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Research Article

Therapeutic Potential of Curcuma Longa and Its Constituents Role in the Treatment of Multiple Sclerosis

Prakash Pralhad Sarwade[1], Santosh Kumar S.R.[2], Yuvraj[3], Rohit Kumar[4], Navin Chandra Pant[5], Kavita Narayan Gaisamudre (Sarwade)[6]

[1]Associate Professor and Head, Department of Botany, Shikshan Maharshi Guruvarya R. G. Shinde Mahavidyalaya, Paranda Dist. Dharashiv (Osmanabad) 413 502, (M.S.) India.

[2**]Assistant professor, Department of Studies in Food Technology, Davangere University, Shivagangothri, Davangere-577007, India

[3]Baba Farid College of Pharmacy, Morkarima, Mullanapur, Ludhiana, India

[4]Associate professor, Department of Pharmacy Practice, Sri Indu Institute of pharmacy, Sheriguda (v) Ibrahimpatnam(M) R.R. Dist. 501510, India

[5]Associate Professor, Faculty of Pharmaceutical Sciences, Amrapali University, Haldwani Nainital, India

[6]Assistant Professor, Department of Botany, Shriman Bhausaheb Zadbuke Mahavidyalaya, Barshi Tal. Barshi, Dist-Solapur 413 401 Maharashtra (India)

A B S T R A C T

A neurodegenerative illness characterised by chronic inflammation and demyelinating symptoms, multiple sclerosis (MS) mostly affects young people's central nervous systems. The condition is complex and variable due to multiple environmental and genetic factors. A disorder mediated by the immune system is what it is. Symptoms of neurological dysfunction that last a few days or weeks and can be recovered are common in the early stages of the disease, which include clinically isolated syndrome and relapsing-remitting multiple sclerosis. Turmeric, whose scientific name is Curcuma longa Linn. (C. longa), is a member of the Zingiberaceae family of plants that has a rich history of use in traditional medicine. In Unani and Ayurvedic medicine, C. longa has been used topically for inflammation and ulcers, and internally for jaundice and liver blockage. Blood purification, asthma, haemorrhoids, bronchitis, tumours, wounds, indigestion, colds, dental problems, skin infections, and hepatic illnesses are all helped by its antiseptic properties. The crucial phase that starts this cascade is when Th17 enters the central nervous system (CNS) through the blood-brain barrier (BBB) through damaged tight junctions. Interleukin (IL)-17 and IL-22 attach to their BBB receptors, allowing the migration to proceed. Then symptoms of neuromuscular diseases, such as axonal degeneration, start to show themselves. The Zingiberaceae family plant Curcuma longa is the source of curcumin, the active ingredient in turmeric. There is hope for the treatment of multiple sclerosis (MS) thanks to recent findings about the properties of curcumin, namely its ability to suppress the release of proinflammatory cytokines. When it comes to treating MS, this study will look at curcumin's many features and major impacts.

Keywords: Curcuma longa, Curcumin, Multiple sclerosis

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*Address for Correspondence:

Santosh Kumar S.R, Assistant professor, Department of Studies in Food Technology, Davangere University, Shivagangothri, Davangere-577007, India

INTRODUCTION

Multiple sclerosis (MS) is a neuroplastic degenerative disorder that affects the central nervous system and is characterised by demyelinating lesions. MS is a chronic, heterogeneous, inflammatory, and neuroplastic disorder. There are several types of multiple sclerosis, including relapsing-remitting MS (RRMS), primary progressive MS (PPMS), clinically isolated syndrome (CIS), and secondary progressive MS (SPMS) [1]. Brain magnetic resonance imaging (MRI) abnormalities

characterise the radiologically isolated condition (RIS), the first stage of asymptomatic multiple sclerosis (MS). Multiple sclerosis (MS) is an immune-mediated disease characterised by demyelination and axonal degeneration in the central nervous system (CNS) [2]. Women are afflicted at a rate double that of men, and the average age of diagnosis is between 20 and 40 years. The prevalence of multiple sclerosis (MS) in the United States increased dramatically between 1970 and 2019, going from 58 cases per 100,000 people in 1975 to 309.2 cases per 100,000 people (or 450.1 per 100,000 women). Nearly one in three hundred Americans live with multiple sclerosis; the rate of occurrence was highest among Black people (10.2 per 100,000 person-years), compared to 6.2 among white people. The increase in instances could be attributed to a combination of reasons, including heightened public awareness, better magnetic resonance imaging (MRI), and stricter diagnostic criteria. There is growing worry about the increasing frequency of multiple sclerosis on a global scale [3]. There are more over 100 instances per 100,000 people in North America, Western Europe, and Australasia, whereas there are less than 30 cases per 100,000 people in tropical nations. Around one million people are impacted, according to a recent US study [4]. In RMS, women are almost three times more likely than males to develop the disease, and the average age of onset is around 30 years; in PPMS, however, the incidence rates are equal for the sexes, and the typical age of onset is around 40 years. A great success that has greatly increased the chances of living a life without handicap is the development of increasingly effective drugs for RMS, as well as partially effective treatments for PPMS and SPMS [5-7]. There has been a marked rise in the average time it takes for RMS patients to proceed to SPMS during the therapy era, from an estimated 19 years post-onset in the prior. With appropriate therapy, relapses are greatly reduced or eliminated altogether. Though RMS attacks and remissions used to mask the disease's true course, recent developments in RMS management have revealed a "silent" progression unaffected by relapses [8].

Material and methods

A Narrative Review paper was conducted by searching Google Scholar, PubMed, and Research Gate for relevant keywords, excluding any unique instances and case reports.

Inclusion and exclusion criteria

The primary criterion is publications published in pertinent journals; we utilize keywords and titles for online searches (Google Scholar and PubMed). We reject outdated articles and those unrelated to our title. We also exclude publications published in predatory or improperly citable journals.

RESULTS AND DISCUSSION

Epidemiology and aetiology

Although it is not entirely true, the exact cause of multiple sclerosis is typically thought of as mysterious. Crucial elements in the cascade of events leading to multiple sclerosis (MS) include an individual's genetic makeup, the Epstein-Barr virus (EBV), UVB radiation, cigarette smoking, and vitamin D [9]. According to research on migration patterns, environmental factors play a supporting role in the development of multiple sclerosis (MS). Although the risk of developing multiple sclerosis may be low for migrants from low-risk areas like the West Indies, the risk is higher for children born to these migrants in Europe [10]. Further research into reducing environmental risks is required because migration studies provide strong evidence that environmental impacts surpass genetic influences. A perfect negative result for EBV is required to avoid MS. Still, infectious mononucleosis, the medical term for symptomatic EBV infection, increases the risk [11]. There has been a lot of talk about molecular mimicry, but there is conflicting evidence about whether or not EBV increases the risk of multiple sclerosis. The significance of EBV-induced B-cell immortalisation and/or transformation in disease progression has been significantly reevaluated recently [12]. An increasingly worldwide epidemic of multiple sclerosis is on the rise. Although studies have shown that the incidence of multiple sclerosis (MS) increases with increasing latitude, this gradient is beginning to flatten out in the two nations where the disease has been researched the most, Norway and the US. Since exposure to UVB promotes the cutaneous generation of vitamin D, there is a strong correlation between the latitudinal gradient in MS prevalence and this factor [13]. Low vitamin D levels are connected with an increased susceptibility to multiple sclerosis (MS), decreased vitamin D intake, decreased outdoor exercise, and innately low vitamin D levels. Vitamin D has been linked to the development of multiple sclerosis in several studies. Multiple sclerosis has not traditionally been more common in women [14]. Case series from the early 1900s nearly always had equal representation of the sexes. In many developed nations, the gender ratio has been steadily rising since then and is now around 3:1 (male:female). The increased risk of multiple sclerosis in women is over 50% higher when compared to men, and smoking is responsible for as much as 40% of this increase. Several sclerosis was more common in women after WWII, coinciding with a dramatic uptick in female smoking [15]. One possible reason why chemical solvents and smoked tobacco (not including oral tobacco or snuff) are linked to multiple sclerosis is because these substances cause post-translational changes through lung-mediated antigen presentation. Changes to the risk of multiple sclerosis probably begin during pregnancy and continue into adulthood [16]. Although the exact causes of the higher concordance in dizygotic twins compared to siblings and the impact of the month of birth on MS risk remain unknown, these findings do point to a strong correlation between the prenatal environment and the disease. There is evidence that MS susceptibility is hereditary, since one in eight people with the disease have a family history of it. When it comes to female monozygotic twins, the concordance rate in the United Kingdom and Canada is above 30%, whereas it drops to around 8.5% in southern Europe [17]. The results of genome-wide association studies have shown that PPMS and RRMS share genetic variations that were previously unknown, suggesting that PPMS was probably under-represented in these studies. There is an over-representation of some genetic variations in MS compared to other forms of progressive neurological disease [18]. There is an extra risk for progressive disease beyond the intrinsic genetic predisposition, since the genetic risk is consistent when all MS-associated genes are considered [19]. Within a similar genetic risk framework, changes in gene transcription

between RRMS and PPMS provide further evidence of individual differences [20].

Pathogenesis of Multiple sclerosis

In the first stage of multiple sclerosis, inflammation of the central nervous system's white and grey matter tissues is caused by immune cell infiltration and the cytokines they produce [21]. T helper (Th) cells, also called CD4+ T cells, and adaptive immune responses set off when antigen-presenting cells (APCs) communicate with T lymphocytes are believed to have a role in the initiation and progression of multiple sclerosis (MS). It all starts when chemicals linked to the infection bind to toll-like receptors on APCs. Certain cytokines, including as interleukin (IL)-12, IL-23, and IL-4, are synthesised as a result of this [22]. Subsequently, these cytokines cause CD4+ T cells to differentiate into Th1, Th2, or Th17 phenotypes, which allow them to release these particular cytokines. A group of cytokines that are important for the immune system's innate and adaptive functions, including IFNγ, TNF-α, and type II interferon, are known as proinflammatory cytokines. The production of these cytokines is carried out by Th1 cells [23]. They have the ability to worsen inflammation by inhibiting Th2 differentiation. The IL-4 and IL-13 cytokines, which are anti-inflammatory, are released by Th2 cells. Through a process wherein it promotes the development of M2 macrophages, which aid in tissue repair, and conversely activates M1 macrophages, which cause inflammation, IL-4 reduces pathological inflammation. While IL-4 influences immune cells, IL-13 does the same [24]. It is through the production of matrix metalloproteinase that this cytokine exerts its anti-inflammatory effects in cases of allergic inflammation. Many inflammatory cytokines, such as IL-17, IL-21, IL-22, and IL-26, are secreted by the Th17 fraction of CD4+ T cells. B cells and the cytokines they produce are also involved in multiple sclerosis. According to [25], these cells exacerbate inflammation through secreting lymphotoxin and tumour necrosis factor-alpha (TNF-α). This type of cell can also produce the anti-inflammatory cytokine interleukin-10. There are positive and negative ways in which B lymphocytes contribute to MS progression [26]. In multiple sclerosis (MS) lesions, researchers have found CD8+ T cells, also called cytotoxic T cells, according to various studies. Cytolytic proteins, like perforin, are produced by these cells to inhibit and deactivate CD4+ T cells. In oligodendrocyte mortality, glial cell loss, and increased vascular permeability, these cells play important roles in the pathophysiology of multiple sclerosis [27]. The inflammation within the central nervous system is caused by the loss of oligodendrocytes, which limits myelin regeneration. The Fas ligand, also known as FasL, is produced by lymphocytes. Cell surface receptors that are members of the TNF receptor superfamily and bind to the Fas receptors on oligodendrocyte cells, triggering apoptosis. Reducing the number of cells responsible for this process compromises the formation of the myelin sheath [28].

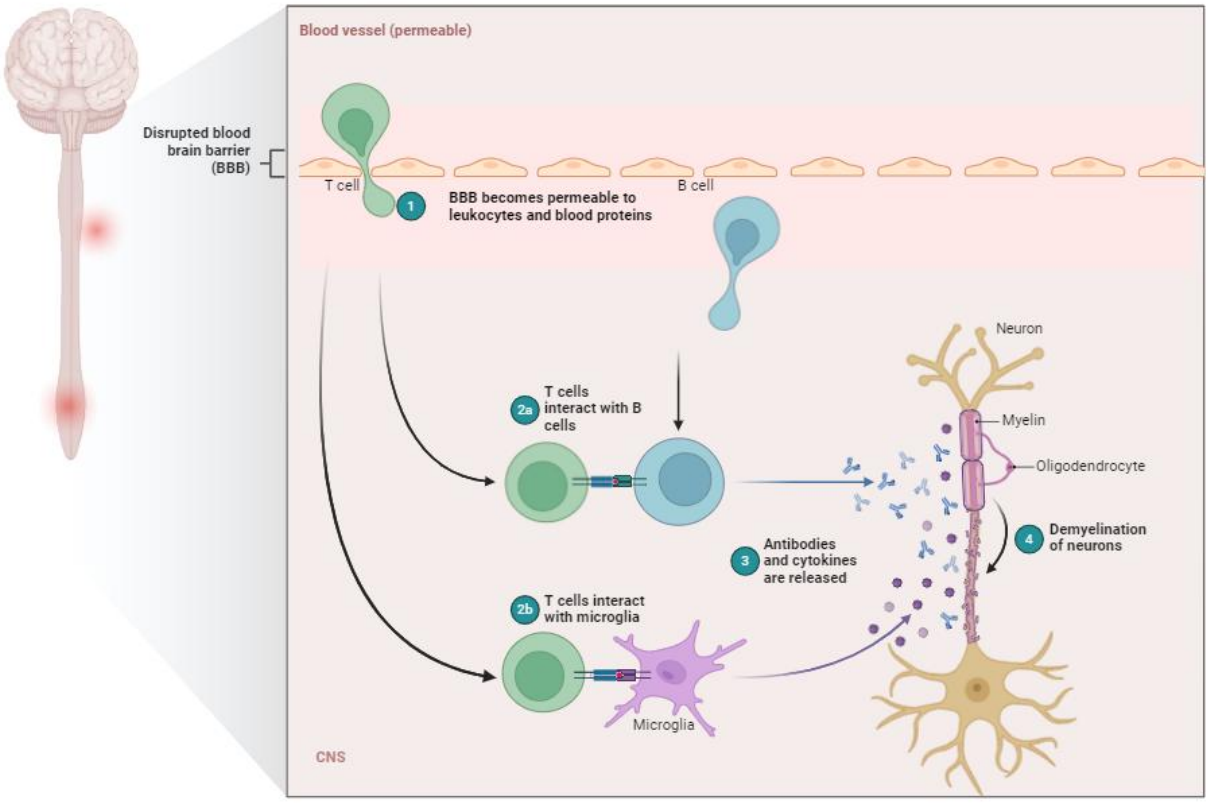

Figure1: Pathogenesis of Multiple sclerosis (created in biorender)

Diagnosis of multiple sclerosis

The ability to seek therapy and make future preparations is dependent on the early diagnosis of multiple sclerosis [29]. Lumbar punctures (LP) for cerebrospinal fluid (CSF) analysis, evoked potentials, blood assays, and magnetic resonance imaging (MRI) are some of the imaging modalities used in a neurological examination that must accompany a thorough review of the patient's medical history in order to arrive at a definitive diagnosis of multiple sclerosis (MS). Gathering details about the patient's medical history is crucial. This includes when symptoms first appeared, any neurological abnormalities, the patient's eating habits, where they lived, medications they took, and any substance abuse they may have had. It is possible that Babinski's visual and reflex evaluations will also be useful. Any damage or scarring in the brain or spinal cord can be detected using an MRI. Demyelination of the optic nerve and central nervous system can be better understood with the use of visual, brainstem auditory, and somatosensory evoked potential evaluations. The diagnosis could be improved by checking for vitamin deficiencies using blood tests and cerebrospinal fluid (CSF) analysis, particularly for levels of myelin basic protein and immunoglobulin-gamma (IgG) [32].

Curcuma longa

There are around 133 species of Curcuma plants, and they've been popular for a long time because of the therapeutic properties they possess. A number of species of Curcuma are found across the world. These include *C. longa* (Haridra), *C. aromatica Salisb* (Vana Haridra), *C. angustifolia* Roxb., *C. zanthorrhiza* Roxb., *C. amada* Roxb (Amaragandhi Haridra), *C. caesia* Roxb (Kali Haridra), and *C. zedoaria* Rosc (Zedoary) [33]. *Curcuma longa* Linn., a common tall herb, grows well in tropical climates and in some parts of India. The spice, food preservative, and colourant known as "Indian saffron" or "The Golden Spice of India" has numerous uses in Indian medicine [34]. Many Asian countries cultivate *C. longa*, a perennial plant of the Zingiberaceae family. One of the earliest spices to come out of India, it has a long history of use in the West and the South and is an essential part of Ayurvedic medicine [35]. Dashemani Lekhaniya, Kusthagna, and Visaghna are three Ayurvedic books that mention *C. longa's* anti-emaciating, anti-dermatosis, and anti-toxic characteristics, respectively. A superb cure for jaundice, it has many names: Haridra in Sanskrit, Haldi in Hindi, Jianghuang (yellow ginger) in Chinese, manjal in South Indian languages, and Kyoo or Ukon in Japanese. *C. longa* is an essential part of any Hindu girl's beauty routine; it is extensively discussed in the Indian medical text Dravyaguna Shastra. An integral part of Hindu ceremonies involves applying a paste made of C. longa on the bride [36]. The pharmacopoeias of Korea, Japan, and China all acknowledge its broad applicability, which it uses to treat a variety of medical issues. Conditions including urticaria, dermatitis, inflammatory joint diseases, sore throats, wounds, and hepatitis infections are some of the illnesses that it helps with in China. It is described in Hindu mythology texts as a stimulant with carminative and fragrant properties. Make a powerful home remedy for injury oedema and sprains by mixing turmeric powder with calcium hydroxide and applying the mixture topically to the afflicted area. The use of dried curcumin powder in traditional medicine dates back many centuries. The anti-inflammatory, anti-cancer, anti-toxic, and antibacterial properties of *C. longa* have been well-documented. The caudex of *C. longa* is a tuberous rhizome with rough, segmented edges. Underneath the leaf, the rhizomes multiply in the dirt [37]. At maturity, the rhizomes take on a yellowish-brown hue on the outside and a little orange hue on the inside. From the main rhizome emerge a succession of tiny, pointed or tapered tubers, 2.5–7.0 cm in diameter and 1–3 inches long. The dried rhizome is transformed into a golden powder that has a bittersweet flavour [38]. An oil-resin hybrid with a yellow hue, curcumin (1,7-bis[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione) is produced by the rhizome. According to some, rhizome powder has multiple uses, including enhancing the flavour of food and treating a wide range of medical issues like flatulence, jaundice, inflammation, dysmenorrhea, haematuria, and haemorrhage [39]. When used topically, it alleviates a wide range of skin conditions. Curcumin, diferuloylmethane, and a plethora of volatile oils merge. What sets Indian *C. longa* apart from other varieties is its high curcumin content [40]. The medicinal effectiveness of *C. longa* is supported by curcumin, the active biological component. Curcumin is a flavonoid that has lipophilic characteristics, which make it stable in acidic stomach environments and practically insoluble in water. Both water-soluble and lipid-soluble extracts of curcumin and *C. longa* exhibit antioxidant characteristics that are on par with those of vitamins C and E [41].

Health benefits of Curcumin

There is mounting evidence that the polyphenol curcumin targets many signalling molecules and exerts a biological effect, both of which contribute to its many health benefits. Use of it has been associated with improvements in inflammatory disorders, metabolic syndrome, pain, and inflammatory and degenerative eye diseases [42]. According to studies, it has positive effects on the kidneys as well. Because of its antioxidant and anti-inflammatory properties, curcumin is believed to have several medicinal uses. Oral administration of curcumin has several drawbacks, the most significant of which is its poor bioavailability, which may be due to fast metabolism, rapid excretion, and insufficient absorption, despite curcumin's anti-inflammatory and antioxidant properties. In order to increase curcumin's bioavailability, researchers have investigated a number of compounds that target different pathways [43]. The main purpose of most of these compounds was to block the metabolic pathway of curcumin, making it more bioavailable. The active ingredient in black pepper, piperine, is known to increase the bioavailability of curcumin by a factor of 2,000. One spice that makes use of this effect is black pepper [44]. It seems that the problem of restricted bioavailability is being addressed by adding substances that increase bioavailability, such as piperine, which results in a curcumin complex. Curcumin is gaining a lot of attention and use all over the world because of its many possible health advantages [45]. Indian curry, Japanese tea, Thai cosmetics, Chinese colourant, Korean beverages, Malaysian antiseptic, Pakistani anti-inflammatory, and various American forms of mustard sauce, cheese, butter, chips, pills, and powder are just a few examples of its many uses [46]. Curcumin, a component of

turmeric, is used in various Asian countries. Energy drinks, soaps, ointments, pills, and cosmetics are just a few of the many products that contain curcumin [47-50]. At dosages ranging from 4000 to 8000 mg/day, as well as up to 12,000 mg/day of a 95% concentration of three curcuminoids (demethoxycurcumin, bisdemethoxycurcumin, and curcumin), the acceptability and safety profiles were shown to be favourable in clinical trials. As far as the United States is concerned, curcuminoids are GRAS according to the FDA [51].

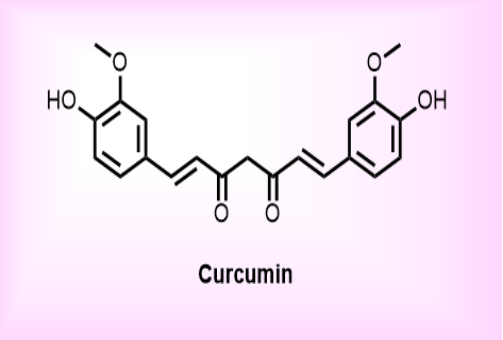

Figure 2: Structure of Curcumin

Curcumin role in the treatment of Multiple sclerosis

Curcumin inhibits multiple sclerosis (MS) symptoms by acting on multiple possible MS pathophysiological sites. Molecular patterns associated with illnesses or dangers trigger the activation of toll-like receptors (TLRs), a subset of pattern recognition receptors [52]. Macrophages, dendritic cells, monocytes, activated microglia, and reactive astrocytes are among the cell types that produce inflammatory mediators that are crucial for the host's defence. The release of inflammatory cytokines and worsening of the sickness is caused by the elevation of the expression of specific toll-like receptors (TLRs) in innate immune cells, according to research conducted by Gooshe, Abdolghaffari, Gambuzza, and Rezaei (2014) [53]. After inducing EAE in female C57BL/6 and SJL/J mice, researchers found that CD4+ and CD8+ T cells expressed more TLR4 and TLR9 than before. Studies with spleen cells taken from C57BL/6 mice that were given 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2) or curcumin while they were alive have shown that curcumin inhibits the expression of TLR4 and TLR9 in the brain when exposed to antigens [54]. These findings suggest that curcumin might have an effect on the Kv1.3 channel, a voltage-gated protein that is upregulated and overexpressed in activated effector memory T cells, leading to increased proliferation and the development of autoimmune diseases like MS [55]. Curcumin (5-100 µM) inhibited hKv1.3 channels at all positive potentials from 0 to +60 mV, according to a study conducted on HEK-293 cells [56]. Subsequent depolarisation of the channels amplified the effect. In vitro experiments shown that curcumin's ability to block Kv1.3 channels significantly reduced the growth of human TEM cells at doses of 10 µM and higher [57]. The innate pharmacological potential of curcumin must be harnessed, notwithstanding the extensive research on its modulatory effects on proinflammatory cytokine production [58-60]. According to Fahey, Adrian Robins, and Constantinescu (2007), tyrosine phosphorylation of JAK1 and TYK2 facilitates the signal transduction pathway of curcumin. Accordingly, studying curcumin's effects on MS might be as simple as looking at the expression of these proteins [61].

Curcumin effect on MS induced neurodegeneration

Multiple sclerosis (MS) is characterised histologically by demyelination and axonal impairment. Demyelinated lesions can happen anywhere in the brain or spinal cord, which greatly increases the clinical variety and complexity of the disease. By penetrating the BBB-ECS, Th17 cells cause neuronal cell death. Additionally, they cross the BBB. There are a plethora of other inflammatory mediators that IL-17 activates [62]. An essential inflammatory second messenger that aids in the death of oligodendroglial cells, inducible nitric oxide synthase (iNOS) produces pathogenic NO during inflammation. Increases in NO levels and iNOS expression are time- and dose-dependent responses seen in several cell types to IL-17 [63]. In response to an inflammatory milieu within the CNS, microglia, astrocytes, macrophages, and dendritic cells undergo substantial activation. The release of IL-17, TNF-α, NO, and osteopontin, in addition to the presentation of antigens to T cells, intensifies the harmful inflammatory milieu by making myelin breakdown worse [64]. Injecting these inflammatory cytokines into the bloodstream, macrophages devour large sections of the myelin sheath. T cells and inflammatory mediators such nitric oxide, osteopontin, and cytokines launch a coordinated assault, demyelinating the affected areas, which hinders axonal electrical transmission [65]. Because of its lipophilic nature, curcumin is able to pass through all cell membranes and have an impact inside cells. Because of its anti-inflammatory properties, it could help with multiple sclerosis treatment [66]. Curcumin crosses the blood-brain barrier to keep the milieu of the central nervous system stable by blocking the major route of proinflammatory cytokine production. By suppressing NF-κB activation and reducing Th17 cell differentiation and proliferation, curcumin reduced TNF-α and NO generation in a way that was dosage dependent [67]. After being treated with curcumin, microglia stimulated with LPS or IFNγ showed a significant decrease in the phosphorylation of STAT1, STAT3, JAK1, and JAK2. By increasing SHP-2 phosphorylation and interacting with JAK1/2, curcumin may reduce the inflammatory response of brain microglial cells. Activated microglia are unable to initiate JAK-STAT inflammatory signalling due to this process [68]. The growth and differentiation of microglia are both inhibited by curcumin. Research using dosages of 4, 5, 10, 15, and 20 µM of curcumin in C-6 rat glioma 2B-clone cells showed that curcumin inhibits the growth and maturation of neuroglial cells or causes their death in a way that is dose-dependent [69]. The astrocyte-identifying glutamine synthetase (GS) assay has demonstrated a decrease. The research showed that curcumin improves the activity of an enzyme used to identify oligodendrocytes, CNP (2′3′-cyclic nucleotide 3′-phosphohydrolase). The effects of curcumin on neuroglial cells are multifaceted, including a reduction in astrocyte proliferation, an increase in myelogenesis, and a stimulation of oligodendrocyte activity and differentiation [70].

CONCLUSION

Developing effective treatment plans is crucial because MS is a disabling disease that greatly reduces quality of life. The current treatments come with a plethora of unwanted side effects and are quite pricey. This has led to a surge in research into phytochemicals and herbal remedies with purported health benefits. Recent studies have shown that curcumin has several useful characteristics, such as anti-inflammatory effects, low cost, lack of side effects, and wide availability. Therefore, this phytochemical represents an option to MS treatment that has promise. Nevertheless, research, particularly clinical studies, have been hindered by curcumin's kinetic constraints. New drug delivery technologies and combo treatments appear to be good alternatives to curcumin that can help overcome its limitations. By reducing hepatic metabolism and increasing absorption, the dual drug-loaded nanoparticulate treatment of curcumin with piperine, quercetin, and silibinin increased bioavailability.

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