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Inflammopharmacology

REVIEW

Curcumin and chemokines: mechanism of action and therapeutic potential in inflammatory diseases

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Abstract

Chemokines belong to the family of cytokines with chemoattractant properties that regulate chemotaxis and leukocyte migration, as well as the induction of angiogenesis and maintenance of hemostasis. Curcumin, the major component of the *Curcuma longa rhizome*, has various pharmacological actions, including anti-inflammatory, immune-regulatory, anti-oxidative, and lipid-modifying properties. Chemokines and chemokine receptors are influenced/modulated by curcumin. Thus, the current review focuses on the molecular mechanisms associated with curcumin's effects on chemoattractant cytokines, as well as putting into context the many studies that have reported curcumin-mediated regulatory effects on inflammatory conditions in the organs/systems of the body (e.g., the central nervous system, liver, and cardiovascular system). Curcumin's effects on viral and bacterial infections, cancer, and adverse pregnancy outcomes are also reviewed.

Keywords Curcumin · Chemokine · Cytokine · Inflammation · Cancer · Infection

Introduction

Chemokines are small (7–13 kDa), signaling proteins that belong to the cytokine family and exert chemoattractant properties. They play an important role in both physiologic and pathological immune responses through the formation of concentration gradients and interactions with their respective receptors on cell surfaces. Almost fifty different chemokines have been identified in humans that induce hemostasis, angiogenesis and regulate chemotaxis and leukocyte adhesion/transmigration. The chemokines are grouped into CC, CXC, CX3C, and XC subfamilies according to the number of amino acids located between the first two structural cysteine residues (Deshmane et al. 2009; Bodnar 2015; Gustavsson 2020). Chemokine receptors are expressed on various cell types, including leukocytes and other non-hematopoietic cells. About twenty types of chemokine receptors have been identified that are 7-transmembrane G protein-coupled receptors (GPCRs). The binding of chemokine to its receptor creates a calcium signaling cascade, activating small

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GTPases. Activation of integrins and actin polymerization are the downstream events that result in the development of a pseudopod, polarized cell morphology, and ultimately cell movement. The chemokines are then internalized via clathrin-based endocytosis (Cabrero-de las Heras and Martínez-Balibrea 2018; Rajagopal et al. 2010; Proudfoot and Uguccioni 2016). Cascade-activation of downstream signaling proteins is associated with inflammatory processes and leukocyte accumulation in infected or injured tissues. This process is a key step in cell migration and a powerful 'checkpoint' in regulating cell migration. Thus, intentional regulation of cell migration could potentially be accomplished using different therapeutic agents or strategies (Marchese 2014; Maryam Saberi Karimian et al. 2017a; Scholten et al. 2012) (Table 1).

Curcumin (diferuloylmethane) is a natural polyphenol from the herb, turmeric. The chemical formula and chemical name are $C_{21}H_{20}O_6$ and 1, 7-bis-(4-hydroxy-3-methoxyphenyl-hepta-1, 6-diene-3, 5-dione, respectively (Shatadal Ghosh et al. 2015; Prasad et al. 2014; Yadollahi and Zargaran 2019), respectively. A molecule of curcumin has a symmetric structure, including two parallel aromatic rings and O-methoxy phenolic groups that are bound to a carbon linker, which has an α, β-unsaturated β-diketone moiety (Yu et al. 2019). Curcumin is the major component of *Curcuma longa* rhizome (turmeric; Zingiberaceae), a perennial plant, which has been used as a spice in cooking and used in traditional Chinese and Indian natural medicine therapy for centuries. In traditional Asian medicine, curcumin is used to treat various disorders, including rheumatism, liver disorders, insect bites, cough, sinusitis, and anorexia (Bahrami et al. 2019; Mohammad Mohajeri et al. 2018). Curcumin is a safe phytochemical that elicits a wide range of biological actions in the human body. It shows anti-inflammatory, antioxidant, lipid-modulating, anti-thrombotic, immunomodulatory, hepatoprotective, anti-diabetic, anti-tumor, and neuroprotective actions (Qadir et al. 2016; Bavarsad et al. 2019; Ghasemi et al. 2019; Iranshahi et al. 2009; Panahi et al. 2017b; Parsamanesh et al. 2018; Sahebkar and Henrotin 2016; Alidadi et al. 2020; Heidari et al. 2022; Vahedian-Azimi et al. 2022; Mohammed et al. 2021).

In addition, curcumin influences various cells and molecular targets like growth factors, cytokines/chemokines, hormones, transcription factors, cell adhesion molecules, protein kinases, redox state enzymes, and receptors (Esatbeyoglu et al. 2012; H. Zhou et al. 2011; Mashayekhi-Sardoo et al. 2021; Mohajeri et al. 2020; Soltani et al. 2021; Ganjali et al. 2017b; Momtazi-Borojeni et al. 2018). The anti-inflammatory effects of curcumin are mediated by down-regulation in the activity of cyclooxygenase-2 (COX-2), lipoxygenase (LOX), inflammasome, and inducible nitric oxide synthase (iNOS) (Goel et al. 2008b, 2008a; Hassanzadeh et al. 2020). Moreover, curcumin also inhibits IL-2, IL-6, IL-8, IL-12, TNF-α, macrophage inhibitory protein (MIP), and the production of monocyte chemoattractant protein-1 (MCP-1) pro-inflammatory cytokines and chemokines (Abe et al. 1999), as well as down-regulates mitogen-activated and janus kinases (Natarajan and Bright 2002; Siwak et al. 2005). These biological effects appear to be achieved by curcumin-mediated inhibition of NF-κB (Surh et al. 2001; Zhong et al. 2012; Lee et al. 2005; Ji et al. 2009; Zhao et al. 2014).

The current review discusses curcumin's anti-inflammatory and regulatory effects on chemokines and chemokine receptors in various in vitro and in vivo (human and experimental animal models) studies in different medical conditions and diseases.

Inhibitory effects of curcumin on chemokines

CCL2 (MCP-1) (Fig. 1)

CCL2 or monocyte chemoattractant/chemotactic protein-1 (MCP-1) is the major chemotactic protein for monocytes (Mohammadi et al. 2019). Inhibition of CCL2 function may reduce immune cell attraction to inflammation sites and slow the inflammatory response's progression. Curcumin was shown to inhibit MCP-1 production in different cell types and attenuate monocyte recruitment (Abe et al. 1999; Young et al. 2014; Karimian et al. 2017b; Liu et al. 2014; Huang et al. 2016; Jain et al. 2009; Tu et al. 2012; Pan et al. 2013a). In addition, studies with animal models have shown that curcumin reduces MCP-1 expression and alleviates inflammatory disorders, although human studies are limited (Maryam Saberi Karimian et al. 2017a).

Most preclinical studies have reported that curcumin exerts its effects by regulating the MAPK and NF-κB signaling pathways (Panahi et al. 2017a; Antoine et al. 2013; Nagaraju et al. 2015; Zhao et al. 2015; Kim et al. 2005; Cao et al. 2015; Bukhari et al. 2014; Mimche et al. 2012; Chung et al. 2012). Zhang et al. reported that curcumin could reduce the mRNA expression of LPS-induced CCL2 in the rat C6 astrocytoma cell line in a dose-dependent manner through inhibition of the JNK signaling pathway (Zhang et al. 2012). However, Herman and colleagues suggested that CCL2 activity could be inhibited via protein kinase C (PKC) and matrix metalloproteinases (MMP) (Herman et al. 2009). Liu et al. reported that curcumin inhibited ox-LDL-induced MCP-1 expression in macrophages via the NF-κB and JNK pathways (Liu et al. 2014). Zhong et al. evaluated the effects of curcumin on LPS-induced MCP-1 production in the RAW264.7 macrophage cell line and demonstrated that curcumin reduced MCP-1 expression in a concentration-dependent manner. These authors showed that this effect

Table 1 Characteristics of chemokines and chemokine receptors

Name	Synonyms	Receptor	Target cell	Major function
C family				
XCL1	Lymphotactin α, SCM-1α, ATAC	**XCR1**	T cell, NK, $CD8\alpha^+$ dendritic cell	T cell and NK recruitment
XCL2	Lymphotactin β, SCM-1β	**XCR1**	T cell, NK, $CD8\alpha^+$ dendritic cell	Unknown
CC family				
CCL1	I-309, TCA3, P500, SISe, SCYA1	**CCR8**	Monocyte, neutrophil, T cell (Th2 > Th1)	Monocyte recruitment and endothelial cell migration
CCL2	MCP-1	**CCR2**	T cell (Th2 > Th1), monocyte, basophil, immature dendritic cell, NK	Mixed leukocyte recruitment
CCL3	MIP-1α, LD78	**CCR1, 5**	Monocyte/macrophage, T cell (Th1 > Th2), NK, basophil, immature dendritic cell, eosinophil, neutrophil, astrocyte, fibroblast, osteoclast	Mixed leukocyte recruitment
CCL4	MIP-1 β	**CCR1, 5**	Monocyte/macrophage, T cell (Th1 > Th2), NK, basophil, immature dendritic cell, eosinophil, B cell	T cell, dendritic cell, monocyte and NK recruitment HIV co-receptor
CCL5	RANTES	**CCR1, 3, 5**	Monocyte/macrophage, T cell (memory T cell > T cell; Th1 > Th2), NK, basophil, eosinophil, immature dendritic cell	Mixed leukocyte recruitment
CCL6	C10, MRP-1, SCYA6	**CCR1**	Monocyte, B cell, $CD4^+$ T cell, NK	Unknown
CCL7	MARC, MCP-3	**CCR1, 2, 3, 5**	Th2 > Th1 cell, monocyte, eosinophil, basophil, immature dendritic cell, NK	Mixed leukocyte recruitment
CCL8	MCP-2	**CCR1, 2b, 5**	Th2 > Th1 cell, monocyte, eosinophil, basophil, immature dendritic cell, NK	Mixed leukocyte recruitment
CCL11	Eotaxin	**CCR3, 5**	Eosinophil, basophil, mast cell, Th2 cell	Eosinophil, basophil and Th2 recruitment
CCL12	MCP-5	**CCR2**	Eosinophil, monocyte, T cell, B cell	Mixed leukocyte recruitment
CCL13	MCP-4, NCC-1, Ckβ6	**CCR2, 3, 5**	Th2 > Th1 cell, monocyte, eosinophil, basophil, dendritic cell	Mixed leukocyte recruitment
CCL14a	HCC-1	**CCR1, 3, 5**	Monocyte	Unknown
CCL14b	HCC-3	**unknown**	Monocyte	Unknown
CCL15	MIP-5, HCC-2	**CCR1, 3**	T cell, monocyte, eosinophil, dendritic cell	Mixed leukocyte recruitment
CCL16	HCC-4, LEC	**CCR1, 2, 5, 8**	Monocyte, T cell, NK, immature dendritic cell	Lymphocyte and monocyte recruitment
CCL17	TARC	**CCR4, 8**	Th2 > Th1 cell, immature dendritic cell, thymocytes, regulatory T cells	T cell recruitment
CCL18	DC-CK1, PARC	**PITPNM3**	Naïve T cell > activated T cell, immature dendritic cell, mantle zone B cell	Lymphocyte and dendritic cell homing
CCL19	MIP-3β, ELC	**CCR7**	Naïve T cell, mature dendritic cell, B cell	T cell and dendritic cell migration into para-follicular zones of lymph nodes
CCL20	MIP-3α, LARC	**CCR6**	Memory T cells, Th17 cells, blood mononuclear cells, immature dendritic cells, activated B cells, GALT development	Th17 recruitment Dendritic cell positioning in tissue
CCL21	SLC, 6Ckine, Exodus-2, Ckβ9	**CCR7**	Naïve T cell, B cell, thymocyte, NK, mature dendritic cell	T cell and dendritic cell migration into para-follicular zones of lymph nodes
CCL22	MDC	**CCR4**	Immature dendritic cell, NK, T cells (Th2 > Th1), thymocyte, endothelial cell, monocyte, regulatory T cell	NK and T cell recruitment

Table 1 (continued)

Name	Synonyms	Receptor	Target cell	Major function
CCL23	MPIF-1, CK-β	**CCR1, FPRL-1**	Monocyte, T cell, resting neutrophil	Monocyte, neutrophil and T cell migration
CCL24	Eotaxin-2, MPIF-2, Ckβ6	**CCR3**	Eosinophil, basophil, T cell	Eosinophil, basophil and Th2 recruitment
CCL25	TECK	**CCR9**	Macrophage, thymocyte, dendritic cell, intraepithelial lymphocyte, IgA plasma cell, mucosal memory T cell	Lymphocyte recruitment into intestine
CCL26	Eotaxin-3, MIP-1α, IMAC, TSC-1	**CCR3**	Eosinophil, basophil, fibroblast	Eosinophil, basophil and Th2 recruitment
CCL27	CTACK	**CCR10**	Skin homing memory T cell, B cell	T cell recruitment into skin
CCL28	MEC	**CCR10**	T cell, eosinophil, IgA^+ B cell	T and B cells homing in mucosa
CXC family				
CXCL1	GRO-α, GRO-1, NAP-3, KC	**CXCR2**	Neutrophil, fibroblast	Neutrophil recruitment
CXCL2	GRO-β, GRO-2, NAP-2α	**CXCR2**	Neutrophil, fibroblast	Neutrophil recruitment
CXCL3	GRO-γ, GRO-1, NAP-3	**CXCR2**	Neutrophil, fibroblast	Neutrophil recruitment
CXCL4	PF4	**CXCR3b**	Fibroblast, endothelial cell	Platelet aggregation
CXCL5	ENA-78	**CXCR2**	Neutrophil, endothelial cell	Neutrophil recruitment
CXCL6	GCP-2	**CXCR2**	Neutrophil, endothelial cell	Neutrophil recruitment
CXCL7	NAP-2	**CXCR1, 2**	Fibroblast, neutrophil, endothelial cell	Neutrophil recruitment
CXCL8	IL-8, NPP-1, MDNCF, GCP-1	**CXCR1, 2**	Neutrophil, basophil, endothelial cell	Neutrophil recruitment
CXCL9	Mig, CRG-10	**CXCR3**	Activated T cell (Th1 > Th2), NK, B cell, endothelial cell, plasmacytoid dendritic cell	Effector T cell recruitment
CXCL10	IP-10, CRG-2	**CXCR3**	Activated T cell (Th1 > Th2), NK, B cell, endothelial cell	Effector T cell recruitment
CXCL11	IP-9, ITAC, β-R1	**CXCR3**	Activated T cell (Th1 > Th2), NK, B cell, endothelial cell	Effector T cell recruitment
CXCL12	SDF-1α/β	**CXCR4, 7**	$CD34^+$ bone marrow cells, thymocytes, monocytes/macrophages, naïve activated T cell, B cell, plasma cell, neutrophil, immature and mature dendritic cells, plasmacytoid dendritic cells	B cell migration into lymph nodes Plasma cell migration into bone marrow
CXCL13	BCA-1, BLC	**CXCR5**	Naïve B cell, activated CD4 T cells, immature and mature dendritic cells	B cell migration into lymph nodes and into follicles T follicular helper cell migration into follicles
CXCL14	BRAK, Bolekine	**unknown**	T cell, monocyte, B cell	Monocyte and dendritic cell migration
CXCL15	Lungkine, WECHE	**unknown**	Neutrophil, epithelial cell, endothelial cell	Unknown
CXCL16	Sexckine	**CXCR6**	Activated T cell, NKT, endothelial cells	Macrophage scavenger receptor
CX_3C family				
CX_3CL1	Fractalkine, Neurotactin, ABCD-3	**CX_3CR1**	Activated T cell, monocyte, neutrophil, NK, immature dendritic cell, mast cell, astrocytes, neurons, microglia	T cell, NK and macrophage recruitment

SCM-1α single C motif-1α, *ATAC* activation-induced T cell-derived and chemokine-related cytokine, *NK* natural killer cell, *Th* helper T cell, *MCP-1* Monocyte chemoattractant protein-1, *MIP-1α* Macrophage inflammatory protein-1α, *HIV* human immunodeficiency virus, *RANTES* Regulated on Activation Normal T Cell Expressed and Secreted, *MCP-4* Monocyte chemoattractant protein-4, *HCC-1* hemofiltrate CC chemokine-1,*TARC* T cell and activation-related chemokine, *ELC* Epstein-Barr virus-induced receptor ligand chemokine, *GALT* gastrointestinal-associated lymphoid tissue, *LARC* liver and activation-related chemokine, *SLC* secondary lymphoid tissue chemokine, *MDC* macrophage-derived chemokine, *MPIF-1* myeloid progenitor inhibitory factor-1, *MPIF-2* myeloid progenitor inhibitory factor2, *TECK* thymus-expressed chemokine, *NAP-3* neutrophil activation peptide-3, *KC* keratinocyte chemoattractant, *ENA-78* epithelial cell-derived neutrophil-activating factor-78 amino acids, *GCP-2* granulocyte chemoattractant protein-2, *Mig* monokine-inducd by γ-interferon, *IP-10* γ-interferon-inducible protein 10, *SDF-1α/β* stromal cell-derived factor, *BLC* B-lymphocyte chemokine

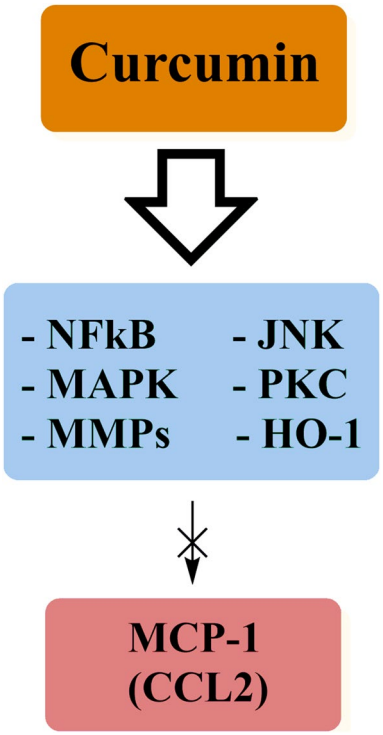

Fig. 1 Various molecular targets through which curcumin inhibits MCP-1

occurred due to upregulation in the expression of heme oxygenase-1 (HO-1), which inhibits the production of LPS-induced reactive oxygen species (ROS) (Zhong et al. 2013). Bao et al. reported that curcumin reduced LPS-induced MCP-1 expression in the fetus-derived glomerular mesangial cells (Bao et al. 2003).. In addition, Tham and colleagues showed that curcumin could downregulate CCL2 expression in human umbilical vein endothelial cells (HUVEC) at concentrations lower than 12.5 µM after 24 h of exposure to curcumin (Tham et al. 2015). Moreover, Ziaei et al. reported that concentrations of curcumin lower than 12.5 µM were able to significantly inhibit TNF-α-induced expression of MCP-1 in HUVECs after 3 h of exposure (Ziaei et al. 2015). Meng et al. also showed that curcumin pre-treatment (3–50 µM/L) could attenuate the LPS-induced expression of MCP-1 in a dose-dependent manner in vascular smooth muscle cells (VSMCs) (Meng et al. 2013). These studies demonstrate the universal CCL2-inhibitory effects conferred by curcumin.

CXCR4/CXCL12

CXCR4 and its ligand, CXCL12, or stromal cell-derived factor-1 (SDF-1), are involved in the development of hematopoietic, endothelial, and nervous system tissues and regulate the migration, homing, and survival of progenitor cells during embryogenesis. In addition, the CXCR4/CXCL12 axis plays a key role in HIV infection, stem cell mobilization, autoimmune disorders, cancers, and tissue regeneration (Shishodia 2013; Peled et al. 2012). Several studies have shown that curcumin induces CXCR4 expression in the follicular lymphoma cell line (Skommer et al. 2007) and mediates the migration of retinal endothelial cells in humans (Sameermahmood et al. 2008). In addition, curcumin has been shown to impair the expression of CXCL12 and decrease select proteins in human tumor cell lines. Interestingly, using an orthotropic mouse model, it has been demonstrated that curcumin-mediated inhibition of CXCL12 expression serves to sensitize colorectal cancer cells to capecitabine by modulating the expression of CXCR4 (Kunnumakkara et al. 2009).

CCR7/CCL21

Fu et al. conducted a study to evaluate the effects of curcumin on healthy human circulatory leukocyte-derived fibrocytes and reported that curcumin treatment (20 µM for 72 h) significantly reduced CCR7 expression (Fu et al. 2015). It appears that the differentiation and migration of human circulatory fibrocytes occurs via regulation of the CCR7/CCL21 axis, in particular, reduction in the expression of CCR7 (Sun et al. 2017).

Chemokine-based therapeutic effects of curcumin (Table 2)

Inflammatory diseases

Nervous system (Fig. 2)

Astrocytes are the most abundant glial cells in the central nervous system (CNS) and are involved with maintaining hemostasis and neuronal function (Röhl et al. 2007; Farina et al. 2007). Astrocytes influence the migration of immune cells across the blood–brain barrier (BBB) via MCP-1 expression (Ransohoff et al. 2003). Curcumin has been documented to significantly reduce the production of pro-inflammatory cytokines and chemokines, including MCP-1 and MIP-1β, in astrocytes and microglial cells through the inhibition of JNK phosphorylation (Qureshi et al. 2018; Chen et al. 2015; Zhang et al. 2012). Seyedzadeh and colleagues evaluated the immunomodulatory effects of curcumin on the LPS-induced U373-MG human astrocyte cell line as an in vitro model of multiple sclerosis and demonstrated that curcumin could attenuate the expression of the MCP-1, which serves as the key chemoattractant for recruitment of immune cells into the CNS (Seyedzadeh et al. 2014). In

Table 2 Chemokine-based therapeutic effects of curcumin in experimental models

			Curcumin dose/concentration	Type of model	Findings	Ref
Inflammatory diseases	Nervous system	In vitro models	0, 2.5 and 5 μM	LPS-induced U373-MG human astrocyte cell line as a model of MS	The MCP-1 expression ↓	(Seyedzadeh et al. 2014)
			1, 5, 10, 15 and 20 μM for 24 h	Mouse N9 microglial cells	HIV-1 gp120-induced expression of MCP-1 ↓	(Guo et al. 2013)
			10 and 25 μM curcumin 30 min prior to LPS treatment	LPS-treated microglial cells and astrocytes	The LPS-induced expression of MCP-1 ↓	(Chen et al. 2015)
			40 mg/kg	Rat model of acute SCI LPS-challenged astrocytes	RANTES expression ↓	(M. S. Lin et al. 2011)
			100 mg/kg for 14 days	Rat model of sciatic nerve CCI	NF-κB p65 and CX3CR1 in the spinal cord and DRG ↓ CCI-induced neuropathic pain ↓	(H. Cao et al. 2014)
		In vivo models	100 mg/kg	PTZ-induced rat model of chronic epilepsy	Glial cell activation ↓ MCP-1 expression in the hippocampus and cortex ↓ Cognitive deficits ↓	(Kaur et al. 2015)
			20 mg/kg PLGA-encapsulated Cur-NPs	Mouse model of EBI after experimentally-induced SAH	The expression of MCP-1, MIP-2, and CINC-1 ↓	(Z. Y. Zhang et al. 2017)
			100 mg/kg	Both in vitro experiments and an in vivo rat model	The expression of MCP-1, CXCL10, and RANTES ↓ Infiltration of T cells and macrophages ↓ Glial scar formation ↓ Inflammation-induced fibrosis ↓	(Yuan et al. 2017)
			50, 100 and 200 mg/kg for 10 days	Arthritic pain in a rat model of spinal cord inflammation	Activation of glial cells ↓ Production of MCP-1 and MIP-1α inflammatory mediators in the spinal cord ↓	(Chen et al. 2015)
			0.8 g/kg for 12 weeks	p25Tg transgenic mice as experimental animal model for AD	Neuro-inflammation and neurodegeneration ↓ Production of MIP-1α ↓	(Sundaram et al. 2017)
	Liver	In vivo models	100 mg/kg	Rat model of metabolic and chemical-induced NASH	CX3CL1 ↑ RANTES ↓	(Pickich et al. 2019)
			200 mg/kg for 4 weeks	Mouse model of CCl_4-induced liver fibrosis (in vivo) RAW264.7 cells (in vitro)	MCP-1 and CCL7 ↓ Infiltration of $Ly6C^{high}$ monocytes in the liver ↓	(X. A. Zhao et al. 2018)

Table 2 (continued)

		Curcumin dose/concentration	Type of model	Findings	Ref
		200 mg/kg for 6 weeks	Rat model of CCl_4-induced liver fibrosis	MCP-1 expression ↓ Liver injuries ↓	(Tu et al. 2012)
		50 mg/kg for 8 weeks	Rat model of CCl_4-induced liver fibrosis	CXCL12/CXCR4 biological axis ↓ Hepatic stellate cell activation and migration ↓	(Qin et al. 2018)
		200 mg/kg	Murine model of ConA-induced hepatitis	CXCL10 ↓ Disease severity ↓	(Tu et al. 2011)
Cardiovascular disorders	In vitro models	0.1, 1, 5 and 10 μM curcumin + 0.1, 0.5, 1 and 5 μM luteolin	TNF-α-induced vascular inflammation in EA.hy926 human endothelial cell line	MCP-1 expression ↓	(L. Zhang et al. 2019)
		combined curcumin (500 mg/kg) and luteolin (500 mg/kg) therapy for 1 week	Mouse aortic endothelial cells		
		Not mentioned	oxLDL-treated macrophages	MCP-1 expression ↓	(T. Liu et al. 2014)
Kidney diseases	In vivo models	1 and 5 mg/kg for 3 days	Murine renal cells (in vivo) Human HK-2 renal tubular epithelial cell line (in vitro)	MCP-1 and CXCL8 expression ↓	(F. Zhong et al. 2011)
		30 mg/kg over a 5-week period	Factor-H-deficient mice	MCP-1 expression ↓	(Jacob et al. 2013)
		100 mg/kg/day for 8 weeks	STZ-induced diabetic nephropathy rat model	Levels of inflammatory mediators (*i.e.*, MCP-1) ↓ Macrophage recruitment into the renal tissue ↓	(Soetikno et al. 2011)
		120 mg/kg for 5 days both as pre-treatment and post-treatment	Rat model of cisplatin-induced nephrotoxicity	Pre-treatment; the levels of the CXCL8 chemokine ↓ and inflammation and toxicity ↓ Post-treatment; no positive effects	(Kumar et al. 2017)
		100 mg/kg with/without cisplatin	Mice with cisplatin-induced nephrotoxicity	The expression of MCP-1 ↓	(Ueki et al. 2013)
Lungs	In vitro models	Not mentioned	Hydrogen peroxide-treated human A549 alveolar epithelial cells	IL-8 and ROS production ↓	(Biswas et al. 2005)
		100 μM for 24 h	AEC II isolated from the rat model of COPD	IL-8, MCP-1, and MIP-2α inflammatory mediators ↓	(Gan et al. 2016)
		Not mentioned	BEAS-2B human bronchial epithelial cell line	Ovalbumin and IL-4-induced MCP-1 overexpression ↓	(Zhu et al. 2019)
	In vivo models	0.2, 0.5, 1 and 2% w/w for 7 days as pre-treatment	NTHi lysate exposured mice	KC expression in BALF ↓ Neutrophil recruitment to the lungs ↓	(Moghaddam et al. 2009)
		75, 150 and 300 mg/kg	Murine model of bleomycin-induced ALI	CXCL1, CXCL5 and CXCR12 in the lungs ↓	(Gouda and Bhandary 2018)

Table 2 (continued)

			Curcumin dose/concentration	Type of model	Findings	Ref
			Not mentioned	Mouse model of acute LPS-induced lung injury	MIP-2 in the BALF ↓	(J. Kim et al. 2016)
			50 mg/kg	Murine model of *staphylococcus aureus*-induced ALI	MCP-2 and KC levels ↓ Infiltration of neutrophils into lung tissue ↓	(Xu et al. 2015)
			50 mg/ kg for 5 days as prophylaxis	mice with viral-induced ARDS	MCP-1 expression in both in inflammatory infiltrates and lung tissue ↓	(Avasarala et al. 2013)
			Not mentioned	Murine model of chronic asthma	Ovalbumin and IL-4-induced MCP-1 overexpression ↓	(Zhu et al. 2019)
			5 mg/kg	Mouse model of ovalbumin-induced chronic asthma	CCL11 expression ↓ Fibrosis ↓	(Chauhan et al. 2017)
			20 and 100 mg/kg	Mouse model of ovalbumin-induced allergic asthma	Eotaxin expression ↓	(Shahid et al. 2019)
	Bowel diseases	In vitro models	50 µg/mL	CEC	Mucosal infiltration of neutrophils ↓ MIP-2, KC, and MIP-1α expression and secretion ↓	(Larmonier et al. 2011)
			50 µM	T-84 human colorectal carcinoma cells and young adult mouse colonocytes (YAMC)	The colonic expression of CXCL9, CXCL10, and CXCL11 ↓	(Midura-Kiela et al. 2012)
		In vivo models	0.2% w/w nanoparticle curcumin 7 days before model induction	DSS-induced murine model of experimental colitis	Mucosal expression of CXCR1 and CXCR2 ↓	(Ohno et al. 2017)
	Joints	In vitro models	1–20 µM liposomal curcumin (Lipocurc™)	SW982 human synovial fibroblast and RAW264 murine macrophage cell line	The expression of inflammatory chemokines ↓	(Kloesch et al. 2016)
			3 µM; pre-treatment for 30 min	human OASFs	The MCP-1-induced VCAM-1 expression ↓	(Y. M. Lin et al. 2012)
	Others	In vivo models	0.3 and 1 µM curcumin and its analog, CUR-Br before induction	TPA-induced ear edema murine mode (in vivo)	KC/CXCL1 ↓	(Rakariyatham et al. 2019)
			10 µM	Murine model of RP (in vivo)	Progression of retinal degeneration ↓ Activation of microglia cells ↓ following the CCL2 expression inhibition	(Y. Wang et al. 2017b)
			6, 30 and 60 µg/kg	New Zealand white rabbits (in vivo)	Improved the wound healing process via the significant ↓ in IL-1, IL-6, and IL-8	(Jia et al. 2014)
			50 µM	LPS-stimulated neutrophils (in vitro)	Neutrophil infiltration ↓ MIP-1α, MIP-1β, IL-8, and GRO-α expression ↓	(Antoine et al. 2013)

Table 2 (continued)

			Curcumin dose/concentration	Type of model	Findings	Ref
				Murine model of air pouch inflammation (in vivo)		
Infectious diseases	Bacterial infections	In vitro models	Not mentioned	HMEECs	CXCL5 expression ↓	(Konduru et al. 2016)
			200 µM for 5 to 60 min	Live *Moraxella catarrahalis* bacteria-exposed Detroit 562 pharyngeal cell line as in vitro model of mucositis	The release of IL-8 and MCP-1 ↓	(Lüer et al. 2012)
		In vivo models	500 mg/kg for 6 and 18 weeks	Mouse model of *H. pylori*-induced infection	CCL20, CCL5, CXCL1, CXCL10, CXCL11, and CCL25 expression ↓	(Santos et al. 2015)
			50 mg/kg for 1 h before and 1 h after induction	Murine model of NTHi-induced OM	CXCL5 expression ↓	(Konduru et al. 2016)
	Viral infections	In vivo models	PLGA-encapsulated curcumin	HSV-2-infected mice	Severity of HSV-2 infection and risk for HIV ↓ The production of MCP-1 and other inflammatory mediators ↓	(Vitali et al. 2020)
		In vitro models	Pre-treatment with 5 or 50 µM	gp-120- exposed GECs	CXCL8, RANTES, and IP-10 expression ↓	(Ferreira et al. 2015)
Cancer		In vitro models	30 µM	Human PC3 prostate cancer cell line	Adhesion, invasion and motility ↓ CCL2 activity ↓	(Herman et al. 2009)
			25 µM	MDA-MB-231 human metastatic breast cancer cell line and human primary mammary cancer-derived cells	CXCL1 and CXCL2 expression ↓	(Kronski et al. 2014)
			15 µM	Human PC3 prostate cancer cell line	CXCL1 and CXCL2 expression ↓	(Killian et al. 2012)
			Oxaliplatin and curcumin	Primary colorectal cancer cells with liver metastasis-derived cells	CXCL1 expression ↓	(Ruiz de Porras et al. 2016)
			5–40 µM for 24 h	SW620 colorectal cancer cell line	NKD2-Wnt-CXCR4 signaling pathway ↓	(Z. Zhang et al. 2016)
			10, 25 and 50 µM for 24, 48 and 72 h	SKOV3 human ovarian cancer cell line	CXCL12 and CXCR4 expression ↓	(Xiaoling et al. 2010)
		In vivo models	Curcuminoids formulated for 8 weeks	Patients with solid tumors	Serum levels of MCP-1 ↓	(Panahi et al. 2014a)
			500 mg, three times a day for 4 weeks	Male patients with pulmonary complications arising from sulfur mustard intoxication	MCP-1 ↓	(Panahi et al. 2015b)
			FOLFOX + 2 g/day curcumin	Colorectal cancer patients	No significant changes in the serum levels of CXCL1 following treatment	(Howells et al. 2019)
			50 mg/kg for 4 days	Murine model of colon cancer	CXCL1 and CXCL2 expression ↓	(Sakai et al. 2016)

Table 2 (continued)

		Curcumin dose/concentration	Type of model	Findings	Ref
		Topical curcumin (2 µM) and urosilic acid combined therapy	Murine model of skin tumor	CXCL2 expression ↓	(Tremmel et al. 2019)
		Curcumin gum formulation (30 min chewing and packing)	Human healthy volunteers	Serum CXCL1 levels ↓	(Boven et al. 2019)
		Curcumae radix extract (CRE)	Murine model of breast cancer metastasis (MMTV-PyMT transgenic mice) (in vivo)	CCR7 expression ↓ Motility and cellular migration ↓	(Kaya et al. 2019)
			MCF7 cells (in vitro)		
		500 mg capsule form of phytosomal curcumin (CCP)	Murine model of GBM	MCP-1 expression in TAM ↑ Destruction of GBM cells ↑	(Mukherjee et al. 2018)
Pregnancy	In vivo models	100 µg/kg	LPS-induced adverse pregnancy outcomes in a mouse model	MIF, MCP-1, and MIP-1 expression ↓	(J. Zhou et al. 2017)
		0.36 mg/kg	LPS-induced pre-eclampsia in a rat model	MCP-1 expression ↓ Blood pressure ↓ Concentration of urinary proteins ↓	(Gong et al. 2016)
	In viro models	1, 5, 10, 20 and 40 µg/ml for 24, 48 and 72 h	EESC cells	MCP-1 and RANTES expression ↓	(Chowdhury et al. 2019)

LPS lipopolysaccharide, *MS* multiple sclerosis, *PTZ* pentylenetetrazole, *PLGA* poly lactide-co-glycolide, *Cur-NPs* curcumin nanoparticles, *EBI* early brain injury, *SAH* subarachnoid hemorrhage, *CINC-1* chemokine-induced neutrophil chemoattractant-1, *CCI* chronic constrictive injury, *DRG* dorsal root ganglion, *SCI* spinal cord injury, *AD* Alzheimer's disease, *NASH* non-alcoholic steatohepatitis, CCl_4 carbon tetrachloride, *ConA* Concavalin A, *oxLDL* Oxidized low-density lipoprotein, *STZ* streptozotocin, *ROS* reactive oxygen species, *KC* keratinocyte chemoattractant, *BALF* broncho-alveolar lavage fluid, *COPD* Chronic obstructive pulmonary disease, *NTHi* typeable *Heamophilus influenza*, *AEC II* alveolar epithelial cell type II, *ALI* acute lung injury, *ARDS* acute respiratory distress syndrome, *CEC* colonic epithelial cells, *DSS* dextran sodium sulfate, *YAMC* young adult mouse colonocytes, *OASF* osteoarthritis synovial fibroblasts, *CUR-Br* 7 7'-bromo-curcumin, *TPA* 12-O-tetradecanoylphorbol-13-acetate, *RP* retinitis pigmentosa, *H. pylori Helicobacter pylori*, *OM* otitis media, *HMEEC* human median ear epithelial cell, *HSV-2* herpes simplex virus-2, *HIV* human immunodeficiency virus, *GEC* gp-120- exposed genital epithelial cell, *FOLFOX* folinic acid/5-fluorouracil/oxaliplatin chemotherapy, *HNSCC* head and neck squamous cell carcinoma, *CRE* curcumae radix extract, *CCP* phytosomal curcumin, *GBM* glioblastoma, *TAM* tumor-associated macrophage and microglia, *EESC* eutopic endometrium-derived stromal cells

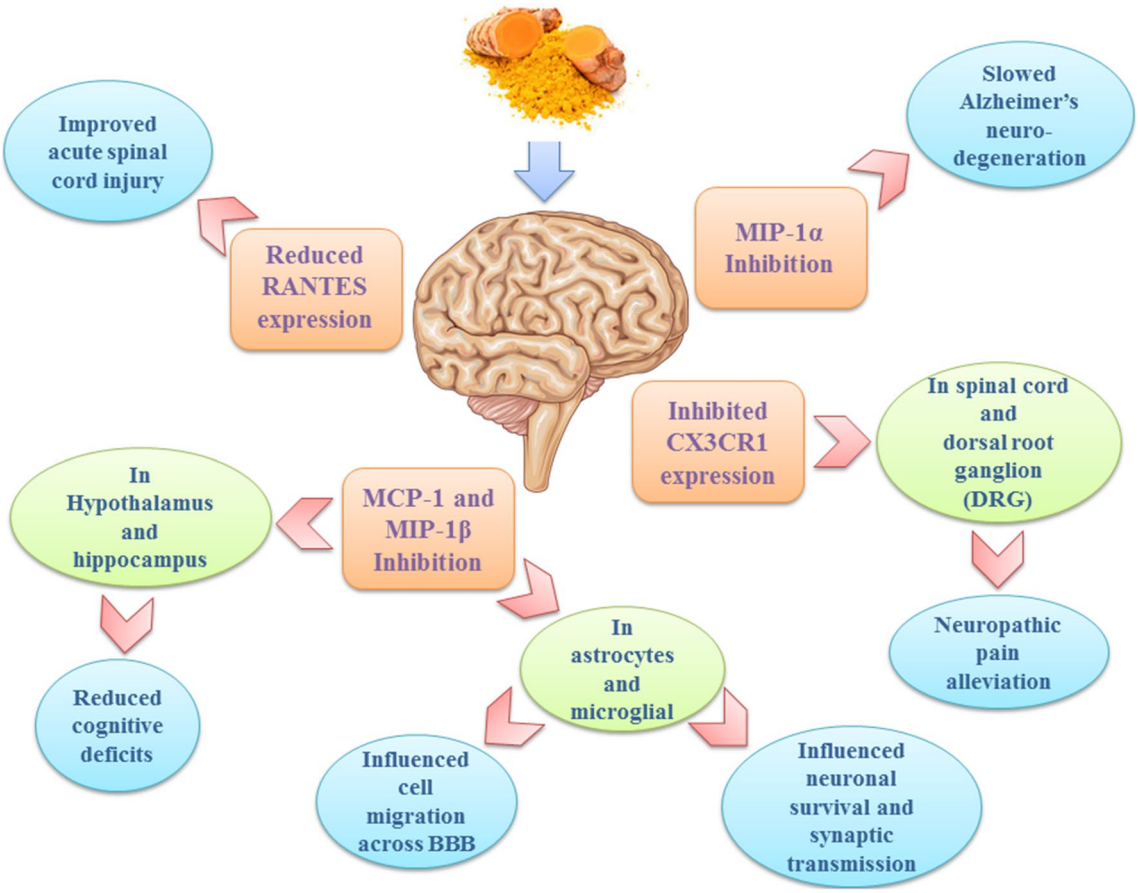

Fig. 2 Chemokine-based therapeutic effects of curcumin on nervous system

addition, Guo et al. reported that curcumin pre-treatment could attenuate the production of MCP-1 in the mouse N9 microglial cell line (Guo et al. 2013).

Following brain injury, microglial cells and astrocytes release inflammatory cytokines and chemokines that influence neuron survival and synaptic transmission, as well as increase brain excitability in epilepsy (Solito and Sastre 2012; Walker and Sills 2012; Vezzani et al. 2012). Kaur et al. evaluated the effects of curcumin on glial cell activation and the reduction in cognitive deficits in the pentylenetetrazole (PTZ)-induced rat model of chronic epilepsy and showed that 100 mg/kg of curcumin significantly inhibited glial cell activation. In addition, the expression of MCP-1 was reduced in the hippocampus and cortex with improved cognitive (Kaur et al. 2015). Furthermore, Zhang et al. evaluated the anti-inflammatory effects of poly (lactide-co-glycolide) (PLGA)-encapsulated curcumin nanoparticles (Cur-NPs) in subarachnoid hemorrhage-induced BBB disruption. Using a mouse model of early brain injury (EBI) after experimentally-induced subarachnoid hemorrhage (SAH), these authors demonstrated that the expression of inflammatory chemokines, including MCP-1, MIP-2, and CINC-1 (chemokine-induced neutrophil chemoattractant-1), were significantly reduced following treatment with 20 mg/kg nano-curcumin suggesting that curcumin conferred protective effects in SAH (Zhang et al. 2017).

Spinal cord injury leads to glial scar formation by astrocytes, which severely hinders neuron regeneration. Using both in vitro experiments and an in vivo rat model, Yuan et al. reported that curcumin inhibits glial scar formation and inflammation-induced fibrosis. The authors demonstrated that curcumin downregulated the expression of MCP-1, CXCL10, and RANTES chemokines, as well as reduced the infiltration of T cells and macrophages by inhibiting NF-κB signaling in astrocytes (Yuan et al. 2017).

Chen et al. evaluated the anti-inflammatory effects of curcumin on arthritic pain in a rat model of spinal cord inflammation and demonstrated that oral treatment with curcumin attenuated both the activation of glial cells and the production of MCP-1 and MIP-1α inflammatory mediators in the spinal cord. Additionally, it was shown by these authors that the LPS-induced expression of MCP-1 was significantly reduced in cultured microglial cells and astrocytes (Chen et al. 2015). In another study using an experimental rat

model, Cao and colleagues evaluated the effects of curcumin on pain threshold and NF-κB and CX3CR1 expression following sciatic nerve chronic constrictive injury (CCI). Cao et al. reported that curcumin significantly reduced the elevated expression of NF-κB p65 and CX3CR1 in the spinal cord and dorsal root ganglion (DRG) and alleviated CCI-induced neuropathic pain (Cao et al. 2014). In another study, Lin et al. showed that curcumin reduced the expression of RANTES both in a rat model of acute spinal cord injury (SCI) and LPS-challenged astrocytes in vitro (Lin et al. 2011).

To evaluate the therapeutic effects of curcumin on neuroinflammation and neurodegeneration in Alzheimer's disease (AD), Sundaram et al. treated p25Tg transgenic mice (which overexpress p25 and act as an experimental animal model for AD) and demonstrated that curcumin efficiently counteracts glial cell activation and the production of inflammatory cytokines and chemokines such as MIP-1α. These authors convincingly demonstrated that curcumin inhibited p25-mediated neuroinflammation and the progression of neurodegeneration in this experimental animal model of AD (Sundaram et al. 2017).

Th17 lymphocytes can migrate across the BBB and induce the recruitment of immune cells, which leads to inflammation in the CNS (Xie et al. 2011; Kebir et al. 2007). IL-17, the major cytokine secreted by Th17 cells, induces the production of CXCL1, CXCL2, and CXCL8/IL-8 chemokines and their receptors (*i.e.*, CXCR1 and CXCR2). These chemokines and their receptors are involved in the recruitment of lymphocytes and monocytes from the circulation into the CNS and, therefore, have been suggested to play a critical role in the pathogenesis of multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE). Additionally, CXCL8 is involved with the infiltration of neutrophils (Carlson et al. 2008). Using the well-established EAE animal model, curcumin treatment was shown to decrease the recruitment and differentiation of inflammatory cells, especially Th17, in the CNS (Xie et al. 2009; Natarajan and Bright 2002). It would appear that these inhibitory functions result from the downregulation of NFκB and disruption of CXCL1 and CXCL2 signaling pathways (Bachmeier et al. 2008; Choi et al. 2010).

Liver

Potential antioxidant, anti-inflammatory, and antifibrogenic effects of curcumin have been suggested to account for its beneficial hepatoprotective properties (Ghosh et al. 2011). All of these effects result from the pleiotropic and multi-target activity of curcumin. Accordingly, the numerous effects of curcumin on multiple organs and signaling pathways serve to regulate a wide variety of biochemical processes and influence the expression of different genes involved in liver health and homeostasis (Vera-Ramirez et al. 2013). We now present multiple lines of evidence that highlight the hepatoprotective effects of curcumin via chemokine-dependent processes.

Pickich et al. evaluated the effects of curcumin on the serum levels of cytokines and chemokines in a rat model of metabolic (i.e., Western diet (WD)) and chemical (i.e., carbon tetrachloride (CCl_4))-induced non-alcoholic steatohepatitis (NASH). They reported that curcumin treatment resulted in a 121% increase in Fractalkine (or CX3CL1, which may have an anti-inflammatory and anti-fibrotic role in the liver) (The levels of RANTES or CCL5 that has increased expression in hepatocytes in both toxic and diet-induced liver injury and is associated with the pathogenesis and progression of non-alcoholic fatty liver disease was decreased by 22% Kirovski et al. 2010; Seki et al. 2009).

$Ly6C^{high}$ monocytes facilitate liver fibrosis by inducing the production of pro-inflammatory and pro-fibrotic cytokines and chemokines (Pellicoro et al. 2014). MCP-1 and CCL7 are major players in the recruitment and migration of $Ly6C^{high}$ monocytes (Brempelis and Crispe 2016). Zhao et al. reported that the mRNA expression of both MCP-1 and CCL7 was dramatically increased in a mouse model of CCl_4-induced liver fibrosis and that treatment with curcumin significantly reduced the expression of these inflammatory chemokines and decreased the infiltration of $Ly6C^{high}$ monocytes in the liver. Moreover, these same authors noted that RAW264.7 cells co-cultured with curcumin resulted in a significant decrease in the expression of MCP-1 and CCL7. Interestingly, macrophages were induced to the M1 phenotype in a dose-dependent manner (Zhao et al. 2018). In another study, Tu et al. demonstrated that curcumin treatment (200 mg/kg for 6 weeks) in a rat model of CCl_4-induced liver fibrosis significantly reduced liver injuries due to MCP-1 and the inhibition of other mediators of inflammation (Tu et al. 2012).

It has been reported that curcumin influences various chemokines and exerts protective effects in the liver. Qin et al. reported the anti-fibrotic effects of curcumin in liver fibrosis via a dose-dependent inhibition of the CXCL12/CXCR4 biological axis, which leads to blockage of hepatic stellate cell activation and migration (Qin et al. 2018). Furthermore, using a murine model of Concavalin A (ConA)-induced hepatitis, Tu et al. demonstrated that pre-treatment with 200 mg/kg curcumin reduced the levels of inflammatory mediators, including the CXCL10 chemokine, and alleviated disease severity (Tu et al. 2011).

Cardiovascular disorders

The cardiovascular protective effects of curcumin have been demonstrated in recent studies. Curcumin has previously been shown to ameliorate cardiac fibrosis, atherosclerosis,

and myocardial ischemia and infarction, as well as provide anti-inflammatory, antioxidant, and anti-apoptotic properties in various cardiovascular-related disorders (Pourbagher-Shahri et al. 2021; Li et al. 2020). There is an association between cardiovascular disease (CVD) and secreted cytokines, which serve as biomarkers of primary-phase inflammation (Karimian et al. 2017b). In other words, elevated chronic inflammation plays a key role in the development and progression of CVD (Ruparelia et al. 2017). Increased levels of inflammatory mediators lead to the simultaneous activation and adhesion of monocytes to the endothelium and the uptake of oxidized low-density lipoproteins (oxLDL). These processes facilitate the migration of monocytes to the sub-endothelial space and induce the proliferation of smooth muscle and foam cells and, subsequently, the formation of plaque (Ganjali et al. 2017a). MCP-1 and CXCL8/IL-8 chemokines are considered essential mediators in these events. Zhang et al. evaluated the effects of combined curcumin and luteolin therapy on the synergistic inhibition of TNF-α-induced vascular inflammation in human and mouse vascular cells. They reported that MCP-1 expression was significantly reduced in human endothelial cells with umbilical vein endothelial cell properties and mouse aortic endothelial cells. They showed that this effect resulted from the inhibition of NF-κB translocation to the nucleus (Zhang et al. 2019). Additionally, Liu et al. reported that curcumin significantly reduced MCP-1 expression in oxLDL-treated macrophages by inhibiting the JNK and NF-κB pathways, which suggests that the vascular protective effects of curcumin are related to anti-inflammation and anti-atherosclerosis (Liu et al. 2014). Hence, it would appear that preparing drug formulations of curcumin that overcome obstacles such as low oral absorption and rapid metabolism might suggest its use for the treatment of CVD and CVD-associated disorders via a chemokine-dependent mechanism of action.

Kidney diseases

Different kidney disorders are often characterized by significant metabolic and nutritional disruptions that lead to oxidative stress, as well as uncontrolled and chronic inflammatory responses (de Almeida Alvarenga et al. 2018). Hence, curcumin has been proposed as an important nutritional adjuvant and therapeutic agent for various kidney-associated disorders, since it targets several signaling pathways important to kidney function.

As previously discussed, MCP-1 is essential for monocyte/macrophage infiltration and may play an important role in the development of tubulointerstitial fibrosis (TIF). Blocking the MCP-1/CCR2 pathway can inhibit the progression of fibrosis via the reduction in the recruitment of M1 macrophages (Wada et al. 2004; Kitagawa et al. 2004). In the rat model of unilateral ureteral obstruction (UUO), subcutaneous administration of curcumin significantly attenuated the overexpression of MCP-1 mRNA in the obstructed kidney (Jones et al. 2000). In a model of LPS-induced nephritis, the therapeutic effects of curcumin were mediated by the inhibition of MCP-1 expression and a decrease in monocyte recruitment. Zhong et al. reported that curcumin could

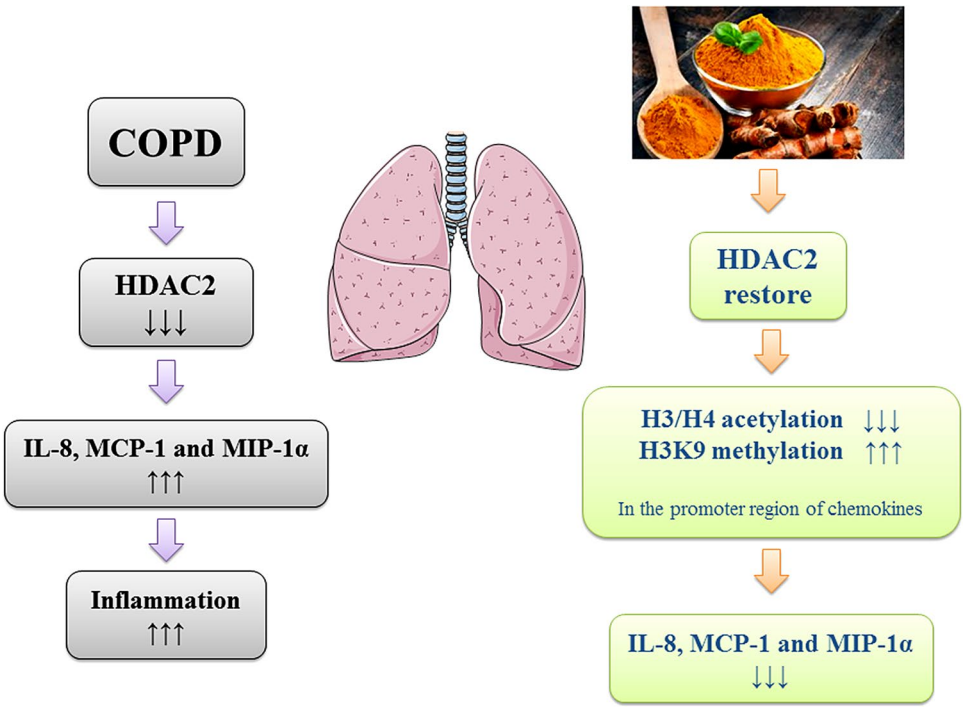

Fig. 3 Chemokine-based anti-inflammatory effects of curcumin in COPD

efficiently reduce LPS-induced mRNA overexpression of MCP-1 in both murine renal cells and the HK-2 renal tubular epithelial cell line. These same authors further reported that curcumin partially controlled the secretion of MCP-1 and CXCL8 chemokines (Zhong et al. 2011). Similar downregulation of MCP-1 levels has also been reported in factor-H-deficient mice resulting from the intraperitoneal administration of curcumin (30 mg/kg) over a 5-week period (Jacob et al. 2013).

Soetinko and colleagues evaluated the effects of 100 mg/kg/day of curcumin for 8 weeks in the streptozotocin (STZ)-induced diabetic nephropathy rat model. These authors demonstrated that curcumin dramatically reduced the levels of inflammatory mediators (*i.e.*, MCP-1) and macrophage recruitment into the renal tissue of diabetic mice. Macrophage infiltration into glomeruli leads to progressive glomerular injury and ultimately results in tubular and glomerular destruction (Soetikno et al. 2011). Similar results have been reported for a couple of curcumin derivatives (B06 and C66), which effectively reduced plasma levels of TNF-α and MCP-1 and improved renal fibrosis, histological abnormalities, and dysfunction in STZ-induced diabetic mice (Adhikary et al. 2004; Pan et al. 2013b).

Cisplatin is a chemotherapy agent for various types of cancers, and several reports have shown that high doses lead to nephrotoxicity in about 20% of patients (Yao et al. 2007). Kumar et al. evaluated the protective effects of curcumin both as pre-treatment and post-treatment in a rat model of cisplatin-induced nephrotoxicity. They reported that curcumin pre-treatment significantly reduced levels of the CXCL8 chemokine, as well as other inflammatory mediators, and attenuated inflammation and toxicity, while curcumin post-treatment showed no positive effects (Kumar et al. 2017).. In another study using the same mouse model of cisplatin-induced nephrotoxicity, Ueki and colleagues reported that curcumin treatment dramatically reduced the expression of MCP-1 and other mediators in the kidney (Ueki et al. 2013).

Lungs

Chronic obstructive pulmonary disease (COPD) is associated with bronchial damage due to injury to both the epithelial and endothelial cell layers. Elevated levels of CXCL2 and IL-8 chemokines have been reported with COPD, which induce neutrophil recruitment to the lung parenchyma and the production of both proteinases and elastases (Lelli et al. 2017; Overbeek et al. 2013; Kobayashi and DeLeo 2009). It has been shown that in hydrogen peroxide-treated human A549 alveolar epithelial cells, curcumin decreased IL-8 and the production of reactive oxygen species (ROS) (Biswas et al. 2005). Additionally, curcumin significantly reduced the levels of the keratinocyte chemoattractant (KC) chemokine (which is a murine homologuehomolog for human IL-8) in broncho-alveolar lavage fluid (BALF), and also led to the inhibition of neutrophil recruitment to the lungs (Moghaddam et al. 2009).

Using an experimental rat model of COPD, Gan et al. reported that the expression of inflammatory mediators, including IL-8, MCP-1, and MIP-2α, were upregulated in alveolar epithelial cells type-II (AEC-II), and that the expression of histone deacetylase-2 (HDAC2) protein was significantly reduced. Following curcumin supplementation in this model, HDAC2 expression was restored, and H3/H4 acetylation and H3K9 methylation in the promoter region of the chemokines was decreased and increased, respectively, which led to a downregulation in the expression of the aforementioned inflammatory chemokines (Gan et al. 2016) (Fig. 3).

In another study, Gouda et al. investigated inflammatory pathways that are regulated by curcumin in a murine model of bleomycin-induced acute lung injury (ALI) and reported that the mRNA expression of CXCL1, CXCL5, and CXCR12 were significantly reduced in lung homogenates of curcumin-treated mice (Gouda and Bhandary 2018). Additionally, Kim and colleagues showed that curcumin dramatically reduced the expression of MIP-2 and other inflammatory mediators in the BAL fluid of mice with acute LPS-induced lung injury (Kim et al. 2016).

Xu et al. previously demonstrated that curcumin improved the respiratory condition in mice with *staphylococcus aureus*-induced ALI and reduced the levels of inflammatory cytokines and chemokines (e.g., MCP-2 and KC) but also decreased the infiltration of neutrophils into lung tissue (Xu et al. 2015). Additionally, Avasarala et al. have evaluated the anti-inflammatory and immunomodulatory effects of curcumin in mice with viral-induced acute respiratory distress syndrome (ARDS) and determined that curcumin prophylaxis (treatment) before the induction of inflammation significantly reduced the expression of inflammatory cytokines and chemokines (including MCP-1) in both inflammatory infiltrates and lung tissue (Avasarala et al. 2013).

Asthma is an inflammatory disorder that is characterized by pulmonary infiltration of eosinophils, neutrophils, and lymphocytes, as well as mucosal hypersecretion and airway hyper-responsiveness (AHR) (Elias et al. 2003). Importantly, MCP-1 (CCL2) is a critical inflammatory mediator in asthmatic airway epithelial cells (Hwang et al. 2017). Zhu et al. reported that curcumin significantly attenuated ovalbumin and IL-4-induced MCP-1 overexpression both in lung tissue of mice in a murine model of chronic asthma, as well as in the BEAS-2B cell line (human bronchial epithelial cells), and it appears that the inhibitory effects of curcumin were mediated by inactivation of the PPARγ-dependent NFκB signaling pathway (Zhu et al. 2019). Chauhan et al. evaluated the impact of intranasal curcumin on the inhibition of

pulmonary fibrosis in a mouse model of ovalbumin-induced chronic asthma and reported that curcumin dramatically reduced the expression of eotaxin (CCL11). CCL11 binds to its specific receptor, CCR3, on eosinophils, basophils, and mast cells and leads to the recruitment of these inflammatory cells to the airways. Moreover, CCL11/CCR3 interaction plays a vital role in the pathogenesis of asthma and airway remodeling and has pro-fibrotic effects on lungs and bronchial fibroblasts (Chauhan et al. 2017). Lastly, using the mouse model of ovalbumin-induced allergic asthma, Shahid et al. reported that curcumin significantly reduced the mRNA expression of inflammatory mediators such as eotaxin (Shahid et al. 2019).

Bowel diseases

In a very interesting in vitro study using colonic epithelial cells (CECs), it was shown that curcumin (50 μg/mL) decreased mucosal infiltration of neutrophils and significantly reduced the expression and secretion of MIP-2, KC, and MIP-1α chemokines by neutrophils and CECs (Larmonier et al. 2011). Along these lines, Ohno et al. reported that curcumin nanoparticles significantly reduced the mucosal mRNA expression of inflammatory cytokines and chemokines, including CXCR1 and CXCR2, in the dextran sodium sulfate (DSS)-induced murine model of experimental colitis. These same authors also reported that there was a dramatic decrease in the infiltration of Gr-1 neutrophils into the colon mucosa in the aforementioned model of experimental colitis (Ohno et al. 2017). Finally, Midura-Kiela and colleagues reported that curcumin decreased the colonic expression of CXCL9 (Mig), CXCL10 (IP-10), and CXCL11 (I-TAC), which are all CXCR3 ligands. All three chemokines are involved in epithelial dysfunction and the pathogenesis of inflammatory bowel disease (IBD). Specifically, these chemokines are secreted by colonic epithelial cells in an IFN-γ-induced manner and are a chemoattractant for activated T-lymphocytes and NK cells, although it should be noted that curcumin inhibits IFN-γ signaling (Midura-Kiela et al. 2012).

Osteoarthritis joints

Kloesch et al. reported that a liposomal curcumin formulation could significantly reduce the expression of inflammatory cytokines and chemokines both in SW982 human synovial fibroblast and RAW264 murine macrophage cell lines (Kloesch et al. 2016). Interestingly, Lin et al. have previously shown that in the synovial fluid of osteoarthritis (OA) patients, MCP-1 production is increased and that its interaction with CCR2 leads to enhanced VCAM-1 expression in osteoarthritis synovial fibroblasts (OASFs). This overall process of increased MCP-1 and elevated VCAM-1 expression is involved in the inflammatory process in synovial fibroblasts. This same group of authors also reported that a 30-min period of curcumin pre-treatment (3 μM) could inhibit the MCP-1-induced increase in VCAM-1 expression (Lin et al. 2012).

Other inflammatory diseases

Rakariyatham et al. have demonstrated that the curcumin analog, 7, 7'-Bromo-curcumin (CUR-Br), exhibits higher chemical stability and greater anti-inflammatory effects when compared to curcumin. Using the 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced ear edema murine model, these same authors also reported that CUR-Br could more efficiently reduce the expression of inflammatory cytokines and chemokines, including KC/GRO (CXCL1), which is a key factor for the recruitment of neutrophils (Rakariyatham et al. 2019).

Wang et al. evaluated the therapeutic effects of curcumin in a murine model of retinitis pigmentosa (RP) in which retinal degeneration (rd1) occurs. Using this model, they showed that curcumin could effectively inhibit the expression of inflammatory mediators such as CCL2, as well as inhibit the activation of microglia cells and, as a result, slow the progression of retinal degeneration (Wang et al. 2017b).

In a study by Jia and colleagues, the effect of intravenously-administered curcumin was assessed for its role in wound healing in New Zealand white rabbits. They demonstrated that curcumin could improve the wound healing process by significantly reducing inflammatory cytokines and chemokines, including IL-1, IL-6, and IL-8 (Jia et al. 2014).

Lastly, Antoine et al. evaluated the anti-inflammatory effects of curcumin on neutrophil activation and infiltration and showed that the expression of MIP-1α, MIP-1β, IL-8, and GRO-α chemokines were reduced in LPS-stimulated neutrophils in vitro, whereas, in the well-established murine model of air pouch inflammation, curcumin significantly decreased the production of multiple inflammatory cytokines and chemokines, including MIP-1α and MIP-1β, as well as dramatically reduced neutrophil infiltration (Antoine et al. 2013).

Infectious diseases

Bacterial infection

Recently, a number of studies have investigated various antibacterial effects of curcumin. Suppressing bacterial DNA replication, inhibiting pathogen motility, and influencing the integrity of the microbial cell membrane are among the most important antibacterial mechanisms of action (Teow et al. 2016). In addition, curcumin administration has been shown

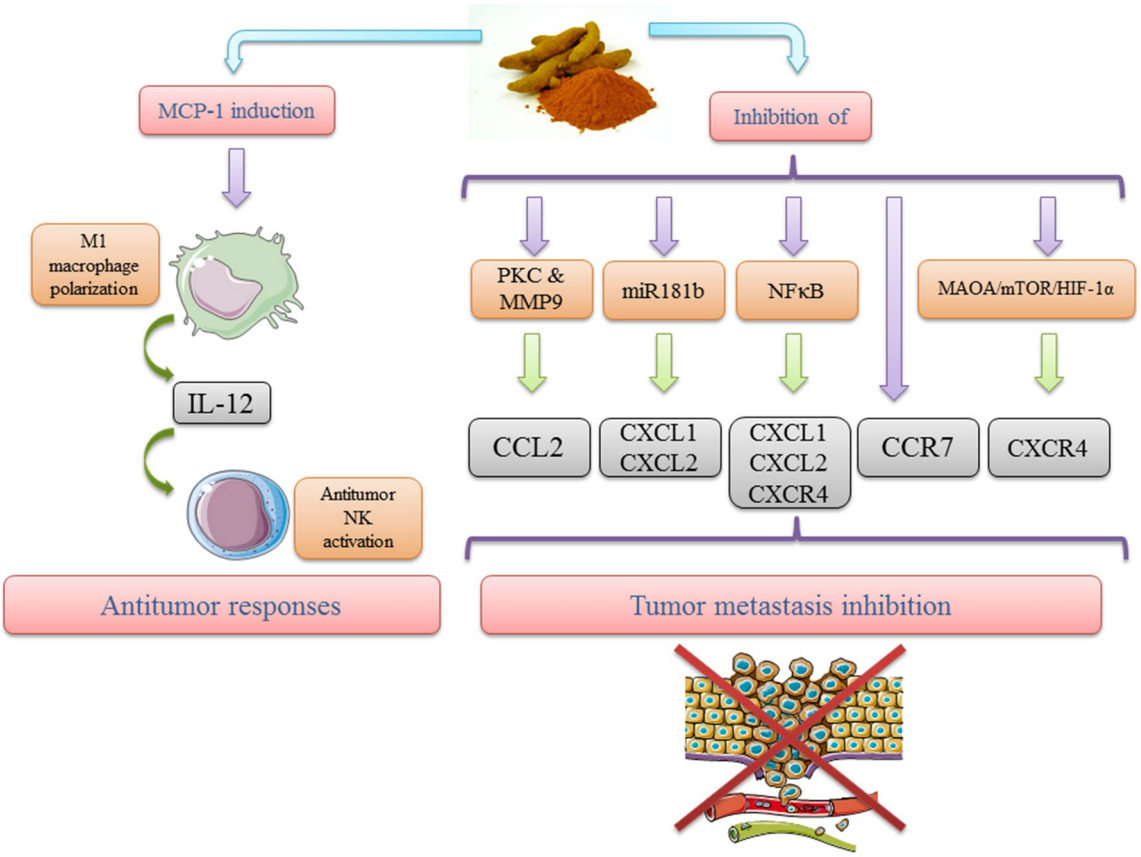

Fig. 4 Chemokine-based anti-tumor effects of curcumin

to affect the expression of specific microbial genes, such as mecA (Rai et al. 2008), as well as toxin binding activity (Na et al. 2011). In this review, we have focused on how curcumin affects both chemokine-related, as well as host-related protective mechanisms in the context of bacterial infections.

Curcumin has been suggested as a dietary supplement for preventing mucosal destruction associated with *Helicobacter pylori* (H. pylori) infection. Santos and colleagues evaluated the anti-inflammatory effects of curcumin on H. pylori-induced infection in an experimental mouse model and reported that curcumin significantly reduced the expression of pro-inflammatory mediators including CCL20, CCL5, CXCL1, CXCL10, CXCL11, and CCL25 in the infected mice (Santos et al. 2015).

In another study, Konduru et al. evaluated the therapeutic effects of curcumin on CXCL5 expression in both an in vivo murine model (non-typeable *Haemophilus influenza* (NTHi)-induced otitis media (OM)) and an in vitro model using human median ear epithelial cells (HMEECs). These authors reported that NTHi-induced CXCL5 expression was significantly reduced via direct inhibition of IκK-β phosphorylation, together with inhibition of p38 MAPK (Konduru et al. 2016).

Lastly, Luer et al. evaluated the anti-inflammatory effects of curcumin on mucositis in an in vitro model. The Detroit 562 pharyngeal cell line was exposed to live *Moraxella catarrahalis* bacteria. These authors showed that treatment with curcumin (200 μM) for 5 to 60 min completely inhibited the release of inflammatory cytokines and chemokines, including IL-8 and MCP-1. Moreover, they determined that repetitive exposure to curcumin led to repetitive inhibition of these mediators for 4 to 6 h (Lüer et al. 2012).

Viral infection

In addition to the antifungal and antimicrobial properties of curcumin, recent studies have shown that curcumin also possesses antiviral activity against several infections caused by a virus (Jennings and Parks 2020). Therefore, below we present the chemokine-related antiviral effects of curcumin.

Herpes simplex virus-2 (HSV-2) is a common sexually transmitted virus that induces the recruitment of HIV-targeted immune cells and is considered a risk factor for human immunodeficiency virus (HIV) infection in female genital tracts. Vitali et al. reported that intravaginal (but not oral or intraperitoneal) delivery of curcumin nanoparticles to the

genital tract of mice could attenuate tissue inflammation and diminish the production of pro-inflammatory mediators, including TNF-α, IL-6, and MCP-1, and potentially lead to both a reduction in the severity of HSV-2 infection and decreased risk for HIV (Vitali et al. 2020).

In a different study, Ferreira and colleagues evaluated the anti-inflammatory potential of curcumin in genital epithelial cells (GECs) as a means to protect them from HIV-1 and HSV-2 viruses. These authors demonstrated that curcumin pre-treatment could restore the integrity of the mucosal barrier, along with inhibition of gp120-mediated upregulation of inflammatory cytokines and chemokines, which included CXCL8, RANTES, and IP-10. These are critical chemoattractants for recruiting HIV target cells to the female genital tract (FGT). Thus, it would appear that curcumin can inhibit and/or control virus proliferation in the FGT (Ferreira et al. 2015).

Cancer (Fig. 4)

Many different studies have documented the efficacy of curcumin as an adjunct chemotherapeutic agent for a variety of cancers. Some of these cancers include breast cancer, prostate cancer, squamous cell carcinoma of the head and neck, lung cancer, and brain tumors. The proposed mechanism of action underlying the beneficial effects of curcumin in various cancers is related to the induction of apoptosis and curcumin-mediated suppression of tumor cell proliferation and invasion. The therapeutic effects of curcumin in cancer occur through a variety of cell signaling pathways (Tomeh et al. 2019). Below, we describe and summarize different studies that have been conducted to evaluate the anticancer potential of curcumin as it pertains to the regulation of chemokines.

It has been previously reported that curcumin can inhibit lung metastasis in mice (Bachmeier et al. 2007). Another study reported that curcumin supplementation for 5 days following the removal of a primary mammary tumor in mice leads to a reduced incidence of metastasis to the lungs (Aggarwal et al. 2005). Interestingly, curcumin decreases both the expression of MCP-1 and IL-1β inflammatory mediators, which are critical for tumorigenesis (Abe et al. 1999). Panahi et al. reported that curcuminoids formulated to have an increased bioavailability (since curcumin alone is poorly absorbed after oral administration) reduced the serum levels of MCP-1 in patients with solid tumors after 8 weeks of treatment (Panahi et al. 2014b). These same authors also determined that 500 mg curcumin, taken three times a day for 4 weeks, modulated the expression of MCP-1 in male patients with pulmonary complications arising from sulfur mustard intoxication (Panahi et al. 2015a).

In addition, in prostate cancer, CCL2 has an important role in the development of metastasis to the bone (Bandyopadhyay 2014). Herman et al. reported that 30 μM curcumin could downregulate CCL2 activity by inhibiting protein kinase C (PKC) and matrix metalloproteinase-9 (MMP-9) in human PC-3 and decreasing adhesion, invasion, and motility in a PC3 cell line in vitro (Herman et al. 2009).

Notably, curcumin can significantly regulate the gene expression of 62 genes in MDA-MB-231 breast cancer cells, and the genes for the pro-inflammatory chemokines CXCL1 and CXCL2 are among the genes that are most strongly downregulated (Bachmeier et al. 2008). Both chemokines have pivotal roles in the migration, proliferation, metastasis, and angiogenesis of tumor cells of various organs (Youngs et al. 1997; Loukinova et al. 2000). Kronski et al. reported that curcumin treatment of both MDA-MB-231 (human metastatic breast cancer cell line) and human primary mammary cancer-derived cells could downregulate the expression of CXCL1 and CXCL2 chemokines via downregulation of miR181b (Kronski et al. 2014). It was shown that miR181b modulation could influence tumor progression and metastasis (Bachmeier et al. 2018). Moreover, studies conducted with the prostate cancer metastasis model showed that curcumin could influence the CXCL1 and CXCL2 chemokines, induce apoptosis, inhibit proliferation, and modulate several metastasis-accelerating factors. In an independent study, Killian and colleagues reported that curcumin could inhibit NFκB activation and reduce the expression of CXCL1 and CXCL2, which leads to the abolishment of the autocrine/paracrine loop between these two chemokines and NFκB, as well as reduces the development of metastasis (Killian et al. 2012).

In breast cancer cells, it appears that after curcumin inhibits NF-κB and the chemokines CXCL1 and CXCL2, the downregulation of CXCL1 leads to reduced expression of CXCR4 as a CXCL12/SDF-1 receptor. This overall process represents a metastasis-accelerating axis that could potentially serve as an avenue for therapeutic intervention (Bachmeier et al. 2008; Burger and Peled 2009). However, CXCL1 expression is limited to only a few types of breast cancer cells; however, it exists in the signature of metastasis to the lung (Albini et al. 2008; Minn et al. 2005). In addition, there is evidence that CXCL1 is associated with metastatic development of colorectal cancer, and tumors that highly express this chemokine have poor prognosis and survival (Wang et al. 2017a; Zhuo et al. 2018). Ruiz de Porras and colleagues have demonstrated that a cell culture of primary colorectal cancer cells with liver metastasis-derived cells had a high baseline expression of CXCL1 that was responsive to combination therapy employing oxaliplatin and curcumin, and these authors suggested that curcumin regulates the expression of CXCL1 via downregulation of NF-κB (Ruiz de Porras et al. 2016). However, in a study by Howells et al., comparing the effects of FOLFOX (folinic acid/5-fluorouracil/oxaliplatin chemotherapy) and

CUFOX (FOLFOX + 2 g/day of oral curcumin) as therapeutic approaches in colorectal cancer patients, no significant differences were seen between plasma levels of CXCL1 before and after the intervention (Howells et al. 2019). 5-fluorouracil (5-FU) is a cancer chemotherapeutic agent that upregulates the expression of CXCL1 and CXCL2 in the bowel and also triggers neutrophil recruitment. Unfortunately, 5-FU treatment for colon cancer typically results in diarrhea. To this end, Sakai et al., using a murine model of colon cancer, reported that curcumin could inhibit 5-FU-mediated diarrhea by downregulating the expression of CXCL1 and CXCL2 in an NFκB-dependent manner (Sakai et al. 2016).

Tremmel and colleagues evaluated the inhibitory effects of topical curcumin and ursolic acid on skin tumor progression and reported that this combination therapy could significantly reduce the expression of inflammatory cytokines and chemokines such as CXCL2. The combination therapy more efficiently abrogates tumor development compared to either agent used alone as monotherapy (Tremmel et al. 2019).

In head and neck squamous cell carcinoma associated with the oral cavity (HNSCC), Boven et al. evaluated the effects of a curcumin gum formulation as a means to prevent HNSCC associated with the oral cavity and showed that chewing and packing the gum against the buccal mucosa for 30 min in healthy volunteers could significantly reduce the serum levels of inflammatory mediators. Among the chemokines measured in this pilot study, which included CXCL1, IL-8, IP-10, and MIP-1α, a significant reduction in serum CXCL1 levels was observed at 30 min and 4 h after chewing the curcumin gum (Boven et al. 2019).

Notably, CCR7 also plays a crucial role in metastasis and has emerged as a novel biomarker for metastasis to lymph nodes in breast cancer. Additionally, this chemokine receptor has been proposed as a prognostic indicator of metastasis in esophageal carcinoma (Legler et al. 2014; Cabioglu et al. 2005; Liu et al. 2013). Kaya et al. reported that curcumae radix extract (CRE) has anti-metastatic effects on MCF7 cells and in the murine model of breast cancer metastasis (MMTV-PyMT transgenic mice) and dramatically inhibits motility and cellular migration, as well as regulation in the gene expression of metastatic markers, including CCR7, metalloproteinase-9, and c-fus and c-jun proto-oncogenes (Kaya et al. 2019).

Downregulation of CXCR4 as a 'metastasis-accelerating' chemokine is another effect of curcumin on chemokines. It has been shown that CXCR4 is associated with tumor motility and invasion, and curcumin has been suggested for CXCR4-mediated inhibition of colorectal cancer progression (Zhang et al. 2016). Zhang et al. previously reported that curcumin inhibits the NKD2-Wnt-CXCR4 signaling pathway in the SW620 colorectal cancer cell line and decreases tumor development (Zhang et al. 2016). In another study, Du et al. demonstrated that cancer-associated fibroblasts (CAFs) could induce epithelial-to-mesenchymal transition (EMT) in prostate cancer cells, as well as accelerate CXCR4 expression and invasion via the monoamine oxidase A/mammalian target of rapamycin (mTOR)/hypoxia-inducible factor-1α (MAOA/mTOR/HIF-1α) signaling pathway. Moreover, these same authors showed that curcumin abrogates invasion and CAF-induced EMT, as well as decreases ROS production and the expression of CXCR4 and IL-6R (Du et al. 2015). Finally, Xiaoling et al. reported that curcumin could dramatically inhibit the expression of CXCL12 and CXCR4, as well as invasion and motility potential, in the SKOV3 human ovarian cancer cell line in a dose-dependent manner (Xiaoling et al. 2010).

It has also been previously suggested that MCP-1 activates and induces M1 macrophages to produce IL-12, a natural killer (NK) cell activator. Thus, the release of MCP-1 in the brain could potentially recruit anti-tumor cells and activate anti-tumor responses. Mukherjee et al. reported that phytosomal curcumin (CCP) could significantly induce the expression of MCP-1 in tumor-associated macrophage and microglia (TAM) in a murine model of glioblastoma (GBM; a primary cerebral tumor) and facilitate the destruction of GBM cells (Mukherjee et al. 2018).

Adverse pregnancy outcomes

Zhou et al. reported that curcumin could ameliorate LPS-induced adverse pregnancy outcomes in a mouse pregnancy model by (1) upregulating Akt phosphorylation in the placenta, (2) reducing the expression of chemokines, such as macrophage migration inhibitory factor (MIF), MCP-1, and MIP-1, and (3) inhibiting the recruitment of $CD86^+$ macrophages to the placenta (Zhou et al. 2017). In another independent study, pregnant rats received LPS to induce pre-eclampsia and then received treatment with curcumin. This study showed that curcumin could reduce blood pressure and the concentration of urinary proteins, as well as reduce the expression of inflammatory mediators such as TLR4, NFκB, IL-6, and MCP-1 (Gong et al. 2016).

Lastly, Chowdhury and colleagues evaluated the effects of curcumin on the secretion of pro-inflammatory and pro-angiogenic cytokines and chemokines in cell culture of eutopic endometrium-derived stromal cells (EESC) in comparison to normal endometrial stromal cells (NESC). They demonstrated that curcumin significantly reduced the expression of inflammatory cytokines and chemokines, such as MCP-1 and RANTES, in a dose- and duration-dependent manner (Chowdhury et al. 2019).

Conclusion

The regulatory and anti-inflammatory effects of curcumin are well established, and it exerts its pharmacological effects through various molecular targets. In general, the biological effects of curcumin are broadly thought to be achieved by inhibition of NF-κB, although, more specifically, the actual anti-inflammatory effects of curcumin are primarily mediated by downregulation in the activity COX-2, LOX, and iNOS. The present review article discussed the effects of curcumin on chemokines and chemokine receptors both in in vitro studies and in vivo experimental animal models of different pathologies that included inflammation in various organs, autoimmune diseases, cancer, and bacterial and viral infections. The findings of these studies have shown that curcumin can exert its inhibitory effects on chemokines, which generally function as pro-inflammatory mediators and are responsible for the recruitment of immune cells to sites of inflammation. As it relates to the neuroprotective effects provided to neuroglia and neurons, curcumin modulates the expression of different chemokines and reduces degeneration, injuries, and deficits associated with these cells' neuroinflammation.

Moreover, the inhibitory effect of curcumin on hepatic, cardiovascular, pulmonary, and renal inflammatory conditions results in decreased fibrosis and other inflammation-associated histological complications. Lastly, in the case of cancer, curcumin can inhibit chemokine expression, leading to inhibition of tumor metastasis and activating specific chemokines that recruit anti-tumor immune cells to the tumor microenvironment. However, clinical trials to treat these various disease states/pathologic disorders with curcumin in humans are limited. Thus, we would suggest that additional clinical studies evaluating curcumin use in humans are needed to reach unequivocal conclusions about the therapeutic effects of curcumin on these various disorders/disease states.

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Declarations

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