Neurospine

Review Article

Corresponding Author

Kyoung-Tae Kim

https://orcid.org/0000-0003-4867-6854

Department of Neurosurgery, Kyungpook
National University Hospital, 130
Dongdeok-ro, Jung-gu, Daegu 41944,
Korea
Email: nskimkt7@gmail.com

Co-corresponding Author

Inbo Han

https://orcid.org/0000-0002-0834-9325

Department of Neurosurgery, CHA
Bundang Medical Center, 59 Yatap-ro,
Bundang-gu, Seongnam 13496, Korea
Email: hanib@cha.ac.kr

Curcumin as a Promising Neuroprotective Agent for the Treatment of Spinal Cord Injury: A Review of the Literature

Subum Lee[1], Dae-Chul Cho[2], Inbo Han[3], Kyoung-Tae Kim[2]

[1]Department of Neurosurgery, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Korea
[2]Department of Neurosurgery, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, Korea
[3]Department of Neurosurgery, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea

Curcumin is a polyphenolic chemical derived from the rhizomes of *Curcuma longa*. It has been used throughout the Indian subcontinent for medicinal purposes, religious events, and regional cuisine. It has various pharmacological benefits owing to its anti-inflammatory and antioxidant properties. Its neuroprotective effects on the brain and peripheral nerves have been demonstrated in several *in vivo* neuronal tissue studies. Because of these functional properties of curcumin, it is considered to have great potential for use in the treatment of spinal cord injuries (SCIs). Numerous immunopathological and biochemical studies have reported that curcumin can help prevent and alleviate subsequent secondary injuries, such as inflammation, edema, free radical damage, fibrosis, and glial scarring, after a primary SCI. Furthermore, following SCI, curcumin administration resulted in better outcomes of neurological function recovery as per the Basso, Beattie, and Bresnahan locomotor rating scale. However, to date, its utility in treating SCIs has only been reported in laboratories. More studies on its clinical applications are needed in the future for ensuring its bioavailability across the blood-brain barrier and for verifying the safe dose for treating SCIs in humans.

Keywords: Antioxidant, Curcumin, Inflammation, Neuroprotective agent, Recovery of function, Spinal cord injury

INTRODUCTION

Spinal cord injuries (SCIs) have 2 phases—primary and secondary injuries.[1] A primary injury is caused by mechanical insult and structural damage, whereas a secondary injury is a sequence of systemic and local neurochemical and physiological alterations. Subsequent edema, ischemia, inflammation, cytokine production, free radical damage, glial scar formation, apoptosis, and necrosis contribute toward the development of secondary injuries.[2] A primary injury is immediate and irreversible; in contrast, a secondary injury worsens with time and ne-

cessitates therapeutic intervention. Thus, preventing or aggressively treating secondary injuries is the mainstay of care for acute SCIs.[3,4]

Curcumin is a promising therapeutic drug for SCI treatment because it reduces the incidence of secondary injuries. It is a yellow extract derived from *Curcuma longa* that is frequently used as a spice and food-coloring ingredient in India (Fig. 1). Curcumin has antioxidant and nonsteroidal anti-inflammatory pharmacological properties.[5,6] Preclinical and clinical trials have revealed its various pharmacological activities, including its anti-inflammatory, antibacterial, anticancer, and neuroprotective

effects on neurodegenerative disorders. Curcumin also has hepatoprotective, nephroprotective, cardioprotective, neuroprotective, hypoglycemic, and antirheumatic activities, and its neuroprotective activity against several neurodegenerative disorders is gaining researchers' attention.[7] As an anti-inflammatory agent, curcumin suppresses the production of many proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), in-

Fig. 1. *Curcuma longa* plant and powder. Curcumin is a yellow substance produced by *Curcuma longa*. Curcumin is the primary curcuminoid found in turmeric, a member of the ginger family. It is marketed as an herbal supplement, cosmetic ingredient, food-flavoring agent, and food colorant.

terleukin (IL)-1, IL-8, and monocyte chemoattractant protein 1.[8,9] In a recent study, curcumin inhibited the hypoxia-induced upregulation of glial fibrillary acidic protein (GFAP) and neurofilament-H following hypoxia and downregulated the expression of proinflammatory cytokines, such as TNF-α and IL-1.[10] It also suppresses glial scar formation and GFAP expression, contributing toward the development of a more favorable environment for neurological recovery (Fig. 2).[11]
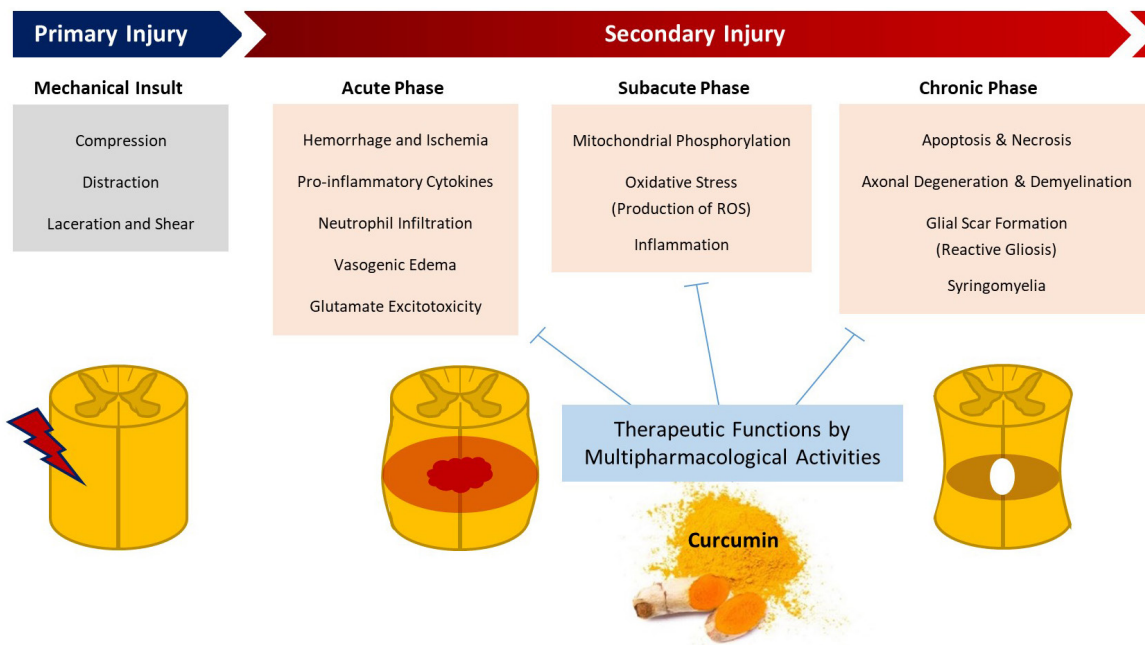
This study aimed to consolidate the knowledge essential for spine surgeons and related clinicians to understand how curcumin can alleviate secondary injuries observed in SCIs. Herein, we discuss the basics of neuroprotective effects and accumulate experimental evidence regarding the neuroscience of curcumin.

PHARMACOLOGY

Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is a complex pharmacophore that has the potential to serve as an antioxidant, chelate metals, and trigger the Michael reaction.[12] Additionally, it is a hydrophobic molecule with a strong affinity toward cellular membranes and consists of 2 ferulic acid residues connected by a methylene bridge.[13] The structure of the molecule is symmetrical. The 3 major components of curcumin molecules are the keto-enol tautomer in the

Fig. 2. Pathophysiological process following spinal cord injury and the targeted therapeutic function of curcumin. ROS, reactive oxygen species.
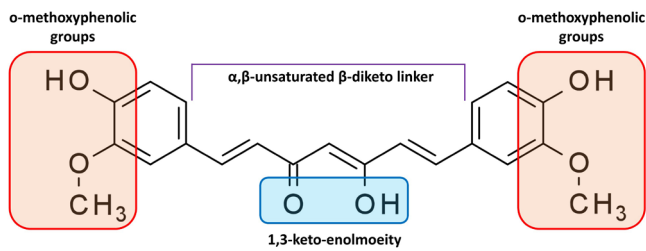
Fig. 3. Molecular structure of curcumin. The keto-enol tautomer in the center, flexible α,β-unsaturated β-diketo linker, and terminal o-methoxyphenolic groups make up the curcumin molecule, which has an asymmetric structure.
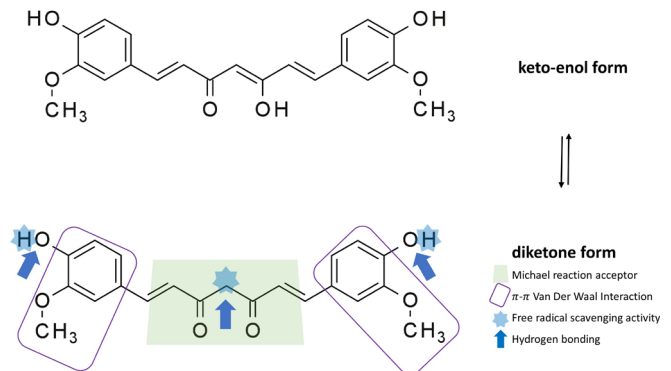

Fig. 4. Curcumin has a wide range of interactions. Curcumin contains a complex pharmacophore that can function as an antioxidant; chelate metals; and facilitate Michael reactions (used in the mild formation of C–C bonds), hydrogen-bonding interactions, π-π van der Waals interactions, and free radical scavenging.

middle, flexible α,β-unsaturated β-diketo linker, and terminal o-methoxyphenolic groups (Fig. 3).

The structure of curcumin contains various functional groups (diketo group, carbon-carbon double bonds, and phenyl rings). Thus, curcumin is a unique and strong antioxidant. Structure-activity correlations have shown that the β-diketone (keto-enol) moiety acts as a chelator of cationic metals in protein-binding sites and as a Michael reaction acceptor for nucleophilic compounds that form covalent bonds with curcumin, such as reduced selenocysteine and sulfhydryl.[14] The antioxidant activity of curcumin is dependent on the phenolic hydroxyl group.[15] This group and methylene hydrogen are essential for curcumin's free radical scavenging activity, which involves electron transfer or H-atom abstraction from reactive oxygen species (ROS) and nitrogen species (Fig. 4).[16]

The wide range of interactions of curcumin might explain why it binds to various proteins. Curcumin affects the function of roughly 100 biological targets in various ways,[17] including the modification of the phosphorylation state of cellular proteins.[18] Curcumin has effects at doses above the micromolar level in general. This low binding affinity has aided various attempts to use a structure-based drug design to improve the efficacy of curcumin.

ANTI-INFLAMMATORY EFFECT

One of the most promising alternatives for primary SCI treatment is an anti-inflammatory multimodal neuroprotection strategy.[19] Spinal cord edema, which is accompanied by acute inflammation and precedes fibrosis, plays a critical role in neurological impairment. This provides a fundamental explanation for the clinical use of corticosteroids in patients with SCIs. Curcumin is an anti-inflammatory molecule that suppresses transcription factors including nuclear factor-kappa B (NF-κB) and sig-

nal transducer and activator of transcription (STAT) in the upstream signaling pathways of inflammatory mediators such as prostaglandins, cytokines, and chemokines, resulting in the global inhibition of the inflammation network.[20] Given the fundamental nature of NF-κB signaling pathway activation to neuroinflammation and SCI pathophysiology,[21] modulating NF-κB signaling could help minimize inflammation, lessen the severity of secondary injury, and maintain neuronal function.

Curcumin can also directly bind to inflammatory mediators and enzymes involved in downstream inflammatory pathways, such as IL-1 converting enzyme, TNF-α, TNF-α converting enzyme, p38 mitogen-activated protein kinase, myeloid differentiation protein-2, 1-acid glycoprotein, and glycogen synthase kinase-3 beta.[14,22] Additionally, curcumin suppresses the production of transforming growth factor-beta (TGF-β)1, TGF-β2, and sex-determining region Y-box transcription factor 9. It also facilitates the development of a microenvironment appropriate for nerve development.[23] Curcumin suppresses the upregulation of aquaporin 4 and GFAP and the atypical activation of the Janus kinase–STAT signaling pathway associated with SCI.[24] Recent *in vivo* studies on the anti-inflammatory function of curcumin are summarized in Table 1.

ANTIOXIDANT EFFECT

Numerous experiments have been conducted to determine the antioxidant capabilities of curcumin for SCI treatment. There is a strong correlation between SCI and inflammation-induced free radical formation.[25] Curcumin is a potent antioxidant that

Table 1. Anti-inflammatory properties of curcumin: list of recent evidentiary studies

Study	Specimen/sample size/ SCI method	Study design (experimental groups)	Curcumin treatment method	Summary of results
Zu et al.,[24] 2014	Male Sprague-Dawley rats/N=64/ Striking bar falling (diameter: 3 mm) 5-cm height (150 gcf) on T8 level	Sham/DMSO (n=16) Sham/Curcumin (n=16) SCI/DMSO (n=16) SCI/Curcumin (n=16)	40 mg/kg Single IP injection 30 min after SCI	Curcumin increased gray–white matter interface, tissue edema/AQP-4 expression, and GFAP/pJAK-STAT expression Moderately improved BBB scores
Wang et al.,[59] 2014	Female BALB/c mice/N=No description/10-g force clip for 3 sec, extradural on T9 level	Sham SCI/DMSO SCI/Curcumin	50 mg/kg Single IP injection Immediately after SCI	Curcumin decreased tissue expression of GFAP and Iba-1 and increased NF-200 Decreased levels of IL-1β, NO, and NF-κB Increased neuromotor scores (Basso mouse scale)
Lin et al.,[60] 2015	Wild-type C57BL/6JNarl mice/ N=18/Weight dropped Guide was lifted up to 4 mm to perform a hemitransection	Sham control (n=6) SCI (n=6) SCI+Curcumin (n=6)	40 mg/kg Single IP injection 30 min after SCI	Curcumin attenuated the downregulation of CISD2 in SCI and LPS-treated astrocytes. (CISD2 exerts antiapoptotic and anti-inflammatory effects on neural cells)
Yuan et al.,[23] 2015	Female Sprague-Dawley rats/ N=No description/Aneurysm clip (fixed force of 50 g) for 60 secon T9 level	Sham SCI SCI+Curcumin 30 SCI+Curcumin 100 SCI+Curcumin 300 SCI+Methylprednisolone	Various dose of curcumin (300, 100, and 30 mg/kg) IP injection once per day for 7 days	Curcumin inhibited the expression of proinflammatory cytokines (TNF-α, IL-1β, and NF-κb) Reduced the expression of the intracellular components and GFAP through its anti-inflammatory effects. Suppressed reactive gliosis. Inhibited the generation of TGF-β1, TGF-β2, and SOX-9 Improved BBB scores
Ni et al.,[61] 2015	Male Sprague-Dawley rats/ N=48/30-g force extradural compression with a clip for 30 sec on T8–9 level	Sham (n=16) SCI (n=16) SCI+Curcumin (n=16)	100 mg/kg IP injections at 15 min after SCI	Curcumin modulated the TLR4/NF-κB inflammatory signaling pathway and significantly ameliorated SCI-induced spinal cord edema and apoptosis. BBB scores significantly increased
Yuan et al.,[9] 2017	Female Sprague-Dawley rats/ N=280/50-g force clip compression for 60 sec on T9 level	Sham (n=70) SCI (n=70) SCI+Curcumin (n=70) SCI+DMSO (n=70)	100 mg/kg IP injections Immediately after surgery and once every 24 hr for 7 days	Curcumin regulated both the NF-κB and SOX-9 signaling pathways. Downregulated the expression of chemokines, MCP-1, RANTES, and CXCL10, released by astrocytes. Decreased macrophage and T-cell infiltration
Ruzicka et al.,[40] 2018	Wistar rats/N=135/Balloon-induced compression using Fogarty catheter on T8 level	Saline (n=34) Curcumin (n=27) MSC (n=28) Curcumin+MSC (n=26)	High dose once a week (60 mg/kg diluted in olive oil) intrathecally 4 times (immediately after SCI followed up for 3 subsequent weeks), low-dose IP injection daily (6 mg/kg diluted in olive oil) (immediately after SCI and on the 28th day)	The combined therapy facilitated axonal sprouting and modulated the expression of proregenerative factors and production of inflammatory responses. Both curcumin and curcumin combined with MSC therapy improved BBB score and the combined treatment group showed additional improvement in advanced locomotor performance.

(continued)

Table 1. Anti-inflammatory properties of curcumin: list of recent evidentiary studies (continued)

Study	Specimen/sample size/ SCI method	Study design (experimental groups)	Curcumin treatment method	Summary of results
Ruzicka et al,[62] 2018	Wistar rats/N=131/Balloon-induced compression using Fogarty catheter for 5 min	Behavioral group study: Saline (n=10) Curcumin (n=13) EGCG (n=19) Curcumin+EGCG (n=9) Cytokine group study: Saline (n=20) Curcumin (n=20) EGCG (n=20) Curcumin+EGCG (n=20)	Curcumin 6 mg/kg, EGCG 17 mg/kg IP daily Curcumin 60 mg/kg EGCG 17 mg/kg IM weekly for 28 days	Curcumin and EGCG alone or in combination increased axonal sprouting, decreased glial scar formation, and altered the levels of macrophage inflammatory protein 1-alpha, interleukin-1β, interleukin-4, and interleukin-6. All treatments displayed significant behavioral recovery (BBB score) with no obvious synergistic effect after the administration of the combined therapy of curcumin and ECGC
Lee et al,[4] 2019	Sprague-Dawley rats/N=35/Clip with 30-g force for 2 min	Sham (n=32) SCI only (n=32) SCI+Hyperglycemia (n=32) SCI+Hyperglycemia+ Curcumin (n=32)	200 mg/kg/day for 8 weeks, IP	SCI+hyperglycemia+curcumin group: SOD activity increased, malondialdehyde and ED-1 macrophage marker levels decreased, IL-6, IL-8, TNF-α, phosphorylated extracellular signal-regulated kinase, phosphorylated JNK, and phosphorylated p38 levels decreased, Better BBB score
Yardım et al,[63] 2021	Male Sprague-Dawley rats/N=35/ PTX-induced SCI	Control (n=7) Curcumin (n=7) PTX (n=7) PTX+Curcumin100 (n=7) PTX+Curcumin200 (n=7)	100 mg/kg or 200 mg/kg Oral daily for 10 days	Curcumin reduced mRNA expression levels of NF-κB, TNF-α, IL-6, iNOS, and GFAP and increased the levels of Nrf2, HO-1, and NQO1. Curcumin suppressed the activation of apoptotic and autophagic pathways by increasing Bcl-2 and Bcl-xL and decreasing p53, caspase-3, Apaf-1, LC3A, LC3B, and beclin-1 mRNA expression levels

SCI, spinal cord injury; DMSO, dimethyl sulfoxide; AQP-4, aquaporin 4; GFAP, glial fibrillary acidic protein; pJAK-STAT, phosphorylated Janus kinase-signal transducer and activator of transcription; BBB, Basso, Beattie, Bresnahan; BALB, Bagg albino; IP, intraperitoneal; NF-200, neurofilament-200; IL, interleukin; NO, nitric oxide; NF-κB, nuclear factor kappa B; LPS, lipopolysaccharide; TNF, tumor necrosis factor; TGF, transforming growth factor; SOX-9, sex-determining region Y-box transcription factor 9; MCP-1, monocyte chemoattractant protein-1; RANTES, regulated upon activation, normal T cell expressed and presumably secreted; CXCL10, C-X-C motif chemokine ligand 10; MSC, mesenchymal stem cells; EGCG, epigallocatechin gallate; IM, intramuscular; iNOS, inducible nitric oxide synthase; Nrf2, nuclear erythroid 2-related factor 2; HO-1, hemeoxygenase 1; NQO1, NAD(P)H:quinone oxidoreductase 1; PTX, paclitaxel; LC3A, light chain 3 A; LC3B, light chain 3 B.

is reported to be superior to vitamin E, resveratrol, and other commonly used antioxidants.[26] Curcumin interacts with ROS directly and also acts as an activator of antioxidant signaling systems, making its effects more comprehensive and long lasting.[27] Curcumin can also neutralize free radicals via electron transfer and/or H-atom donation. The antioxidant ability of curcumin is influenced by 3 distinct functional dissociation groups and a β-diketone site.[28,29]

Curcumin binds to lipid radicals in cell membranes and converts them into phenoxyl radicals. Because phenoxy is more polar than curcumin, it diffuses to the membrane surface, where it can be repaired by any water-soluble antioxidant such as ascorbic acid. Thus, curcumin can protect cell membranes against oxidative damage by acting as a lipid radical scavenger.[30] It has the potential to enhance the activity of antioxidant enzymes, such as plasma catalase, erythrocyte superoxide dismutase (SOD), and plasma glutathione peroxidase.[31] Furthermore, malondialdehyde (MDA), which is the end product of lipid peroxidation, is a reliable marker of oxidative stress-mediated lipid peroxidation.[32] Curcumin decreased MDA based on a fixed-effects model (n = 56; pooled mean difference [MD] = -1.00; 95% confidence interval [CI], -1.59 to -0.42; p = 0.00008) in a meta-analysis of 4 studies on MDA levels.[8]

Additionally, curcumin could stimulate antioxidant protection genes via the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway.[33] It increases intracellular antioxidant defense responses by activating the Nrf2/antioxidant response element pathway, which results in the development of several antioxidants and detoxification and cytoprotective proteins.[34] Recently, Ni et al. showed that SCI caused a considerable increase in la-

Table 2. Antioxidant property of curcumin: list of recent evidentiary studies

Study	Specimen/sample size/SCI method	Study design (experimental groups)	Curcumin treatment method	Summary of results
Akar et al.,[64] 2017	Wistar rats/N = 40/ Spinal cord ischemia induced by clamping the aorta	Sham (n = 10) Ischemia–reperfusion (n = 10) Curcumin (n = 10) Solvent (n = 10)	100 mg/kg, IP at 30 min before ischemia Dissolved in 5 N NaOH	Decreased MDA levels in the spinal cord Increased SOD and GPx levels caused by curcumin Neurological outcome scores were significantly better when compared with those of the IR group.
Xi et al.,[65] 2019	Sprague-Dawley rats/ N = 24/A hammer was dropped on T8 level	Sham/control (n = 8) SCI (n = 8) Tetrahydrocurcumin treatment (n = 8)	80 mg/kg/day, IP Tetrahydrocurcumin for 2 weeks	Oxidative stress and apoptosis (caspase-3 activity and B cell lymphoma 2-associated X protein levels) were suppressed Tetrahydrocurcumin inhibits oxidative stress response by regulating FOXO4 in SCI model rats. Tetrahydrocurcumin increased the BBB scores
Daverey et al.,[10] 2020	Male Wistar rats/ N = 18/30-mm spinal cord section/ Hypoxia	Sham Hypoxia Hypoxia+Curcumin Sham Hypoxia Hypoxia+Curcumin Hypoxia+BAY11-7082	One hour incubation with 50 μM curcumin in 95% N2 and 5% CO2	Curcumin inhibited hypoxia-induced HIF1-α expression and tissue damage by improving the morphology of astrocytes and remarkably reducting vacuolation. It inhibited the hypoxia-induced upregulation of GFAP and neurofilament-H (NF-H) after hypoxia and downregulated the expression of pro-inflammatory cytokines such as TNF-α and IL-1. Curcumin exerted its neuroprotective effect through cross-talk between the NF-κB and Nrf2 signaling pathways.
Daverey and Agrawal,[66] 2020	Human astrocytes Male Wistar rats/ N = 21/30-mm spinal cord section/ Hypoxia	Human astrocytes Sham Hypoxia Hypoxia+Curcumin Hypoxia+Riluzole Hypoxia+Riluzole+ Curcumin	Human astrocytes: Riluzole (1 μM) Curcumin (1 μM) Rat SCI model (white matter injury) Riluzole (10 μM) Curcumin (50 μM)	Riluzole protects white matter injury by the activation of Nrf2/HO-1 and caspase 9. Curcumin's neuroprotective effect is mediated through the inhibition of HIF-1α, GFAP, NF-H, and caspase 9. Curcumin is more effective than riluzole in reducing GFAP and NF-H injury.

SCI, spinal cord injury; IP, intraperitoneal; MDA, Malondialdehyde; SOD, serum superoxide dismutase; IR, ischemia–reperfusion; FOXO4, forkhead box protein O4; BBB, Basso, Beattie, Bresnahan; HIF1-α, Hypoxia inducible factor 1-α; GFAP, glial fibrillary acidic protein; TNF, tumor necrosis factor; IL, interleukin; Nrf2, nuclear erythroid 2-related factor 2; HO-1, hemeoxygenase 1; NF-H, neurofilament protein-H.

bile Zn and inflammatory cytokines in an injured rat's spinal cord, and curcumin decreased the accumulation of labile Zn.[35] Zn is important in decreasing oxidative stress and generating inflammatory cytokines. Recent studies that demonstrate the antioxidant function of curcumin are summarized in Table 2.

STEM CELL PROLIFERATION

While research on stem cells for SCI treatment is ongoing, there still exist significant barriers in achieving excellent therapeutic results. It is critical to promote neural stem cell (NSC) proliferation for treating SCI, and several investigations have reported the contribution of curcumin to this process.[36-38] An improved therapeutic effect can be achieved by modifying stem cell proliferation and differentiation and reducing the inflammatory microenvironment in injured regions.[39]

Curcumin enhances the functional recovery of SCIs when combined with NSC or mesenchymal stem cell (MSC) therapy.[37,40] In a study by Ormond et al.[2] the combination of curcumin and NSC therapy led to a significant recovery of severe SCIs *in vivo*, which was evidenced by better functional locomotor recovery, body weight, and soleus muscle mass. Wanjiang et al.[41] confirmed that in combination with MSC therapy, curcumin suppressed human umbilical cord-derived MSC (hUC-MSC) apoptosis via the ERK1/2 signaling pathway, and the combined curcumin and hUC-MSC therapy improved the motor function of rats with SCIs. A study by Bonilla et al.[42] evaluated a combination therapy comprising human NSCs derived from induced pluripotent stem cells (iPSC-NSCs), human MSCs, and a pH-responsive polyacetal–curcumin nanoconjugate (PA–C) that allows the sustained release of curcumin. The combination of stem cell transplantation and PA–C therapy exerted higher neuroprotective effects compared with individual therapies. Representative studies showing that curcumin enhances stem cell proliferation are summarized in Table 3.

NEUROLOGICAL FUNCTIONAL IMPROVEMENT

Neurological function was found to be improved by curcumin in a random-effects model of a comprehensive meta-analysis.[8] The magnitude of the effect, as measured by the Basso, Beattie, and Bresnahan (BBB) locomotor rating scale, was significantly increased when the curcumin dosage was elevated (4 trials; total, 132 rats; pooled MD = 3.09; 95% CI, 3.40–4.45; p = 0.04).[8] Several studies on functional recovery had the advantage of

adopting a uniform scale (BBB score) for interstudy comparisons, making aggregated results reliable. In an animal trial, 60 Wistar rats were randomly assigned to receive either curcumin therapy (30 rats) or placebo (30 rats).[43] Curcumin therapy (immediately applied to the injured spinal cord surface and then administered intraperitoneally daily) resulted in behavioral recovery within the first week following SCI, as shown by better BBB and plantar scores for sensory function. This functional improvement was induced by the anti-inflammatory effects of curcumin. In another animal study investigating antioxidative characteristics and functional recovery, the curcumin-treated group demonstrated enhanced locomotor scores (BBB scores), increased SOD levels, reduced MDA levels, and reduced macrophage markers following SCI.[3]

One study found that curcumin was more effective than methylprednisolone, which is frequently used in clinical practice to treat secondary injury in patients with SCIs 2 weeks after primary injury based on BBB scores.[44] The study concluded that curcumin has a greater therapeutic potential than methylprednisolone, showing a longer duration of action in SCIs. Thus, *in vivo* studies on rats and their BBB scores offer substantial evidence of the efficacy of curcumin in causing functional recovery after SCIs. In many *in vivo* studies, neurological function was assessed using BBB scores (Tables 1–3). Other studies that evaluated functional recovery using BBB scores are summarized in Table 4.

OBSTACLES AND FUTURE DIRECTION

Although curcumin has been reported to be a promising neuroprotective agent, its practical applications are limited owing to a number of issues. Curcumin has limited bioavailability because of its low water solubility, poor absorption, rapid metabolism, and fast elimination. It cannot cross the blood-brain barrier, making it unsuitable for use in treating central nervous system injuries, including SCIs. Toxicity is also an issue. Curcumin induces damage to the DNA both *in vitro* and *in vivo*.[45] Curcumin acts as a dose-dependent antioxidant to inhibit ROS as well as a pro-oxidant to produce ROS.[46,47] Superoxide anion and hydrogen peroxide are the 2 types of ROS that may play an important role in carcinogenesis.[48] At high doses, curcumin can react with the thiol groups of cysteine residues,[49] causing DNA damage or p53 inactivation.[50,51]

However, these limitations are being addressed by encapsulating curcumin into nanoformulations. Encapsulation of curcumin into nanocarriers via various methods is an appropriate

Table 3. Recent studies showing proliferation enhancement through the combination of curcumin and stem cells

Study	Stem cell types and specimen/SCI method	Study design (experimental groups)	Curcumin treatment method	Summary of results
Son et al.,[36] 2014	Neural progenitor cell (NPC) from the spinal cord of Sprague-Dawley rats	Examine cellular proliferation (MTS assay) in control (no curcumin) and curcumin groups at 6 different dose levels	In culture medium at 0.1, 0.5, 1, 10, 20, and 50 μM	Lower dosage (0.1, 0.5, 1 μM) of curcumin increased SC-NPC proliferation. However, higher dosage decreased SC-NPC proliferation. Curcumin stimulates the proliferation of SC-NPCs via the MAP kinase signaling pathway, especially involving the p-ERK and p-38 proteins.
Requejo-Aguilar et al.,[39] 2017	Ependymal stem/progenitor cells of the spinal cord (EpSPCi) of Sprague-Dawley rats Contusion 250 kdyn Infinite Horizon Impactor	PA (as vehicle) (n = 12) PA-curcumin–Cy5.5 (n = 15)	Intrathecal administration PA–curcumin–Cy5.5 (10 μM) (combination treatment: epSPCs and a pH-responsive polymer–curcumin conjugate)	PA–C enhances neuroprotection, increases axonal growth PA–C can improve functional recovery in acute SCI Also enhances functional recovery in a rodent model of chronic SCI. *PA (polyacetal): enhances blood bioavailability and stability and provides a means for highly localized delivery.
Bang et al.,[37] 2018	Neural stem/progenitor cells derived from Sprague-Dawley rats N = 60/Clip with a closing force of 30 g & a 2-min compression	Sham (n = 20) SCI-Curcumin (n = 20) SCI-Vehicle (n = 20)	Implanting indwelling intrathecal catheters/ A concentration of 1 μmol/L for curcumin	SCI-Curcumin group: The co-immunoreactivity of nestin/BrdU was higher The GFAP immunoreactivity and lesion cavity was lower The BBB score was better (up to 14 days)
Wanjiang et al.,[41] 2020	hUC-MSC/Female Sprague-Dawley rats/N = 180/50-g aneurysm clip compression on for 60 sec on T9 level	Sham (n = 30) SCI+Veh (n = 30) SCI+cur (n = 30) SCI+hUC-MSC (n = 30) SCI+cur+hUC-MSC (n = 30) SCI+cur+hUC-MSC+U0126 (n = 30)	IP, 100 mg of curcumin, dissolved in 1 mL of DMSO and 0.5 mL of NS 1st injection: 30 min after the operation Once/day for 14 days.	Curcumin suppressed hUC-MSC apoptosis through the ERK1/2 signaling pathway The combination of curcumin and hUC-MSC therapies improved motor function after SCI in rats.
Bonilla et al.,[42] 2021	Induced pluripotent stem cells (iPSC-NSC) & Human MSC Female Sprague-Dawley rats/200 kdyne contusion on T8 level iPCS-NSC (n = 8)	Control (n = 16) MSC (n = 11) iPCS-NSC+MSC (n = 11) PA-C (n = 6) iPSC-NSC+MSC+PA-C (n = 7)	A pH-responsive polyacetal–curcumin nanoconjugate (PA-C) delivery into the intrathecal space in contusive SCI with stem cell transplantation.	PA–C-treated or PA–C and iPSC-NSC + MSC-treated groups: Smaller scars, whereas PA–C and iPSC-NSC + MSC therapy induced the preservation of β-III tubulin-positive axons. iPSC-NSC + MSC transplantation fostered the preservation of motoneurons and myelinated tracts, whereas PA–C therapy polarized microglia into an anti-inflammatory phenotype.
Elkhenany et al.,[67] 2021	Human induced neural progenitor cells (iNPC) Female Sprague-Dawley rats/200 kdyn Infinite Horizon Impactor on T8 level	HA_PM_iNPC (non SCI) (n = 3) HA_PPY_PM_iNPC (non SCI) (n = 3) HA_PM_CURC (n = 3) HA_PPY_PM_CURC (n=3)HA_PM_iNPC (n = 3) HA_PPY_PM_iNPC (n = 3) HA_PM_CURC_iNPC (n = 3) HA_PPY_PM_CURC_iNPC (n = 3)	PM-embedded curcumin	PM-embedded iNPCs and CURC with PPY fibers supported a significant increase in neuropreservation (as measured by higher βIII tubulin staining of neuronal fibers) and decrease in the injured area (as measured by the lack of GFAP staining). *HA: hyaluronic acid *PM: Corning® PuraMatrix™ peptide hydrogel *PPY: polypyrrole-coated fibers

SCI, spinal cord injury; SC-NPC, spinal cord neural progenitor cell; MAP, mitogen-activated protein; p-ERK, phospho-extracellular signal-regulated kinase; PA, polyacetal; PA-C, polyacetal-curcumin; epSPC, ependymal stem/progenitor cells of the spinal cord; GFAP, glial fibrillary acidic protein; BBB, Basso, Beattie, Bresnahan; hUC-MSC, umbilical cord mesenchymal stem cell; IP, intraperitoneal; DMSO, Dimethyl sulfoxide; ERK, extracellular signal-regulated kinase; CURC, curcumin.

Table 4. Other studies showing the property of curcumin in promoting neurological functional recovery as evaluated by measuring the BBB score

Study	Specimen/sample size/ SCI method	Study design (experimental groups)	Curcumin treatment method	Summary of results
Kim et al.,[3] 2014	Male Sprague-Dawley rats/N=36/ clipping 30-g force for 2 min on T9 level	Sham (n=12) SCI/vehicle (n=12) SCI/curcumin (n=12)	200 mg/kg IP daily for 7 days	Curcumin group: Higher BBB scores 7–14 days after surgery (by anti-inflammatory and antioxidant action/ED-1, MDA, and SOD were measured)
Machova Urdzikova et al.,[43] 2015	Male Wistar rats/N=60/or balloon compression using Fogarty catheter (2 Fr) on T8 level	Control (n=30) Curcumin (n=30)	60 mg/kg Epidural locally Immediately after injury and 6 mg/kg in olive oil IP daily for 1–28 days	Curcumin group: Improved behavioral recovery (BBB scores and plantar sensory performance scores) within the first week following SCI (by anti-inflammatory action/NF-κB, MIP1a,IL4, IL1b, IL2, IL6, IL12p70, TNF-α, and RANTES were measured)
Liu et al.,[44] 2018	Male Sprague-Dawley rats/ N=60/10-g rod dropped, from 25-mm height on T9–10 level	SCI-Curcumin (n=27) SCI-MP (n=27) Sham group (n=6)	200 mg/kg IP daily for 56 days	SCI-Curcumin group: Improvement in the BBB score MP-treated group better within the first 14 days Cur-treated group better from 21–49 days after SCI Paralleled BBB scores of the 2 treatment groups on 56 days after SCI (by anti-inflammatory action/Bax, Bcl-2, Caspase-3, and GFAP were measured)
Luo et al.,[68] 2021	Female Sprague-Dawley rats/ N=24/2-mm segment of the spinal cord removed at T9 level	Control (n=6). FC hydrogel (n=6) FC/FI hydrogel (n=6) FC/FI-Cur hydrogel (n=6)	FC/FI-Cur hydrogel was implanted into the lesion area. FC: Fmoc-grafted chitosan FI: Fmoc peptide	FC/FI-Cur hydrogel group: Significantly promoted BBB walking score (by anti-inflammatory action/immunofluorescence staining of antibodies CD68, S100, neurofilament 200, GFAP, myelin basic protein, etc. were measured)

BBB, Basso, Beattie, Bresnahan; SCI, spinal cord injury; ED-1, CD68/SR-D1 antibody (marker for activated macrophages); MDA, malondialdehyde; SOD, superoxide dismutase; NF-κB, nuclear factor kappa B; MIP1a, macrophage inflammatory protein-1 alpha; IL, interleukin; TNF-α, tumor necrosis factor-alpha; RANTES, regulated upon activation, normal T cell expressed and presumably secreted; MP, methylprednisolone; IP, intraperitoneal; GFAP, glial fibrillary acidic protein.

and effective strategy to increase its bioavailability because this method expands its solubility, promotes long-term circulation and retention in the body, and overcomes the physiological barriers of curcumin.[52,53] These nanoformulations can increase the half-life of curcumin in plasma and significantly reduce the administration dosage, resolving the toxicity issue associated with the use of high-dose curcumin.

Among the diverse nanocarriers developed for therapeutic applications, polymer therapeutics are the most successful polymeric nanomedicines.[54] For example, a combination therapy comprising ependymal stem/progenitor cells of the spinal cord and a pH-responsive polymer–curcumin conjugate for SCIs has been reported previously.[39] According to the study, conjugating curcumin with a pH-responsive polymeric carrier main chain, a polyacetal, improved its blood bioavailability and stability and facilitated a highly targeted curcumin distribution. PA–C also enhanced neuroprotection, axonal development, and functional recovery in acute SCIs. Recently, a new method that improves bioavailability by combining curcumin with extracellular vesicles was reported.[55] In the study, 120-nm engineered extracellular vesicles derived from primary M2 macrophages were used and nerve growth factors and curcumin were combined. The extracellular vesicles could effectively accumulate curcumin at the site of SCIs and inhibit uncontrollable inflammatory responses induced by secondary injury.

Further translational research is required to use curcumin in therapeutic settings. Oral intake of curcumin is insufficient for it to penetrate the blood-brain barrier; therefore, studies are needed to determine an effective administration method that would allow curcumin to act directly on injured neuronal tissues in the spinal cord. Furthermore, investigations on the safety of high-dose curcumin administration are required. In addition to nanotechnology, it is necessary to try various methods to enhance curcumin bioavailability. A strategy such as megadose administration might be crucial, and doses of previously commercialized curcumin products should be considered. Continuous or intermittent curcumin therapy has been administered in most animal investigations throughout the acute phase, which occurs within 24 hours of the primary injury, and the chronic phase, which occurs after the primary injury. Therefore, future research should focus on determining the most beneficial timing and duration of administration.

LIMITATIONS

The lack of information on certain aspects of curcumin is a

limitation of this paper. For example, we did not investigate the bioactivity of curcumin in astrocytes.[56] It also lacks detailed information on several signaling pathways that are regulated by curcumin, including the Nrf2/heme oxygenase 1 pathway,[30] the mammalian target of rapamycin,[57] and TGF-β–SOX9 pathway.[58] As a result, there are constraints in providing cutting-edge knowledge regarding curcumin therapy. However, the goal of this review paper is to provide clinicians with basic and comprehensive information regarding the role of curcumin in SCI treatment. The authors believe that this review paper would prove to be helpful to neurospinal clinicians.

CONCLUSION

Curcumin is a neuroprotective polyphenolic compound that has benefits such as pluripotency, oral safety, long usage history, and low cost. Several animal experiments have shown that curcumin can minimize secondary injury following primary SCIs through its anti-inflammatory, antioxidant, and stem cell mobilization properties. Curcumin is an influential therapeutic agent that can potentially treat catastrophic secondary injuries in the spinal cord, including inflammation, edema, free radical injury, fibrosis, and glial scar formation. It can enhance neurological function in rats, as measured using the BBB locomotor rating scale. Studies exploring ways to overcome its limited bioavailability have recently begun. More translational investigations on curcumin are necessary to facilitate its use in clinical settings.

NOTES

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ORCID

Subum Lee: 0000-0003-4732-8137
Dae-Chul Cho: 0000-0002-2899-8015
Inbo Han: 0000-0002-0834-9325
Kyoung-Tae Kim: 0000-0003-4867-6854

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