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

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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 necessitates 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 hepato-protective, nephro-protective, cardioprotective, neuro-protective, hypoglycemic, and anti-rheumatic activities, and its neuro-protective activity against several neurodegenerative disorders is gaining researchers’ attention. As an anti-inflammatory agent, curcumin suppresses the production of many pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-8, and monocyte chemoattractant protein 1. 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 pro-inflammatory cytokines, such as TNF-α and IL-1. It also suppresses glial scar formation and GFAP expression, contributing toward the development of a more favorable environment for neurological recovery (Fig. 2).

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. 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. The structure of the molecule is symmetrical. The 3 major components of curcumin molecules are the keto-enol tautomer in the

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**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.

**Fig. 2.** Pathophysiological process following spinal cord injury and the targeted therapeutic function of curcumin. ROS, reactive oxygen species.
middle, flexible αβ-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. The antioxidant activity of curcumin is dependent on the phenolic hydroxyl group. 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).

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, including the modification of the phosphorylation state of cellular proteins. 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. 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 signal 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. Given the fundamental nature of NF-κB signaling pathway activation to neuroinflammation and SCI pathophysiology, 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. Additionally, curcumin suppresses the production of transforming growth factor-beta (TGF-β1, TGF-β2, and sex-determining region Y-box transcription factor 9. It also facilitates the development of a microenvironment appropriate for nerve development. Curcumin suppresses the upregulation of aquaporin 4 and GFAP and the atypical activation of the Janus kinase–STAT signaling pathway associated with SCI. 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. 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., 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) | 40 mg/kg | Curcumin increased gray–white matter interface, tissue edema/AQP-4 expression, and GFAP/pJAK-STAT expression Moderately improved BBB scores |
| Wang et al., 2014| Female BALB/c mice/N = No description/10-g force clip for 3 sec, extradural on T9 level | Sham SCI/DMSO (n = 16) | Single IP injection | 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., 2015 | Wild-type C57BL/6J Narl mice/N = 18/Weight dropped | Sham control SCI (n = 6) | 40 mg/kg | 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., 2015| Female Sprague-Dawley rats/N = No description/Aneurysm clip (fixed force of 50 g) for 60 sec on T9 level | Sham SCI+Curcumin (n = 6) | 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., 2015  | Male Sprague-Dawley rats/N = 48/30-g force extradural compression with a clip for 30 sec on T8–9 level | Sham SCI+Curcumin (n = 16) | 100 mg/kg | 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., 2017| Female Sprague-Dawley rats/N = 280/50-g force clip compression for 60 sec on T9 level | Sham SCI+Curcumin (n = 70) | 100 mg/kg | 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., 2018 | Wistar rats/N = 135/Balloon-induced compression using Fogarty catheter on T8 level | Saline (n = 34) | 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)
| Study                  | Specimen/sample size/SCI method                                      | Study design (experimental groups) | Curcumin treatment method          | Summary of results                                                                                                      |
|-----------------------|---------------------------------------------------------------------|-----------------------------------|-----------------------------------|------------------------------------------------------------------------------------------------------------------------|
| Ruzicka et al. 2018   | Wistar rats/N = 131/Balloon-induced compression using Fogarty catheter for 5 min | Behavioral group study: Saline (n = 10) Saline (n = 20) Curcumin (n = 13) EGCG (n = 19) Curcumin+EGCG (n = 9) | 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 EGCG |
| Lee et al. 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/d 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. 2021    | Male Sprague-Dawley rats/N = 35/PTX-induced SCI                    | Control (n = 7) Curcumin (n = 7) PTX (n = 7) PTX+Curcumin 100 (n = 7) PTX+Curcumin 200 (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 |
is reported to be superior to vitamin E, resveratrol, and other commonly used antioxidants. Curcumin interacts with ROS directly and also acts as an activator of antioxidant signaling systems, making its effects more comprehensive and long lasting. 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.

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. It has the potential to enhance the activity of antioxidant enzymes, such as plasma catalase, erythrocyte superoxide dismutase (SOD), and plasma glutathione peroxidase. Furthermore, malondialdehyde (MDA), which is the end product of lipid peroxidation, is a reliable marker of oxidative stress-mediated lipid peroxidation. 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.

Additionally, curcumin could stimulate antioxidant protection genes via the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. 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. 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., 2017 | Male Wistar rats/ N = 40/ Spinal cord ischemia induced by clamping the aorta | Sham (n = 10) | 100 mg/kg, IP at 30 min before ischemia | Decreased MDA levels in the spinal cord |
| Xi et al., 2019 | Sprague-Dawley rats/ N = 24/A hammer was dropped on T8 level | Sham (n = 10) | Dissolved in 5 N NaOH | Increased SOD and GPs levels caused by curcumin |
| Daverey et al., 2020 | Male Wistar rats/ N = 18/30-mm spinal cord section/ Hypoxia | Sham (n = 10) | 80 mg/kg/day, IP | Oxidative stress and apoptosis (caspase-3 activity and B cell lymphoma 2-associated X protein levels) were suppressed |
| Daverey and Agrawal, 2020 | Human astrocytes | Human astrocytes: Riluzole (1 μM), Curcumin (1 μM) | Tetrahydrocurcumin for 2 weeks | Tetrahydrocurcumin inhibited oxidative stress response by regulating FOXO4 in SCI model rats. |
| Daverey and Agrawal, 2020 | Human astrocytes | Human astrocytes: Riluzole (1 μM), Curcumin (1 μM) | One hour incubation with 50 μM curcumin | Curcumin inhibited hypoxia-induced HIF1-α expression and tissue damage by improving the morphology of astrocytes and remarkably reducing vacuolation. |
| Daverey and Agrawal, 2020 | Male Wistar rats/ N = 21/30-mm spinal cord section/ Hypoxia | Sham (n = 10) | Rat SCI model (white matter injury) | 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. |
| Daverey and Agrawal, 2020 | Human astrocytes | Human astrocytes: Riluzole (1 μM), Curcumin (1 μM) | Curcumin (50 μM) | Curcumin exerted its neuroprotective effect through cross-talk between the NF-kB and Nrf2 signaling pathways. |
| Daverey and Agrawal, 2020 | Human astrocytes | Human astrocytes: Riluzole (1 μM), Curcumin (1 μM) | Curcumin (50 μM) | Curcumin's neuroprotective effect is mediated through the inhibition of HIF-1α, GFAP, NF-H, and caspase 9. |

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. 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. An improved therapeutic effect can be achieved by modifying stem cell proliferation and differentiation and reducing the inflammatory microenvironment in injured regions.

Curcumin enhances the functional recovery of SCIs when combined with NSC or mesenchymal stem cell (MSC) therapy. In a study by Ormond et al., 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. 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. 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. 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). 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). 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.

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. 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. Curcumin acts as a dose-dependent antioxidant to inhibit ROS as well as a pro-oxidant to produce ROS. Superoxide anion and hydrogen peroxide are the 2 types of ROS that may play an important role in carcinogenesis. At high doses, curcumin can react with the thiol groups of cysteine residues, causing DNA damage or p53 inactivation.

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., 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., 2017 | Ependymal stem/progenitor cells of the spinal cord (EpSPC) of Sprague-Dawley rats | 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., 2018 | Neural stem/progenitor cells derived from Sprague-Dawley rats N = 60/Clip with a closing force of 30 g & a 2-min compression | 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., 2020 | hUC-MSC/Female Sprague-Dawley rats/N = 180/50-g aneurysm clip compression on for 60 sec on T9 level | Sham (n = 20) SCI-Curcumin (n = 20) SCI-Veh (n = 20) | 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., 2021 | Induced pluripotent stem cells (iPSC-NSC) & Human MSC Female Sprague-Dawley rats/200 kdyne contusion on T8 level iPSC-NSC (n = 8) | Control (n = 16) MSC (n = 11) iPSC-NSC +MSC (n = 11) PA-C (n = 6) iPSC-NSC +MSC+PA-C (n = 7) | A pH-responsive polyclonal–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 motorneurons and myelinated tracts, whereas PA-C therapy polarized microglia into an anti-inflammatory phenotype. |
| Elkhenany et al., 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) | 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.
According to the study, conjugating curcumin was found effective in improving neurological functional recovery as evaluated by measuring the BBB score. The study design included 120-nm engineered extracellular vesicles derived from primary M2 macrophages, which were used to deliver curcumin to the site of SCI and inhibit inflammatory responses.

| Study | Specimen/sample size/SCI method | Study design (experimental groups) | Curcumin treatment method | Summary of results |
|-------|---------------------------------|-----------------------------------|--------------------------|--------------------|
| Kim et al., 2014 | Male Sprague-Dawley rats/N = 36/ clamping 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 et al., 2015 | Male Wistar rats/N = 60/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, MAP1a, IL4, IL1b, IL2, IL6, IL12p70, TNF-α, and RANTES were measured) |
| Liu et al., 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 (by anti-inflammatory action) MP-treated group better within the first 14 days Curr-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., 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-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; MP1a, 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.

LIMITATIONS
The lack of information on certain aspects of curcumin is a limitation. Further translational research is required to use curcumin in therapeutic settings. Ongoing investigations throughout the acute phase have allowed curcumin to act directly on the injured neuronal tissue to enhance neuroprotection and inhibition of inflammatory responses. Further studies elucidated by secondary injury.

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limitation of this paper. For example, we did not investigate the bioactivity of curcumin in astrocytes. It also lacks detailed information on several signaling pathways that are regulated by curcumin, including the Nrf2/heme oxygenase 1 pathway, the mammalian target of rapamycin, and TGF-β–SOX9 pathway. 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.

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