al., 2013), nutritional therapies (Myles et al., 2014), and during various metabolic or homeostatic conditions (Fan et al., 2012; Mingomataj & Bakiri, 2016). The neuroprotective effect of IL-10 is one of its most important physiological roles, protecting against hypoxic and ischemic injury, glutamate-induced excitotoxicity, and neuronal apoptosis (Spera et al., 1998; Tukhovskaya et al., 2014).

IL-10 and inflammation

It is well known that IL-10 is an anti-inflammatory cytokine, with various ways to inhibit inflammation. Its anti-inflammatory mechanisms include suppressing the activation and function of immune cells (Locati et al., 2012). This suppression leads to the inhibition of edema, suppression of TNF-α production through down-regulation of cyclooxygenase 2 (COX-2) and inducible nitric oxide synthetase (iNOS) expression, reduction of prostaglandin E2 (PGE2) levels, and inhibition of nerve growth factor production. IL-10 also selectively blocks the expression of pro-inflammatory cytokines, especially IL-1β, (McKinstry et al., 2009; Sabat et al., 2010; Kwilasz et al., 2015). IL-10 action decreases various aspects of inflammation such as fever, acute phase protein release, vascular permeability, and hyperalgesia. The anti-inflammatory actions of IL-10 include suppressing the expression of antigen-presenting and co-stimulatory molecules in monocytes/macrophages, neutrophils, and T cells (Leon et al., 1999; Thaxton & Sharma, 2010; da Silva Lima et al., 2013).

IL-10 is known to play a role in inhibiting delayed-type hypersensitivity reactions and in the suppression of MHC class II expression and macrophage adhesion. The anti-inflammatory role of IL-10 has been demonstrated in different and clinical models (Williams et al., 2004; Da Silva

et al., 2015; Cianciulli et al., 2015). IL-10 limited hyperalgesia with its inhibitory action against inflammatory cytokine-induced pain responses and cytokine production (Poole et al., 1995).

IL-10 is a potent inhibitor of nuclear factor kappa B (NF-κB) with much of its anti-inflammatory activity mediated through this manner (Stewart et al., 2013; Hovsepian et al., 2013). Additionally, inhibition of IFNs-induced signal transducer and activator of transcription 1 (STAT1) activation through suppressor of cytokine synthesis (SOCS)-3 is another anti-inflammatory mechanism of IL-10 (Stewart et al., 2013; Hovsepian et al., 2013).

Another major anti-inflammatory mechanism of IL-10 is through the induction of heme oxygenase-1 (HO-1) in macrophages. The result of this process is to control tissue homeostasis during inflammation by inhibiting pro-inflammatory cytokine synthesis and activation of anti-apoptotic pathways (Naito et al., 2014).

Curcumin effects on chronic conditions mediated by IL-10

Pain

Neuropathic pain (NP) refers to discomfort due to CNS and peripheral nerve system destruction that involves chronic pain, allodynia, and hyperalgesia. IL-10 has anti-nociceptive effects against NP. It has been shown that the concentration of IL-10 in the serum and CNS (sciatic nerve and cerebrospinal fluid) are reduced in NP patients and animal models of NP. The initial rise in IL-10 concentration induced by nerve damage in animal models of NP has been observed, but after that IL-10 decreases. Anti-nociceptive effects of IL-10 have been shown in many studies. Intrathecal injection of IL-10 in the lumbar spinal cord can control allodynia for up to 24 hours through a reduction in pro-inflammatory cytokine production, including TNFα, IL-1β, and IL-6. Aspects of NP, including thermal hyperalgesia, and mechanical allodynia decreased with IL-10 administration. This anti-nociceptive effect lasted from 6 days to 4 weeks, depending on the dose and routes of administration (e.g., centrally, peripherally, plasmid DNA encoding IL-10 and viral vector-mediated delivery) (Milligan et al., 2005; Milligan et al., 2006; Wilkerson et al., 2012).

One of the features of oxidative stress is low serum IL-10 concentration. Research indicates that increased oxidative stress is accompanied by pain. Bilirubin acts as a potent antioxidant and its concentration is dependent on heme oxygenase-1 (HO-1) activity. Curcumin, through effects on IL-10, can increase HO-1 expression (Fattori et al., 2015a). Another mechanism of the anti-

nociceptive effect of curcumin mediated by IL-10 is by augmenting the antioxidant defense. Increased Cu/Zn superoxide dismutase and Nrf2 (as an activator of cytoprotective genes) expression are two examples of the anti-nociceptive mechanisms of curcumin mediated by IL-10 (Fattori et al., 2015b). In a neuropathic pain model in rats, curcumin was able to alleviate mechanical allodynia and thermal hyperalgesia induced by carbon tetrachloride. In this neuropathic model, curcumin's ability to increase IL-10 expression decreased pro-inflammatory cytokine expression via toll-like receptor 4 pathway and contributed to its anti-nociceptive effects in spinal cord (134). In another related study, Sahbaie et al. (Zhu et al., 2014) suggest that the effectiveness of curcumin in alleviating incision-induced inflammation and pain features is more directly related to the increase of TGF-β than to the increase of IL-10 levels (Sahbaie et al., 2014)**.**

Parkinson's Disease (PD)

PD is a progressive neurodegenerative inflammatory disorder affecting the dopaminergic neurons of the striatum. The main strategy for PD treatment is amplifying dopaminergic neurons by use of a precursor of dopamine, levodopa, and/or a dopamine D2 receptor agonist. However these treatments have usually a relatively low tolerability and their effects are largely variable among patients. Currently, at the best of our knowledge, no human study has ever been conducted to evaluate the effect of IL-10 administration in PD patients; however, in animal models of PD, the use of IL-10 has been shown to be effective. IL-10 administration in animal studies was shown to have anti-inflammatory effects, including the inhibition of microglial production of TNF, nitric oxide and reactive oxygen species formation, decreased microglial activation and destruction of dopaminergic neurons, and increased striatal tyrosine hydroxylase expression (Arimoto et al., 2007; Chu et al., 2012; Schwenkgrub et al., 2013.

In a study by Yu et al. (2016), 1-methyl-4-phenylpyridinium (MPP) was used to induce oxidative stress and inflammation in an in vitro astrocyte model of Parkinson's disease. Curcumin showed neuroprotective effects in MPP(+)-stimulated astrocytes *via* its increasing IL-10 effect and inhibiting pro-inflammatory cytokines (Yu et al., 2016).

Alzheimer's disease (AD)

Involvement of ***inflammatory*** processes in the pathogenesis of AD *via* its effects on neurogenesis has been shown in many studies (Akiyama et al., 2000; Lio et al., 2003). Protective effects of IL-10 towards promotion of neuronal survival are mediated by its anti-inflammatory effects, as well as through upregulation of Bcl-2 and Bcl-xL and activation of protein kinase B (Akt). IL-10 increases the expression of anti-apoptotic proteins (e. g. Bcl-2) and the induction of neurogenesis to promote the survival of human B cells. IL-10 may also be beneficial for AD via the induction of stem cell proliferation, attenuation of spatial cognitive dysfunction, and suppression of gliosis (Kiyota et al., 2012).

Curcumin has protective effects against neuronal loss through various mechanisms. Curcumin prevented degradation of synaptophysin, and modulated the PI3K/Akt pathway and PI uptake in hippocampus which are beneficial for AD. Curcumin decreased the expression of TNF-α, IL-1β, and IL-6 by activated glial cells through increasing IL-10 production. Curcumin increased IL-10 expression in hippocampus. Anti-inflammatory effects of IL-10 are mediated through an increase in PI3K pathway activity. PI3K/Akt-mediated inactivation of glycogen synthase kinase-3beta promotes cell survival and stabilization of beta-catenin. Curcumin facilitates this pathway directly and indirectly by its IL-10 increasing property (Hoppe et al., 2013).

Encephalomyelitis

Encephalomyelitis is an inflammatory autoimmune disease of the brain and spinal cord. The anti-inflammatory effects of IL-10 modulated T_H1/T_H17 cell differentiation and their responses in experimental autoimmune encephalomyelitis (Kanakasabai et al., 2012). It has also been reported that curcumin treatment is associated with the up-regulation of IL-10 and Treg cells in the CNS and lymphoid organs during experimental autoimmune encephalomyelitis (Kanakasabai et al., 2012).

Diabetes Mellitus (DM)

Diabetic nephro- and neuro-protective properties of curcumin have been shown in many studies. ACE activation and angiotensin II (AngII) production mediate adverse effects in DM by increasing the secretion of pro-inflammatory cytokines (Gazal et al., 2014; Molina-Jijón et al.,

2016). Also, pro-inflammatory cytokine, especially TNF-α whose plasma levels are higher in diabetic patients, accelerate the onset of DM (Lampropoulou et al., 2014; Pavkov et al., 2015). In contrast, IL-10 concentration has been reported to be lower in DM compared with healthy controls. In many studies, low serum IL-10 has been linked to poor glycemic control and the progression of DM (Li et al., 2016). Protective effects of curcumin against the detrimental effects of diabetes on nervous system and kidney functions is potentially mediated by its potent ACE inhibition and decrease in AgII production, that tends to decrease TNF-α and inflammation in both tissues. Renal macrophage infiltration was also shown to be inhibited by curcumin. Use of curcumin increased serum IL-10 concentrations in diabetic groups after treatment and attenuated DM-adverse effects. Curcumin attenuated DM-induced allodynia and thermal hyperalgesia, and it was associated with a reduction in TNF-α and total peroxide levels in sciatic nerve and an increase in IL-10 level (Abd Allah & Gomaa, 2015).

Cancer

M1 and M2 macrophages produce IL-12 (anti-tumor) and IL-10, respectively. M2 macrophages play a key role in tumor progression and growth. IL-10 concentration is elevated in a variety of solid tumors. The ratio of IL-12 and IL-10 concentration is an important predictor of tumor progression. Curcumin can increase M1 and decrease M2 macrophages, resulting in a decrease in STAT3, IL-10, and arginase I gene expression and secretion. This beneficial effect of curcumin was shown by Shiri et al. (2014) in mice with metastatic breast cancer. By reducing IL-10 levels, curcumin also inhibits Janus Kinase-STAT signaling and increases tumor apoptosis (Shiri et al., 2014).

Curcumin has anti-tumor activity through prevention of tumor-induced T-cell depletion by increasing the production of IFN-γ and IL-2, the most important T_H1 cytokines for the production and function of peripheral T-cell and cytotoxic T lymphocytes (TC), respectively. Several mechanisms are responsible for the potential anti-tumor activity of curcumin, including restoration of activated/effector CD^+4 and CD^+8 T-cells, secretion of IFN-γ, augmentation of tumor-infiltrating lymphocytes (TILs), and upregulation of IFN-γ mRNA expression. Curcumin also reduces the levels of TGF-β and IL-10 in Treg cells and reduces the number of Treg cells in

cancerous states. Consequently, curcumin was able to augment T_H1/TC1-type responses (Bhattacharyya et al., 2010). Cancer angiogenesis promotes its local progression and systemic dissemination, with circulating and resident angiogenic cells being associated with poor prognosis in non-small cell lung cancer (Pirro et al., 2013; Pirro et al. 2016). The influence of IL-10 on endothelial progenitors is inconsistent, since few studies have reported either a reduced or an increased endothelial progenitor function after IL10 exposure (Cates et al., 2015; Wang et al., 2015). In an *in vitro* study, curcumin was able to inhibit endothelial progenitor cell growth by increasing p21 and p53 expression (Vyas et al. 2015). Whether this effect might be mediated by IL10 ability to hamper endothelial progenitor cell differentiation (Cates et al., 2015) needs to be investigated.

Atherosclerosis and cardiac injury

Chronic inflammation and immune reactions are two main features of atherosclerosis (St-Pierre et al., 2003). Agents with some anti-inflammatory effects (e.g., statins) are a useful treatment strategy in treating atherosclerosis (Pirro et al., 2004). An important role of cytokines in atherosclerosis development and progression has been shown in many studies (e.g., elevated IL-1β, TNF-α, MCP-1 and reduced IL-10, TGF-β). IL-10 administration was able to reduce fatty lesion development in IL-10 knock-out mice. Simvastatin has been shown to increase the serum level of IL-10 in unstable angina patients, and it was suggested that this effect plays a role in the atherosclerosis protection (Charoenwanthanang et al., 2011). Sing et al. (2015) showed that in a hamster model of accelerated atherosclerosis, curcuma oil attenuated inflammation and arterial injuryinduced by an oxidant agent. Additionally, macrophage foam-cell formation, arterial macrophage accumulation, and stenosis were decreased in oil-treated group compared with the control group. This may have been related to the increased IL-10 and TGF-β mRNA expression in atherosclerotic arteries observed in curcuma oil treated group. Similarly, curcuma oil decreased mRNA expression of pro-inflammatory cytokines (e. g. TNF-α, IL-6, IL-1β and IFN-γ) and increased IL-10 expression in peritoneal macrophages (Singh et al., 2015).

The impact of endothelial progenitors and angiogenesis on atherosclerosis risk is debated (Mannarino & Pirro, 2008; Pirro et al., 2008; Pirro et al., 2009), this factors being associated

with both increased atherosclerosis complications (e.g., plaque rupture) and also improved perfusion of ischemic tissue and reduced ischemic cardiovascular events. Since IL10 has reduced endothelial progenitor cell differentiation in vitro (Cates et al., 2015), while curcumin decreased endothelial progenitor cell colony forming capacity and their proliferation (Vyas et al., 2015), it is possible that IL10 might mediate the anti-angiogenic effects of curcumin. Irrespective of the interaction between curcumin and IL10, a net beneficial effect of curcumin on endothelial function has been described (Karimian et al., 2017).

Cardiopulmonary bypass or cardiac global ischemia and reperfusion induces cardiomyocytic injury. The main reasons for cardiac injuries are the release of pro-inflammatory cytokines and decreased anti-inflammatory actions. Curcumin increases IL-10 levels in cardiac events and protects against injuries. Reductions in inflammation and cardiomyocytic apoptosis are the consequences of using curcumin in these conditions (Yeh et al., 2005).

Intestinal mucositis

Bastos et al. (2016) reported that curcumin and *Bidens pilosa* L. reduced myeloperoxidase activity by 68% and increased IL-10 levels by 400% (Bastos et al., 2016). Low serum IL-10 and high serum TNF-α and IL-12 concentrations were seen in the experimental trinitrobenzene sulfonic acid- induced colitis model. In this model, lymphocytes and polymorphonuclear cells infiltrate into the colon, and neutrophils produce ROS and worsen the condition. Curcumin was able to diminish colitis through antioxidant and IL-10-elevating effects (Zhang et al., 2006; Camacho-Barquero et al., 2007). The low IL-10 concentration observed in colitis was able to be restored by curcumin treatment, accompanied amelioration of the disease (Camacho-Barquero et al., 2007; Epstein et al., 2010; Sreedhar et al., 2016162--164). COX-2 levels are increased and IL-10 levels are decreased in colon carcinoma and inflammatory models (Shattuck-Brandt et al., 2000). Curcumin-treatment was found to increase the IL-10 level in ileum, spleen and lymph nodes in animals with low serum IL-10 level in an ileitis model. Other mechanisms of curcumin-mediated anti-inflammatory activity include reductions in mucosal T lymphocyte and neutrophilic granulocyte numbers, increased gut colonization of anti-inflammatory lactobacilli and bifidobacteria, and preservation of intestinal barrier function (Bereswill et al., 2010).

Enterocolitis

Positive effects of curcumin were seen against enteritis in various models, including the methotrexate-induced one. In this model, curcumin increased IL-10 expression and production, as well as suppressed T lymphocyte function (Song et al., 2010). In a similar study, the IL-10 increasing effect of curcumin was shown to ameliorate intestinal inflammation (Tham et al., 2010).

Using an enterocolitis model in rats, Jia et al. reported that IL-10 concentration in both treated and untreated necrotizing ***enterocolitis*** rats was higher than a control group. Curcumin was able to attenuate the symptoms of colitis by increasing IL-10 levels (Jia et al., 2010). In a similar study, Jian et al. reported low concentrations of IL-10 in trinitrobenzene sulfonic acid-induced colitis. Curcumin's capacity to increase IL-10 expression in colonic mucosa was shown to play a pivotal role in its protective effects against IBD (Jian et al., 2010).

Inflammatory Bowel Disease (IBD)

Altered innate and adaptive immune cell activities is a common issue in IBD). In many studies, the critical role of IL-10 in the maintenance of intestinal homeostasis and balance between intestinal flora and the digestive system has been shown (Steidler et al., 2000; Shouval et al., 2014). Ishizuka et al. reported a decreased production of IL-10 was associated with severe cases of IBD. Inhibition of IL-1β appears to be the most important mechanism of IL-10 in the prevention and treatment of ulcerative colitis (UC) (Ishizuka et al., 2001). There is no relation between serum IL-10 concentration and risk of IBD; however, IL-10 therapy may decrease the progression of IBD. Despite positive results in the use of IL-10 in animals and *in vitro* models, human clinical trials did not show any benefits of IL-10 in the treatment of Crohn's disease (Colombel et al., 2001).

Use of curcumin has been shown to increase IL-10 expression and production to improve disease outcomes. Induction of IL-10 by curcumin appears to be mediated by its effect on reducing the binding of specificity protein 3 to the IL-10 promoter. This reduction tends to increase IL-10 expression (Epstein et al., 2010; Boobalan et al., 2015).

McCann and colleagues (2014) showed that a single nucleotide polymorphism in the promoter region of the IL-10 gene tends to decrease IL-10 production and increase IBD severity. Curcumin can attenuate IL-10 variant reductions and function in a dose-dependent manner. In this state, IL-10 transcription was increased by curcumin (McCann et al., 2014).

In colonic lamina propria, high levels of IL-10 are also pivotal for Treg development. Curcumin induced the development of Tregs by amplifying IL-10 production. IL-10 is also involved in the modulation of DCs by curcumin. Similarly, curcumin treatment of IL-10-deficient DC did not induce Tregs, and in IL-$10^{-/-}$ mice, curcumin has negligible effects on T_H1-driven colitis. Furthermore, the administration of anti-IL-10 receptor antibody (CD-210) limited the induction of Tregs. TGF-β production was also increased by IL-10 action. Development and maturation of Tregs are dependant on the differentiation of naïve $CD4^+$ T cells promoted by IL-10 induced by curcumin. One anti-inflammatory mechanism of curcumin is mediated by its effect on the production of IL-10 by DCs. In bone marrow DCs, curcumin increased IL-10 expression and induced the differentiation of $CD4^+CD25^+$ $Foxp3^+$Treg and type 1 regulatory cells (that produce IL-10) in the intestine. Consequently, colitis and other inflammatory intestinal conditions were inhibited due to the inhibition of antigen-specific pathogenic T cells. Thus, curcumin-induced IL-10 production increased the ability of naïve T cells to differentiate to protective Tregs in the intestine (Cong et al., 2009; Maynard et al., 2012).

As mentioned above, IL-$10^{-/-}$ mice are an important model for evaluating intestinal inflammation. Intestinal inflammation spontaneously develops because of the lack of IL-10 anti-inflammatory action in these animals. Activation of NF-κB and IL-12/23p40 production is higher in colonic epithelial cells in this model. As one might expect, IL-10 normally down-regulates NF-κB activity. In IL-$10^{-/-}$ mice, curcumin did not suppress NF-κB activation and the inhibitory effects of curcumin on IL-12/23p40 and IFN-γ mRNA expression was very low in the colon. This observation was also seen in LPS-stimulated splenocytes to induce IL-12/23p40 and to increase Treg cell differentiation. Interestingly, curcumin combination with IL-10 acted synergistically to suppress the production of IL-12/23p40 in murine dendritic cells. Similarly, curcumin and IL-10 acted synergistically to inhibit NF-κB activity induced by IL-1β in intestinal

epithelial Mode-K cells (Larmonier et al., 2008; Ung et al., 2010). Thus, evidence suggests that curcumin is effective in Crohn's disease in an IL-10-dependent manner.

Another model of colitis is induced by acetic acid (AA). Inhibition of mitogen-activated protein kinases (MAPK) signaling by curcumin modified the T_H1/T_H2 profile and increased IL-10 production. Curcumin was useful in treating AA-induced colitis by augmenting the anti-inflammatory action of IL-10 (Sánchez-Calvo et al., 2009).

Wounds

Kant et al. (2014) reported a wound healing effect of curcumin, related to increased IL-10 concentration in the cutaneous wounds of diabetic rats in a time-dependent manner. This study also showed that the curcumin-treated group had lower inflammation and better formation of granulation tissue. The effect of curcumin on IL-10 levels was higher in diabetic animals than in controls (Kant et al., 2014).

AIDS

LP-BM5 murine leukemia virus (MuLV) is commonly used in the murine acquired immune deficiency virus (MAIDS) model. Kim et al. (2014) reported that serum IL-10 was decreased in the MuLV-infected group, but *C. longa* L. suppressed TH1/TH2 cytokine imbalance through increasing IL-10 production. The results of this study also showed that curcumin alleviated adverse effects of MAIDS and spleen size, lymph node volume, and liver weights were decreased. Curcumin showed anti-AIDS effects through immunomodulatory properties and IL-10 enhancing effects (Kim et al., 2014).

Allergic rhinitis and Asthma

IL-10 has a prominent role in regulating allergic responses. IL-10 markedly reduced T_H2 cell actions during bronchopulmonary allergic response, which was demonstrated using IL-10-knockout mice in an allergic bronchopulmonary aspergillosis model. In this model, bronchoalveolar lavage fluid IL-4, IL-5, and IFN-ɣ levels and inflammation were higher in IL-10-deficient mice than in wild type mice. In asthmatic patients, the amount of IL-10 secreted

from alveolar macrophages was lower than in non-asthmatic control macrophages (Grünig et al., 1997).

IgE is the main immunoglobulin to induce mast cell degradation and allergic response production. IL-10 induces Treg cell function which suppresses IgE production. By this mechanism of action, curcumin could reduce allergic rhinitis symptoms (Wu et al., 2016). Curcumin increased serum IL-10 and decreased serum IL-17 (as an inducer of lung hypersensitivity and asthma severity). Suppressing Th17 cells and increasing Tregs are other beneficial effects of curcumin on asthma (Ma et al., 2013).

Liver and kidney protection

IL-10 showed a hepatoprotective role in hepatotoxicity models, such as Concanavalin A-induced hepatitis in mice. In this model, IL-10 is reduced with Con-A treatment. Curcumin, however, alleviated Con-A hepatotoxicity through increasing IL-10 level (Tu et al., 2012). In another study, curcumin increased IL-10 concentration in rats with hepatotoxicity induced by CCL4, resulting in a reduction in liver fibrosis and inflammation (Wu et al., 2010).

Curcumin shifts M1 to M2 macrophage polarization and thereby triggers IL-10 expression in tissues. For evaluation of the nephroprotective effects of curcumin, Karuppagounder and colleagues administered curcumin in a daunorubicine-induced renal dysfunction rat model. As a result, curcumin alleviated the symptoms of renal dysfuction (e.g., BUN and serum creatinine levels), renal inflammation and structural lesions in drug-treated animals. Shifting M1 to M2-like macrophages resulted in higher levels IL-10 production. Similarly, IL-10 and M2-like macrophage markers were significantly lower in drug-treated rats (Karuppagounder et al., 2016). In a cisplatin-induced nephrotoxicity model, curcumin was able to alleviate nephrotoxicity with antioxidant and anti-inflammatory effects. Oxidative stress in kidneys was associated with decreased IL-10 concentration. Pathological damage by cisplatin was reduced while normal kidney function was restored with curcumin through its enhancing serum IL-10 serum concentrations (Topcu-Tarladacalisir et al., 2016).

Malaria

Vatasala et al. (2012) showed that use of *Plasmodium berghei* to induce malaria in mice was accompanied by a decrease in IL-10 concentrations. Use of curcumin enhanced IL-10 production and generation of anti-parasite antibodies. Curcumin was able to decrease recrudescence in falciparum and relapse in vivax malaria. In IL-$10^{-/-}$ animals, curcumin failed to show any benefits against recrudescence. IL-10 and curcumin acted synergistically to prolong the survival of beta-arteether-treated mice (Vathsala et al., 2012).

Coccidiosis

IL-10 has an important role in the prevention of infection-related tissue damage. In coccidian infections, free radicals and ROS produced by macrophages and polymorphonuclear neutrophils tend to increase pro-inflammatory cytokine production. As shown by Cervantes-Valencia et al. (2016), curcumin alleviated coccidoidal infection in naturally infected lambs. Effects of curcumin on down-regulating pro-inflammatory cytokines (e.g., IFN-γ) while increasing IL-10 are thought to contribute to its anti-coccidiosis activity (Cervantes-Valencia et al., 2016).

Other Diseases

Potential beneficial effects of curcumin via IL-10 have also been investigated in many other diseases and pathological conditions including sepsis (Wang et al., 2015), acute lung injury (Zhu et al., 2008), recurrent respiratory infections (Zuccotti et al., 2008), myasthenia gravis (Wang et al, 2016) and trypanosomiasis (Wolkmer et al, 2013).

Conclusion

IL-10 plays a relevant role in contrasting the development of a large number of chronic human diseases whose pathophysiology is related to inflammation. Curcumin, a natural anti-inflammatory compound, can induce the expression and production of IL-10 enhancing its action on a large number of tissues (**Table 1** and **Figure 1**). Despite a large number of pre-clinical studies, relatively scarce evidence on the relationship between anti-inflammatory effects of curcumin in humans and its action on IL-10 is available. However, given that exogenous therapy with IL-10 is not effective because of its short half-life and uncertain pharmacokinetic, while

gene therapy could be very expensive, the possible use of curcumin as an IL-10 synthesis inducer could be of strong interest for its use in a wide range of inflammatory diseases.

Conflict of interests

Muhammed Majeed is the Founder & Chairman of Sabinsa Corporation and Sami Labs Limited.

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Table 1. Experimental models showing the impact of curcumin or turmeric extract on IL-10 and related effects.

Model	Dose	Duration of Treatment	Result	Reference
Diabetic rats	100 mg/kg/day	PO, 6 weeks	↑ IL-10, protection against diabetic neuro and nephropathy and hyperalgesia	Abd Allah and Gomma, 2015
Diabetic rats	Curcumin (0.3%) in pluronic gel	Topically, 19 days	↑ IL-10, ↑ wound healing	Kant V et al, 2014
Carcinoma cells isolated from mice	50 mg/kg/day	PO, 7 days	↓ IL-10, ↑ cell-mediated immune responses	Bhattacharyya S et al, 2010
Metastatic breast cancer in mice	40 and 80 mg/kg/day	PO, 35 days	↑ IL-10, ↓ tumor progression	Shiri, S et al, 2014
Coccidoid crossbred lambs	50, 100 and 200 mg/kg/day	PO, 14 days	↑ IL-10, ↓ coccidoidal infection and mortality	Cervantes-Valencia ME et al, 2016
Hyperlipidaemic hamsters	Curcuma oil, 100 and 300 mg/kg/day	PO, 5 weeks	↑ IL-10, attenuation of atherosclerosis	Singh V et al, 2015
TNBS-induced colitis in rat	0.2% curcumin in	PO, 3 days before TNBS	↑ IL-10, ↓ colitis	Jian YT et al, 2005

	the diet	treating to 2 weeks after		
TNBS-induced colitis in rat	30 mg/kg/day	IP, 2 weeks	↑ IL-10, ↓ colitis, ↑ T_H2 activity	Zhang M et al, 2006
TNBS-induced colitis in rat	50 and 100 mg/kg/day	PO, 2 weeks	↑ IL-10, ↓ inflammation	Camacho-Barquero L et al, 2007
NEC in rat	Not found	PO, 3 days	↑ IL-10, ↓ inflammation and histopathological findings	Jia SH et al, 2010
Myofibroblast of UC or CD patient	20 µM	24 hours, in vitro	↑ IL-10, ↓ protein acetylation and inflammation in myofibroblast	Epstein J et al, 2010
UC in rat	50 mg/kg/day of curcumin with flunixin 2.5 mg/kg/day	PO, 14 days	↑ IL-10, restoration of histopathological changes	Gopu B et al, 2015
Colitis in IL-10 (-/-) EGFP mice	Dietary curcumin (0.1-1%)	PO, 10 days	Limited effectiveness in attenuation of colitis	Larmonier CB et al, 2008
IL-10(-/-) gene-deficient mice	200 mg/kg/day	Gavage, 14 days	↑ IL-10 level, ↓ colitis by decrease in proinflammatory cytokines production	Ung VY et al, 2010

HEK293 cells	Turmeric extract	Various concentration	↑ IL-10 gene promoter activity related to IBD severity	Mc Cann MJ, 2014
AA-induced colitis in rat	50- 100 mg/kg/day	PO, 14 days	↑ IL-10 production, ↓ nitrite production and inflammation in colonic mucosa	Sánchez-Calvo JM, 2009
MTX- – induced enteritis in rat	100 mg/kg/day	PO, 7 days	↑ IL-10 expression and production, ↓ enteritis	Song WB, 2010
Superoxide anion-induced pain-like behavior in rat	10 mg/kg	SC, 1 h before stimulus	↑ IL-10 production, ↓ pain reactions	Fattori V, 2015
CcL4- Induced neuropathic pain in rat	40- 60 mg/kg/da	IP, 7 days	↑ IL-10 expression, ↓ mechanical allodynia and thermal hyperalgesia	Zhu L et al, 2010
Hindpaw incision model in C57BL/6 mice	50 mg/kg	IP, 24 h before incision and for 4 days after incision	Not significant alteration in IL-10 level, ↓ spontaneous pain	Sahbaie S et al, 2014
Hippocampal slice cultures of rat	0.5–10 µM	48 hours	↑ IL-10 expression and production in hippocamp, ↑ neuron survival	Hoppe JB et al, 2017

EAE in mice	100 μg	IP, 14 days	↑ IL-10 up-regulation, ↓ inflammation	Cacalini K et al, 2012
Open excision skin wound in STZ-induced diabetic rat	Gel 0.3%	Topically, 19 days	↑ IL-10 level, better granulation tissue and collagen deposition	Kant V et al, 2014
DNR- induced nephrotoxicity in rat	100 mg/kg/day	PO, 6 weeks	↑ IL-10 expression, ↓ symptoms of renal dysfuction	Karuppagounder V et al, 2016
Cisplatin- induced nephrotoxicity in rat	200 mg/kg/day	PO, 2 days before cisplatin injection through 4 days	↑ IL-10 production, ↓ symptoms of renal dysfuction	Topcu-Tarladacalisir Y et al, 2016
LP-BM5 MuLV (murine leukemia viruses)-induced murine AIDS	20% alcohol extract 50, 200 and 500 mg/kg/day	PO	↑ IL-10 production,↓ adverse effects of MAIDS and spleen size, lymph node volume, and liver weights	Kim OK et al, 2014
OVA-induced allergic asthma in mice	50, 100 and 200 mg/kg/day	IP, 7 days	↑IL-10 production, inhibition of eosinophils recruitment and mucus overproduction	Ma C et al, 2013

Con-A- induced hepatotoxicity in mice	200 mg/kg	Gavage prior of Con-A administration	↑ IL-10 production, attenuation of hepatitis	Tu CT et al, 2012
CCl4- induced hepatotoxicity in rat	Dietary curcumin (0.005%)	PO, 8 weeks	↑ IL-10 production, alleviation of liver toxicity markers	Wu T et al, 2010
Plasmodium berghei- induced malaria model in mice	5 mg/mouse	PO, 3 days	↑ IL-10 production and generation of anti-parasite antibodies	Vathsala PG et al, 2016
Patients with allergic rhinitis	500 mg/day	PO, 2 month	↑ IL-10 production and nasal air flow	Wu S and Xiao D, 2016
Cardiopulmonary bypass in rabbit	70 and 100 µg/kg, one dose	IP, 2 h before test	↑ IL-10 production and reduction in cardiomyocytic apoptosis	Yeh CH et al, 2005
LPS -induced sepsis in mice	Curcumin nanoparticle, 30 mg	PO, 30 min before LPS injection	↑ IL-10 production and alleviated the damaged organs	Wang J et al, 2015
Oleic acid-induced lung injury in rat	5, 10 and 20 mg/kg	IP, 2 h before oleic acid injection	↑ IL-10 production and betterment of injury	Zhu RF et al, 2007
R97-116 peptide-induced MG in rat	50 and 100 mg/kg/day	IP, 35 days	↑ IL-10 production, ↓ MG-related symptoms	Wang S et al, 2016
Trypanosoma evansi infection in	20 and 60	PO, 15 and 30 days before	↑ IL-10 production and anti-	Wolkmer P et al,

rat	mg/kg/day	induction of infection	inflammatory response	2013

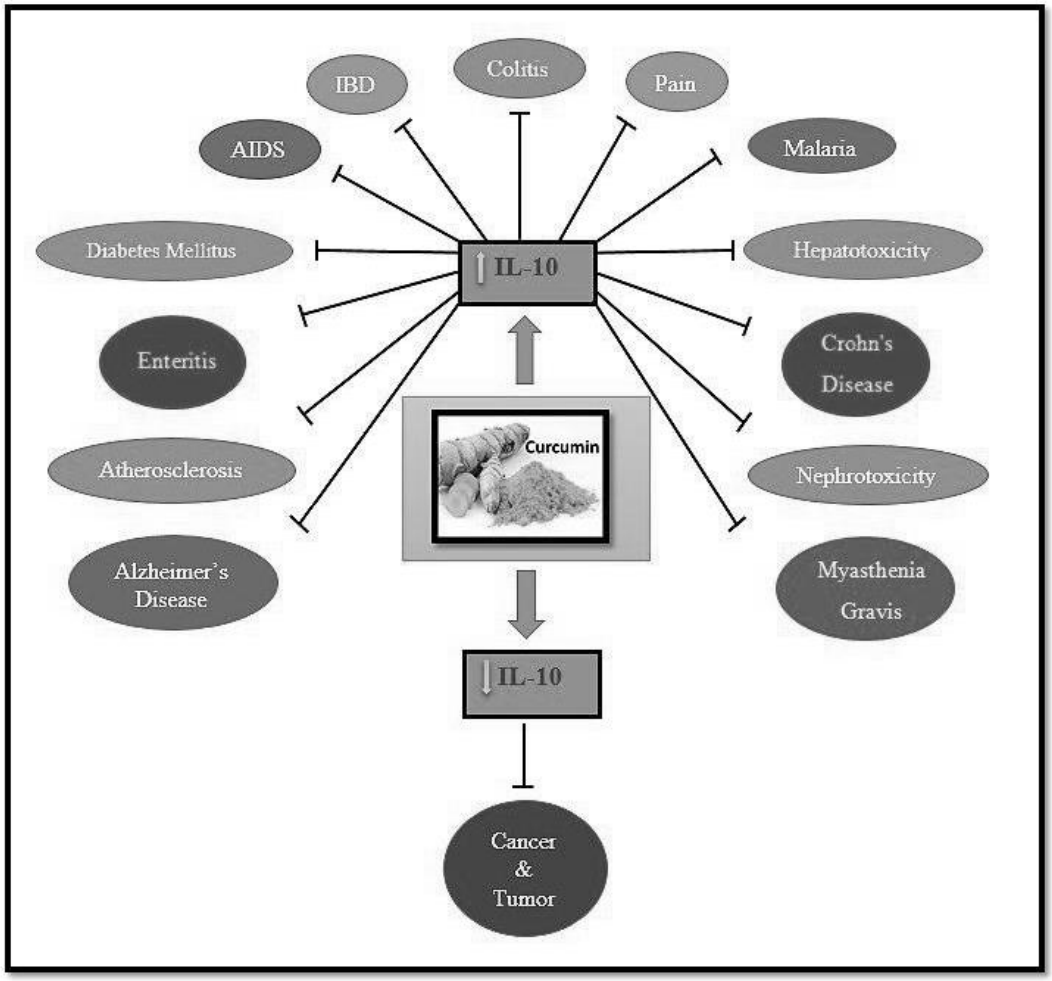

Figure 1. Therapeutic effects of curcumin mediated, at least in part, by modulation of IL-10 levels.