Curcumin as a therapeutic candidate for multiple sclerosis: Molecular mechanisms and targets

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REVIEW ARTICLE

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Curcumin as a therapeutic candidate for multiple sclerosis: Molecular mechanisms and targets

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Abstract

Multiple sclerosis (MS) is a disease that has shown a considerable increase in prevalence in recent centuries. Current knowledge about its etiology is incomplete, and therefore it cannot be managed optimally utilizing targeted therapeutic regimens at each stage of the disease. MS progresses in different stages, beginning with a cascade of inflammation. The pivotal spark to initiate this cascade seems to be the migration of Th17 into the central nervous system across the blood–brain barrier (BBB) through the disrupted tight junctions. Coupling of interleukin (IL)-17 and IL-22 to their receptors in the BBB layer facilitates this migration. Subsequently, axon degeneration and the various manifestations of nerve–muscle disorders appear. Curcumin, a major component of turmeric, is derived from *Curcuma longa*, which belongs to the Zingiberaceae family. Numerous properties of curcumin have been identified recently, some of which can be effective in the treatment of MS, particularly the anti-inflammatory properties via inhibition of secretion of proinflammatory cytokines. In this paper, we will review the various properties and key effects of curcumin for the treatment of MS.

KEYWORDS

curcumin, immune system, inflammation, multiple sclerosis (MS)

1 | INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS). It begins with inflammation and continues with demyelination and neurodegeneration, leading to clinical manifestations of the disease. The incidence and prevalence of MS have risen over time, and young women (around 30 years old) are the highest risk group for MS (Goodin, 2014).

The underlying cause of MS is still unknown, although some factors seem to affect the likelihood of disease development. These include genetics, environmental conditions, and quality of life, such as high butterfat intake, smoking, Epstein–Barr virus (EBV) infection, and vitamin D deficiency (Ascherio, Munger, & Lunemann, 2012). Among these potential risk factors, many studies have indicated a particularly strong linkage between MS and a history of EBV infection in childhood or adolescence, and low vitamin D intake from sunlight, especially in regions distant from the equator (Garg & Smith, 2015).

Immunopathology data has been obtained from an animal model, experimental autoimmune encephalomyelitis (EAE), which is used to study MS. In the initial inflammation phase, T cells, a crucial factor in MS progression, together with IL-17 and IL-22 contribute to developing a break in the blood–brain barrier (BBB). As a consequence of the entry of T cells to the CNS, the inflammatory cascade begins and several pathophysiologic features of MS ensue primarily demyelination and axonal damage (Qureshi, Al-Suhaimi, Wahid, Shehzad, & Shehzad, 2018).

Accordingly, management of the disease is based on the use of anti-inflammatory and antidegenerative compounds (Lassmann, 2011). Currently, there are several immunomodulatory medications approved for the treatment of different types of MS, which utilize different routes of administration. These are beta-interferon, glatiramer acetate, natalizumab, fingolimod, teriflunomide, and dimethyl fumarate (Garg & Smith, 2015). However, the strategy for treatment of relapses (relapsing and remitting multiple sclerosis [RRMS]), which is present in 85–90% patients, remains a controversial issue due to the variety of symptoms manifested in each relapse (Perrin, 2013). In general, a comprehensive management strategy for MS has not yet been attained. The side effects, therapeutic failures, reports of toxicity, and the high cost of current chemical drugs are factors that favor the consideration of medicinal plants for therapeutic purposes.

Curcumin, a major component of the popular South Asian spice turmeric, is a herbal compound considered to have therapeutic potential because of its antioxidant and anti-inflammatory attributes (Darvesh et al., 2012). Two other major compounds are present in turmeric, demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC), but curcumin is the primary component responsible for its therapeutic properties (Agrawal et al., 2012). The component ratio in commercial curcumin is reported as follows: 77% curcumin, 18% DMC, and 5% BDMC (Ravindran, 2007).

Various properties of curcumin, particularly the antioxidant and anti-inflammatory attributes, are beneficial in inhibiting the pathophysiological processes involved in neuronal diseases. On the basis of the recent studies (Darvesh et al., 2012; Tang & Taghibiglou, 2017; Tizabi, Hurley, Qualls, & Akinfiresoye, 2014) curcumin has beneficial potential in the treatment of several neurological disorders, including dementia, Alzheimer's disease, Parkinson's disease, Huntington's disease, and MS. Due to the central importance of inflammation in most autoimmune diseases, curcumin's ability to modulate complicated signaling pathways seems to be essential to its benefit in the management of MS. Here, we will review some of the beneficial properties of curcumin that could be effective in the pathogenesis of MS.

2 | PATHOPHYSIOLOGY OF MS

The first stage in the pathogenesis of MS is inflammation, in which the immune system attacks and damages the myelin sheath in the CNS. Through this process of inflammation, dysfunction of Treg cells lead to activated peripheral T cells. Activated T cells express $\alpha 4\beta 1$ (among other adhesion molecules) that participate in their crossing of the BBB by binding to vascular cell adhesion molecule-1 (VCAM-1), which is induced by inflammation on the endothelial cells. Then the cascade of secretion of various proinflammatory cytokines begins, including tumor necrosis factor-α (TNF-α), IL-1, IL-6, IL-8, macrophage inflammatory protein-2 (MIP-2), and CXC chemokines (Kolls & Lindén, 2004), thereby activating widespread inflammation. The speed of migration of Th17 cells through the BBB is known to be high and, in MS lesions, it is known that these cells pass across the BBB through tight junctions disrupted by the coupling of IL-17 and IL-22 with their receptors on the BBB layer (Kebir et al., 2007; Skarica et al., 2009). After entry of Th17 to the brain, as the inflammation intensifies, the myelin coatings begin to break down and activated microglia use phagocytosis to clear the myelin debris (Qureshi et al., 2018).

The second process in the pathogenesis of MS is axon degeneration, which causes the slowdown in transmission via the axon to nerve endings, resulting in a clinical disability. After the onset of the inflammatory process and demyelination of the nerve cells, sodium channels under the myelin sheath become activated, which leads to sodium entry and activation of the sodium-calcium exchanger with the entry of calcium into the cell. This process, coupled with a considerable increase in the AMPA receptor, leads to an increase in intracellular calcium and sodium, followed by degeneration (Koda-Kimble & Young, 2016).

3 | TREATMENT OF MS: CHEMICAL AND NATURAL COMPOUNDS

The process of inflammation in MS is responsible for the relapses pathognomonic of the disease. Relapses are the dominant clinical feature of RRMS, but also occur in the initial phase of secondary progressive MS. Episodes of paroxysmal symptoms, such as trigeminal neuralgia, may also constitute a relapse. MS can also be associated with muscle stiffness, spasms, pain, and tremor. Here, we

discuss different treatment options that have shown benefit in treating this complex disorder (Myhr & Mellgren, 2009; Zajicek et al., 2003).

Currently, treatment of MS is divided into chemical and natural products. Among the chemical drugs, immunomodulatory therapies (IMTs), aimed at the suppression of the immune response, have been highly effective in treating RRMS and reducing the frequency of relapses. IMTs include: glatiramer acetate, which works via a mechanism that suppresses formation of myelin-reactive T cells and increases expression of GA-specific regulatory T cells, with Th2 then leading to anti-inflammatory cytokine production; natalizumab, which suppresses lymphocyte interaction with VCAM-1 on endothelial cells via an interaction with α4β1-integrin thereby preventing lymphocyte transmigration across the BBB; mitoxantrone, which suppresses proliferation of T and B lymphocytes and macrophages; oral options, such as fingolimod, which prevent migration of activated T cells from lymph nodes via interaction with the S1P1 receptor on the T cells, thereby limiting their entry into the CNS; teriflunomide, which exerts its anti-inflammatory effects by reducing proliferation of T and B lymphocytes; dimethyl fumarate, which inhibits proinflammatory pathways by activation of nuclear factor erythroid 2-related factor 2 as an antioxidant response (Garg & Smith, 2015).

Campath-1H (a humanized monoclonal antibody), which targets the CD52 antigen and modulates serum TNF-α levels, has been observed to be effective in treatment of MS (Coles et al., 1999; Panitch, Hirsch, Schindler, & Johnson, 1987). Other drugs used to treat MS are corticosteroids and adrenocorticotropic hormone. High-dose and short-term, oral or intravenous administration of methylprednisolone can be used in the acute phase of MS. Several mechanisms have been recognized to be involved in their efficacy, such as speeding up recovery from relapses, reduction of the cerebrospinal fluid level of matrix metalloproteinase (MMP) and increase of the tissue inhibitor level of MMP (Myhr & Mellgren, 2009). Indeed, earlier studies have shown that sex hormones, such as estriol and progesterone, play a protective role in MS by reducing Th1 responses and ameliorating both encephalomyelitis and collagen-induced arthritis (Sicotte et al., 2002). Moreover, increased serum estradiol levels are associated with improved blood immune cell response, and both augmented M2-like monocytes and T-helper cells, suggesting a neuroprotective effect induced by this hormone (Habib et al., 2018).

Vitamin D and cannabinoids are two "natural" substances that have also been used for the treatment of MS. As sunlight is critical for the synthesis of vitamin D in the skin, loss of sunlight is an important factor in the pathogenesis of MS. Studies utilizing the EAE model have shown that a low dose of calcium in combination with a high dose of vitamin D can act as a pretreatment of MS. Further studies have demonstrated that vitamin D can stimulate the development of antiencephalitogenic cells and the associated cytokines, such as IL-4 and transforming growth factor-β (TGF-β), indicating a robust anti-inflammatory role in the EAE model of MS (Hayes, 2000). Cannabinoids are considered as another natural treatment of MS. Tetrahydrocannabinol is the main component of *Cannabis sativa* that can be used in the control of spasticity and tremor in MS because of its potential to rapidly cross the BBB and access the CNS (Baker et al., 2000; Zajicek et al., 2003).

3.1 | Curcumin

Curcumin is the major component of turmeric, known as Indian saffron, and is derived from the dried root of the *Curcuma longa* perennial plant (belonging to the family Zingiberaceae). In traditional medical practice in China, India, and generally across Southeast Asia, turmeric had an important functional role as an ameliorating agent for many different ailments, for example, fractures, skin illnesses, chest pains, and colic (Aggarwal, Sundaram, Malani, & Ichikawa, 2007). Turmeric is composed of many different components, most of which are phenolic and terpenoid. The water-insoluble extract of turmeric contains curcuminoid compounds, for example, curcumin, DMC, and BDMC. In total, turmeric contains 235 components, approximately 3–5% of which is curcumin (Aggarwal, Yuan, Li, & Gupta, 2013).

In recent years, various therapeutic properties of curcumin have been studied, for example, antioxidant (Panahi, Ghanei, Hajhashemi, & Sahebkar, 2016; Sahebkar, Serban, Ursoniu, & Banach, 2015), anti-inflammatory (Panahi, Hosseini et al., 2015), antitumor (Iranshahi et al., 2010; Mirzaei et al., 2016; Momtazi et al., 2016), hepatoprotective (Panahi et al., 2017; Rahmani et al., 2016), lipid-modifying (Cicero et al., 2017; Ganjali et al., 2017; Sahebkar, Serban et al., 2016), hypouricemic (Panahi, Kianpour et al., 2016), antidepressant (Panahi, Badeli, Karami, & Sahebkar, 2015), pulmonoprotective (Lei, Sahebkar, Johnston, Pedone 2017) and analgesic (Panahi et al., 2014; Sahebkar & Henrotin, 2016) effects. Despite the wide range of beneficial effects of curcumin, various kinetic problems have limited its use, especially in clinical studies. Curcumin has poor solubility in water, poor absorption from intestinal mucosa and low stability in blood, thus restricting all practical routes of administration (Sahu, Kasoju, Goswami, & Bora, 2011). Another major pharmacokinetic limitation of curcumin is its low bioavailability. Due to its rapid hepatic metabolism, 60–70% of its oral dose is rapidly eliminated (Bansal, Goel, Aqil, Vadhanam, & Gupta, 2011). Because low bioavailability of curcumin is a major drawback for drug delivery and efficacy, scientists have considered novel drug delivery systems, like nanoparticles and liposomes, and also combined curcumin with agents that enhance its bioavailability (Anand, Kunnumakkara, Newman, & Aggarwal, 2007).

Despite these limitations of curcumin, recent studies, which use in vivo and in vitro models and high doses of curcumin, have not reported any signs of toxicity (National Toxicology Program, 1993; Strong et al., 2012). However, due to the low bioavailability of curcumin, there is a justifiable concern that the oral dose is not directly proportional to the systemic serum concentration (Burgos-Morón, Calderón-Montaño, Salvador, Robles, & López-Lázaro, 2010).

Despite the limitations of bioavailability and rapid metabolism, curcumin can play a role in the treatment of MS through a variety of mechanisms. Studies have shown curcumin's inhibitory effect on proliferation and differentiation of CD4+T cells by decreasing the

secretion of proinflammatory cytokines, including IL-6, IL-1β, TGF-β, macrophage chemotactic protein-1 (MCP-1), IL-17, interferon (IFN)-γ, TNF-α, IL-12, and IL-23 (Abdollahi, Momtazi, Johnston, & Sahebkar, 2018; Karimian, Pirro, Majeed, & Sahebkar, 2017; Sahebkar, Cicero, Simental-Mendia, Aggarwal, & Gupta, 2016). It can also reduce oligodendrocyte apoptosis (Kim et al., 2005; Yu & Ma, 2016). Curcumin reduces the secretion of MMP-9, a factor that can enhance the BBB permeability, and thereby ameliorates the manifestations of MS (Seyedzadeh et al., 2014). Preventing reactive oxygen species generation and phosphorylation of myosin light chain is another role of curcumin in preventing BBB disruption (K. Kimura, Teranishi, Fukuda, Kawamoto, & Nishida, 2008). Axon degeneration, the final destructive stage in the pathogenesis of MS, can be controlled by the curcumin's effect on reducing the release of nitric oxide (NO) through the JNK phosphorylation pathway (Tegenge et al., 2014).

3.1.1 | Curcumin delivery systems

Studies of curcumin have, unfortunately, shown only poor absorption and rapid metabolism. Elimination of curcumin is a major reason for its poor bioavailability. One of the major strategies being used to improve the bioavailability of curcumin are adjuvants, which can block metabolic pathways of curcumin. Nanoparticles, liposomes, micelles, and phospholipid complexes are other promising novel formulations, which appear to provide longer circulation, better permeability, and resistance to metabolic processes (Anand et al., 2007; Mirzaei et al., 2017).

Adjuvants piperine (20 mg/kg), a known inhibitor of hepatic and intestinal glucuronidation, can be combined with curcumin to allow an increased serum curcumin concentration for a short period. Time to maximum peak level significantly increases and also elimination, half-life, and clearance of curcumin significantly decrease, resulting in increased bioavailability. Some other agents, like quercetin and genistein, have shown a synergistic effect when used in combination with curcumin. Decreased polyp number, as well as size, from baseline, with minimal adverse side effects, was reported (Anand et al., 2007). Also, the combination of curcumin and genistein completely inhibited the cellular proliferation induced by individual pesticides or a mixture of pesticides, and the inhibitory effect was superior to the individual effects of each of them (Verma, Salamone, & Goldin, 1997). The effect of eugenol and terpineol as enhancers of skin curcumin absorption to increase curcumin levels in the skin has been reported (Fang, Hung, Chiu, Wang, & Chan, 2003).

3.1.2 | Nanoparticles

Nanocurcumin also inhibits activation of the transcription factor nuclear factor kappa light chain enhancer of activated B cells (NF-κB) and reduces steady-state levels of proinflammatory cytokines like interleukins and TNF-R.61. Solid lipid nanoparticles loaded with curcuminoids strongly reduces the light and oxygen sensitivity (Tiyaboonchai, Tungpradit, & Plianbangchang, 2007).

Liposomes, micelles, and phospholipid complexes

Liposomes are excellent drug delivery systems because they can carry both hydrophilic and hydrophobic molecules. Liposomal curcumin inhibits pancreatic carcinoma growth and also exhibits antiangiogenic effects. Liposomal curcumin suppressed the pancreatic carcinoma growth in murine xenograft models and inhibited tumor angiogenesis. Curcumin bioavailability enhancement is also caused by liposomal curcumin (Li, Braiteh & Kurzrock, 2005).

Micelles and phospholipid complexes can improve the gastrointestinal absorption of natural drugs, giving higher plasma levels and lower kinetic elimination and thereby resulting in improved curcumin bioavailability (Suresh & Srinivasan, 2007).

Phospholipid complex formulations such as silymarin (Gatti & Perucca, 1994) and dolichol (T. Kimura et al., 1989), have been found to show improved bioavailability. Curcumin–phospholipid complex showed a maximum plasma curcumin level (Liu, Lou, Zhao, & Fan, 2006).

Microemulsion/microencapsulation

Microstructures result in high drug solubilization capacity along with free and fast drug diffusion that, coupled with their lipophilic nature, give them great potential for delivery of lipophilic compounds like curcumin that not only cross lipophilic cell membranes but are also absorbed through the skin. These microparticles also have the potential to sustain drug levels following subcutaneous administration (Teichmann et al., 2007).

Implantable curcumin

Polymeric implantable drug delivery systems exhibit great potential for systemic delivery of various therapeutic agents (Domb, Israel, Elmalak, Teomim, & Bentolila, 1999; Jain, Modi, Domb, & Kumar, 2005). These implants, with homogeneous entrapment of drugs in a polymeric matrix, achieve sustained localized delivery coupled with complete bioavailability into the systemic circulation by slowly releasing the encapsulated drug at the site of implantation (Langer, 1998). Implants can, therefore, provide drug release ranging from months to years which improves patient compliance, especially for poorly bioavailable and rapidly metabolized compounds like curcumin (Dash & Cudworth, 1998). The polymeric implant delivery system not only provided high local concentrations of curcumin but also enabled the systemic delivery of curcumin (Bansal, 2009). These implants were found to deliver significantly higher levels of curcumin to the plasma, liver, and brain tissues compared with the oral delivery of curcumin (Bansal et al., 2011). Furthermore, curcumin delivery via the implant route was found to inhibit B[a]P-induced tissue DNA adducts, showing the biological efficacy of systemic delivery (Bansal, 2009).

3.1.3 | The targets of curcumin in MS

There are a number of potential targets involved in the pathogenesis of MS that enable curcumin to ameliorate the manifestations of MS. Toll-like receptors (TLRs) are a family of pattern recognition

receptors, activated by pathogen-associated molecular patterns and danger-associated molecular patterns. They are expressed in a wide variety of cell types, including macrophages, dendritic cells, monocytes, activated microglia, and reactive astrocytes, which result in the release of inflammatory molecules important for the host defense. Expression of particular subtypes of TLRs in innate immune cells, as was specified in a study by Gooshe, Abdolghaffari, Gambuzza, & Rezaei (2014), are increased after induction of EAE, leading to the release of proinflammatory cytokines and exacerbation of the disease. A study in which EAE was induced in female C57BL/6 and SJL/J mice showed increased expression of TLR4 and TLR9 in CD4+ and CD8+ T cells. Analysis of spleen cells from C57BL/6 mice, treated in vivo with 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2) or curcumin, showed inhibition of neural antigen-induced expression of TLR4 and TLR9 (Chearwae & Bright, 2008). Lian et al. (2013) have proposed that another target of curcumin is the Kv1.3 channel, a voltage-gated channel that is overexpressed and upregulated in activated effector memory T cells and results in an increase in proliferation which is responsible for the pathogenesis of autoimmune disease such as MS. In a study using HEK-293 cells, curcumin (5–100 μM) had an inhibitory effect on hKv1.3 channels at each positive potential from 0 to +60 mV, and this was increased further when the channels were repeatedly depolarized. In vitro observation proved that, in addition to curcumin's impact on blocking Kv1.3 channels, it markedly decreased the proliferation of human TEM cells at concentrations of 10 μM or higher (Lian et al., 2013).

Although the curcumin's modulatory effect on proinflammatory cytokine production has been widely studied, identifying the inherent pharmacological potential therein is important. Fahey, Adrian Robins, & Constantinescu (2007) provided novel data about the signal transduction pathway of curcumin, which showed that curcumin's effect of blocking the IL-12 receptor is mediated through tyrosine phosphorylation of JAK1 and TYK2, and that their expression could be a definitive target for investigating curcumin's potential in the treatment of MS (Figure 1).

3.1.4 | In vitro and in vivo studies of curcumin in MS

As MS is a disabling disease, it impacts all aspect of a patient's life, and considering the current high cost and side effects of existing therapeutic agents, it is important to provide an effective, low-cost, and safe treatment. As previously stated, curcumin, a natural polyphenolic compound with wide accessibility, low cost, and no evidence of toxicity, has great potential to be an effective alternative treatment of MS. Moreover, curcumin has shown effectiveness against the pathogenetic mechanisms of MS in both in vitro and in vivo studies. This will be discussed below in the next sections.

3.1.5 | In vitro studies

Natarajan and Bright (2002) found that myelin basic protein-stimulated immune spleen cells from 6-week-old female SJL/J mice treated with 20 μg/ml curcumin showed lower proliferation of neural Ag-specific Th1 cells and a reduction in IFN-γ production. Splenic macrophages and microglia from SJL/J mice stimulated with 50 ng/ml IFN-γ and 1 μg/ml lipopolysaccharide (LPS) or anti-CD40 antibody showed a reduction in production of IL-12 during treatment of curcumin in a dose-dependent fashion. Consequently, the curcumin's effect on activated T cells, where IL-12 is induced, was a significant dose-dependent decrease in proliferation and differentiation through blocking of tyrosine phosphorylation in the STAT3 and STAT4 signaling pathway via the upstream JAK2 and TYK2 (Natarajan & Bright, 2002).

When BV2 cells (immortalized murine microglial cells) were pretreated with curcumin before addition of LPS, a significant reduction in release and accumulation of proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, via suppression of NF-κB P65 nuclear protein was observed (Jin, Lee, Park, Choi, & Kim, 2007). Moreover, peripheral blood mononuclear cells taken from patients with MS and exposed to 20 μg/ml curcumin for 18 hr demonstrated contradictory effects of curcumin on the production of cytokines even with the same activation signaling. In this regard, pretreatment of these cells with curcumin reduced IL-12 production, an inducer of IFN-γ, while enhanced IFN-β induced IL-10, and both were modulated via STAT4 activation (Fahey et al., 2007). When MOGp35-55 immune spleen cells from C57BL/6 mice were treated by curcumin, the in vitro observations confirmed the ex vivo results, both studies supporting curcumin's dose-dependent effect on reducing IFN-γ and IL-17 secretion. Further in vitro studies indicated a dose-dependent decrease of IL-12 and IL-23 secretion (Kanakasabai et al., 2012).

Another study in HEK-293 cells demonstrated curcumin's direct inhibitory impact on hKv1.3 channels, which modulate activation of cells associated with inflammation, in a concentration-dependent way (Lian et al., 2013). Indeed, Tegenge et al. (2014) induced primary microglia cultures, obtained from Sprague Dawley rats or C57BL/6J mice, with LPS that resulted in a significant increase of NO production leading to axon degeneration. Preincubation of the cells with curcumin protected the axons from degeneration in a dose-dependent manner through the JNK pathway (Tegenge et al., 2014). Moreover, human astrocyte cells, the most numerous brain glial cell population, play a dual neuroprotection and neurodegeneration role in autoimmune diseases. Pretreatment of LPS-induced astrocytes with the highest dose of curcumin (5 μg) reduced MMP-9 and IL-6, however, at the same time, had no effect on neurotrophin-3 and insulin-like growth factor-1 production, which are factors that play a crucial role in myelinogenesis (Seyedzadeh et al., 2014). Mohajeri, Sadeghizadeh, Najafi, and Javan (2015) using the lumbar spinal cord of EAE induced female Lewis rats treated in culture with 12.5 mg/kg polymerized nanocurcumin (PNC) once daily from Day 12–29, found a reduction in expression of proinflammatory genes, including IL-1, IL-17, TNF-αr1, MCP-1, and NF-κb. Further, they found enhancement of expression of other anti-inflammatory genes such as IL-4 and a Foxp3-regulatory factor of IL-10 production (Mohajeri et al., 2015).

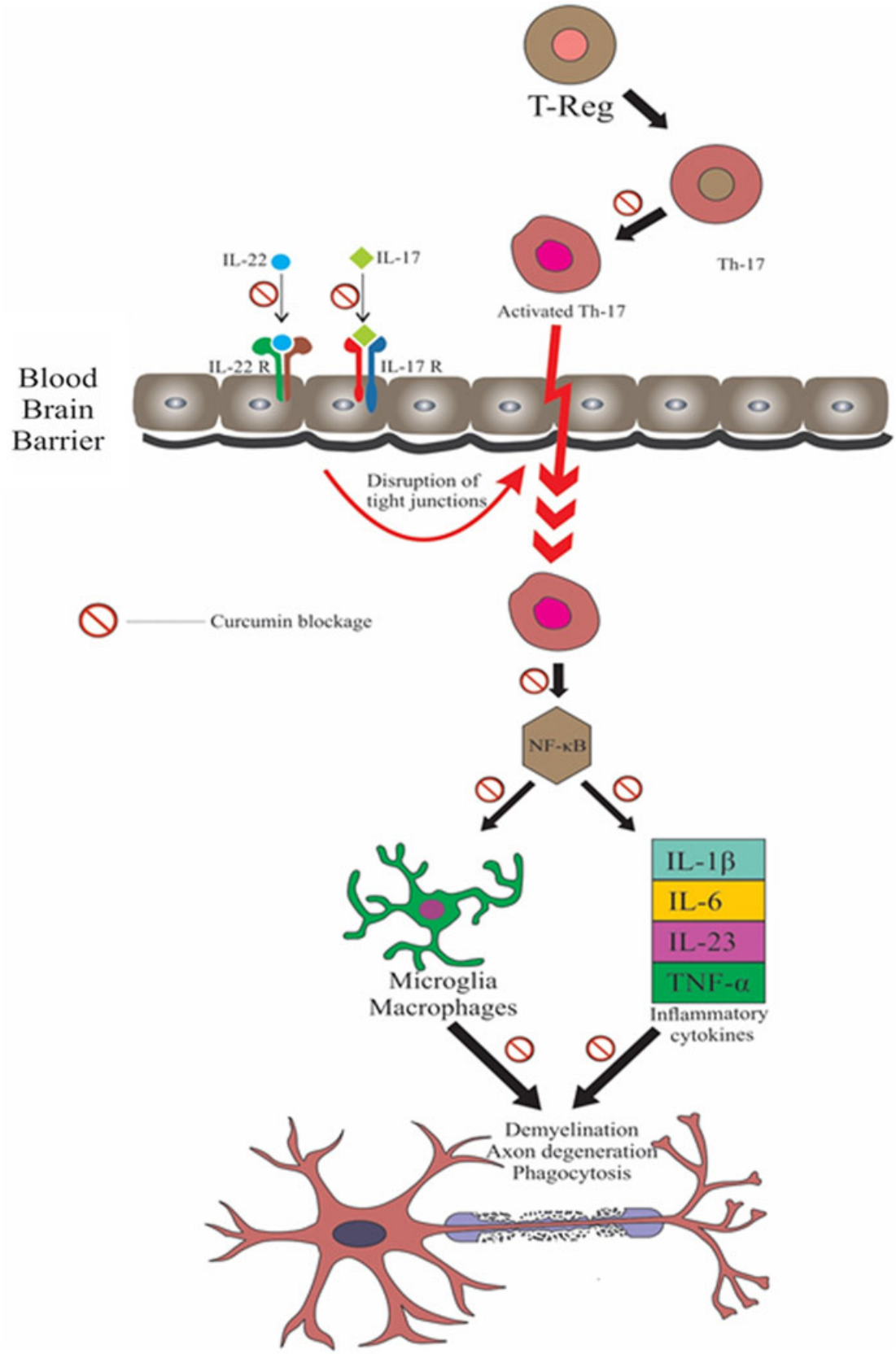

FIGURE 1 Possible pathways and mechanism of MS and inhibition effects of curcumin in different stages. IL: interleukin; MS: multiple sclerosis; NF-κB, nuclear factor kappa light chain enhancer of activated B cells; TNF-α, tumor necrosis factor-α [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 In vitro and in vivo studies on curcumin used for MS

References	Supplement	Type of study /animal	Model induction	Dose drug	Routs	Adverse effect	Outcome
Natarajan and Bright (2002)	Curcumin	6-week-old female SJL/J mice	EAE	50 or 100 μg 25 days	Intravenous injection	–	- ↓Severity and duration of clinical paralysis and adoptive transfer in active EAE dose-dependently - ↓Inflammation and demyelination in the CNS
Natarajan and Bright (2002)	Curcumin	In vitro	MBP-immune spleen cells	20 μg/ml	–	–	- ↓ The proliferation of neural Ag-specific Th1 cell - ↓IFN-∂ production - ↓ Production of IL-12 by
Kim et al. (2005)	Curcumin	In vitro	DC generated from murine BM cells of male 8- to 10-week-old C57BL/6 and BALB/c mice, LPS induced	Curcumin in dimethyl sulfoxide (DMSO) with (0.01% v/v) concentration ≤25 μM	–	–	- ↓ Expression of CD80, CD86, and MHC class II molecules→ inhibit the maturation of BM-derived murine DC - impairs the secretion of IL-12 - ↓ Phosphorylation of MAPKs - inhibits the capacity of DC to induce Th1 responses
Fahey et al. (2007)	Curcumin	In vitro	Peripheral blood mononuclear cells (PBMC)	20 μg/ml 18 hr	–	–	- ↓ IL-12 -induced STAT4 phosphorylation, IFN-∂ production, and IL-12 Rβ1 and β2 expression - ↑IFN-β-induced STAT4 phosphorylation, IFN-α-induced IL-10, and IFNAR1 expression
Chearwae and Bright (2008)	15d-PGJ2 and curcumin	In vitro	Spleen cells of 6-week-old female C57BL/6 and SJL/J mice	100 μg 14 days	–	–	- Block IL-12 signaling and Th1 differentiation - Inhibit the expression of TLR4 and TLR9 in CD4+ and CD8+ T cells
Chearwae and Bright (2008)	15d-PGJ2 and curcumin	6-week-old female C57BL/6 and SJL/J mice	EAE	100 μg	Intravenous injection	–	- ↓ Symptoms and intensity→ ameliorate EAE - inhibit neural antigen-specific T cell response
Zhang et al. (2012)	Curcumin	In vitro	C6 rat astrocytoma cells, LPS induced	2.5, 10, and 25 μM 30 min	–	–	- ↓ Expression of CCL2 mRNA and protein →Downregulation of CCL2 expression through the JNK pathway
Agrawal et al. (2012)	Curcumin, DMC, BDMC	Male albino Wistar rats (200–250 g)	6-Hydroxy dopamine-6-OHDA (10 μg/2 μl; 0.1% ascorbic acid saline)	Pretreatment: 60 mg/kg in 0.5% carboxymethyl cellulose (CMC) 3 weeks	0ral	–	- ↑ Protection against neuronal degeneration in the order CUR>DMC>BDMC - Shield progressive neuronal degeneration from increased oxidative attack

(Continues)

TABLE 1 (Continued)

References	Supplement	Type of study /animal	Model induction	Dose drug	Routs	Adverse effect	Outcome
Kanakasabai et al. (2012)	Curcumin	6- to 8-week-old female C57BL/6 mice	EAE	100 μg 14 days	Intravenous injection	–	- ↓ mean score→ attenuate EAE
Kanakasabai et al. (2012)	Curcumin	In vitro	MOGp35-55 immune spleen cells isolated from DMSO-treated EAE mice	0, 2.5, 5, 10 and 25 μM	–	–	- Inhibition of IL-12/IL-23 and upregulation of Th2/regulatory T cell responses → ↓Th1/Th17 differentiation
Lian et al. (2013)	Curcumin	In vitro	HEK-293 cells	50 mM stock solution in DMSO	–	–	- Blockage of hKv1.3 channels - ↓ Proliferation and interferon-g secretion of TEM cells
Tegenge et al. (2014)	Curcumin	In vitro	Primary microglia cultures from P3-P6 Sprague Dawley rats or C57BL/6J mice		–	–	- Protect axons from NO-mediated degeneration
Seyedzadeh et al. (2014)	Curcumin	In vitro	Human astrocyte cell line (U373-MG) LPS induced	0, 2.5, and 5 μM	–	–	- ↓Release of IL-6 and MMP-9 - Downregulation of MCP-1 mRNA expression
Mohajeri et al. (2015)	Polymerized nanocurcumin (PNC)	Adult female Lewis rats weighing 150–200 g	EAE	12.5 mg/kg 18 days from Day 12–29	–	–	- ↓ Peak EAE score
Mohajeri et al. (2015)	PNC	In vitro	Lumbar spinal cord	12.5 mg/kg	–	–	- ↓ Demyelination - ↓ Infiltrated immune cells - ↓ Expression of IL-17, NF-κB, and TNF-α receptor - ↑ Expression of IL-4 and foxp3
Shoba et al. (1998)	Curcumin+pipermin	Both sex of albino Wistar rats	–	2 g/kg curcumin+20 mg/kg pipermin	Orally, aqueous suspension	–	- Piperine enhances the oral bioavailability of curcumin.

Note. 15d-PGJ2: 15-deoxy-Δ12,14-prostaglandin J2; BDMC: bisdemethoxycurcumin; BM: bone marrow; CMC; DC: dendritic cell; DMC: demethoxycurcumin; DMSO: dimethyl sulfoxide; EAE: experimental autoimmune encephalomyelitis; IL: interleukin; INF: interferon; LPS: lipopolysaccharide; MBP: myelin basic protein; MCP-1: macrophage chemotactic protein-1; MMP: matrix metalloproteinases; mRNA: messenger RNA; MS: multiple sclerosis; NF-κB: nuclear factor kappa light chain enhancer of activated B cells; TLR: toll-like receptor; TNF-α: tumor necrosis factor-α.

3.1.6 | In vivo studies

Curcumin's effect on the reduction in inflammation and demyelination in the CNS was studied in an induced EAE model. By analyzing spinal cord sections from 6-week female SJL/J mice, treated with either 50 or 100 μg curcumin for 25 days, a significant decrease in inflammation and CNS demyelination in a dose-dependent fashion was demonstrated. The same study also investigated the efficacy of curcumin on the reduction of intensity and duration of paralysis induced in the EAE model. Injection of 50 μg curcumin decreased the period of paralysis from 16 down to 10 days (37.5% reduction) and by doubling the injection dose, this duration was reduced to 8 days (50% reduction; Natarajan & Bright, 2002). In chronic and relapsing EAE induced in 6-week-old female C57BL/6 and SJL/J mice, treatment with 100 μg 15d-PGJ2 or curcumin resulted in paralytic disease with only minor symptoms and intensity (Chearwae & Bright, 2008). In another study, investigating curcumin's role on manifestations of EAE, the mean clinical score in 6 to 8-week-old female C57BL/6 mice treated with 100 μg curcumin was 0.6 in comparison to 1.95 in the control group (69% reduction), indicating curcumin's efficacy in attenuating EAE (Kanakasabai et al., 2012).

Treatment of adult female Lewis rats with 12.5 mg/kg PNC for 18 days in an induced EAE model of MS resulted in lowering of the peak EAE score compared to both the control group and a curcumin treatment with nonpolymerized curcumin dissolved in PBS group (Mohajeri et al., 2015).

4 | CONCLUSIONS

MS is a disabling disease that severely impacts the quality of life, hence defining optimal treatment regimens is critical. Current treatment options are costly and have a number of side effects. Therefore, there is an increasing interest in identifying effective herbal therapies and phytochemicals.

Recent research on curcumin has defined a number of key properties, particularly its anti-inflammatory effects, low cost, safety, and wide availability. Therefore, this phytochemical can be regarded as an appropriate candidate for the treatment of MS. However, kinetic limitations of curcumin have slowed the research, especially in terms of clinical studies. Thus, the use of novel drug delivery systems and combination therapy seem to offer promising approaches to overcome curcumin's limitations. For instance, dual drug-loaded nanoparticulate combination therapy of curcumin with piperine, quercetin, and silibinin have shown decreased hepatic metabolism and enhanced absorption, ultimately resulting in bioavailability improvement (Moorthi & Kathiresan, 2013). In particular, the combined use of curcumin with piperine, as an inhibitor of liver and intestinal glucuronidation and an absorption enhancer, can greatly increase serum concentrations of curcumin (Kakarala et al., 2010; Martins, Leyhausen, Volk, & Geurtsen, 2015; Rinwa, Kumar, & Garg, 2013; Shoba et al., 1998). The use of exosomes as curcumin carriers has also been shown to enhance the anti-inflammatory effects of curcumin (Sun et al., 2010). Nanoparticulate encapsulation of curcumin has been shown to provide even better oral bioavailability when compared with piperine coadministration (Shaikh, Ankola, Beniwal, Singh, & Kumar, 2009). In summary, while the available data are promising (Table 1), further evidence from randomized controlled trials on the efficacy of curcumin in MS is required. In addition, it remains to be elucidated whether the putative therapeutic effects of curcumin in MS could be enhanced by using tailored delivery systems.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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