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REVIEW

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Protective effects of curcumin against spinal cord injury

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Abstract

Background: In parallel with population aging, the prevalence of neurological and neurodegenerative diseases has been dramatically increasing over the past few decades. Neurodegenerative diseases reduce the quality of life of patients and impose a high cost on the health system. These slowly progressive diseases can cause functional, perceptual, and behavioral deficits in patients. Therefore, neurodegenerative impairments have always been an interesting subject for scientists and clinicians. One of these diseases is spinal cord injury (SCI). SCI can lead to irreversible damage and is classified into two main subtypes: traumatic and non-traumatic, each with very different pathophysiological features.

Aims: This review aims to gather relevant information about the beneficial effects of curcumin (Cur), with specific emphasis on its anti-inflammatory properties towards spinal cord injury (SCI) patients.

Materials & Methods: The review collates data from extensive in-vitro, in-vivo, and clinical trials documenting the effects of CUR on SCI. It examines the modulation of pathophysiological pathways and regulation of the inflammatory cascades after CUR administration.

Results: Various pathophysiological processes involving the nuclear factor erythroid 2-related factor 2 (Nrf2), nuclear factor kappa B (NF-kB), and transforming growth factor beta (TGF-β) signaling pathways have been suggested to exacerbate damages resulting from SCI. CUR administration showed to modulate these signaling pathways which lead to attenuation of SCI complications.

Discussion: Anti-inflammatory compounds, particularly CUR, can modulate these pathophysiological pathways and regulate the inflammatory cascades. CUR, a well-known natural product with significant anti-inflammatory effects, has been extensively documented in experimental and clinical trials.

Conclusion: Curcumin's potential to alter key steps in the Nrf2, NF-kB, and TGF-β signaling pathways suggests that it may play a role in attenuating SCI complications.

KEYWORDS
curcumin, inflammation, neurodegenerative disease, spinal cord injury

1 | INTRODUCTION

Neurodegenerative diseases (ND) are characterized by slow progressive loss of neuronal cells in the central nervous system (CNS), which can affect different areas in the brain. Alzheimer's disease (AD), Parkinson's disease (PD), spinal cord injury (SCI), traumatic brain injury (TBI), stroke, and multiple sclerosis (MS) are the most common forms of neurodegenerative disorders. The accumulation and deposition of different intracellular and extracellular proteins is the main characteristic of neurodegenerative disorders. Oxidative stress (OS), inflammation, lack of sufficient antioxidant capacity due to dietary deficiencies, aging, and genetic factors represent the primary etiological factors involved in neurodegenerative impairments. Extrapyramidal, behavioral, and cognitive deficits are reported to be the most common symptoms of such diseases.[1]

SCI is one of the most common and important diseases neurodegenerative impairments. SCI is sub-classified into traumatic and non-traumatic SCI. Additionally, the pathophysiology of SCI is organized into two different categories termed primary and secondary. Primary cases lead to the initiation of the disease, while secondary pathophysiology of SCI leads to an increase in limitations, as well as mortality, in affected subjects. In SCI cases, the signs, symptoms, and clinical manifestations are different due to the nature of the injured area and the amount of uninjured tissue. Respiratory deficit, hypotension, bradycardia, paralysis, neuropathic pain, gastrointestinal complications, and immunodeficiency are the main clinical features of SCI. The therapeutic approaches used to treat SCI are diverse and based on the patient's complications, although regulation of hemodynamic parameters, use of prednisolone sodium succinate, anti-oxidants, painkillers, and surgical procedures are all common treatments for SCI.[2] Inflammatory responses associated with ND such as AD, PD, and SCI may cause substantial deterioration within the body organs and tissues. For instance, the PI3K/AKT pathway plays an essential role in cell survival and apoptosis. This pathway is directly associated with the survival of cells with noticeable anti-apoptotic function, although it has been proposed that the PI3K/AKT pathway involves in the process of cell proliferation.[3] Inflammatory signaling pathways are critical in SCI, including, but not limited to, signaling pathways such as Nrf2, mTOR, NF-κB, and TGF-β, which are intricately involved in SCI pathophysiology. There is evidence that a number of anti-inflammatory drugs improve the quality of life in SCI patients. For instance, naproxen (50 mg) or ibuprofen (60 mg) given daily for 4 weeks in SCI rat models attenuated inflammation and pain following acute SCI.[4] In addition, another investigation using a rat model of SCI revealed that administration of ketorolac (30 or 60 mg via intrathecal administration) 1 h before ischemic-induced SCI significantly decreased neuronal apoptosis and improved functional properties of the hindlimb.[5] In 2020, Samarghandian et al.[6] reported that the inhibition of the Nrf2 pathway could alleviate complications following SCI. In addition, Xu et al.[7] indicated that resveratrol, as an NF-κB signaling pathway inhibitor, reduced inflammation in the spinal cord and decreased neuronal cell death. Recent studies indicate a rising trend in use of natural herbal-based products as either monotherapy, or as adjunctive treatment with a conventional drug substance of non-plant origin. Higher accessibility and lower side effects contribute to frequent usage of herbal-based natural products.[8,9]

Curcumin (Cur) is a plant-derived natural product with an extensive scientific profile due to the large number of pre-clinical and clinical studies conducted to date.[10–21] Cur is a polyphenol derived from the rhizomes of *Curcuma longa* L., known as turmeric. Solid scientific evidence has confirmed the neuroprotective potential of Cur in some disorders such as ischemic stroke, AD, PD, SCI, and the ND that are induced by alcohol. Cur has shown significant anti-inflammatory activities by impacting on various signaling pathways,[22–25] and therefore, it might be an additional option for the management of SCI.[26] This study aimed to investigate the use of Cur for the treatment of SCI via its impact on signaling pathways involved in inflammation. We have included all literature that pertains to in vitro, in vivo, and clinical studies with Cur that advances either basic science, or elucidates its clinical effects, for the potential treatment of SCI.

2 | METHOD OF SEARCH

In vitro, in vivo, and clinical studies with Cur have been extracted from published literature (only articles in English) between 2004 and May 2024. The published articles were obtained from PubMed, Google Scholar, Scopus, and the Cochrane library. In addition, search terms included "SCI" OR "spinal cord injury" AND "curcumin" AND "neurodegenerative disease" OR "inflammatory signaling pathways" OR "inflammation" OR "inflammatory response."

3 | INFLAMMATORY AND OXIDATIVE PATHWAYS INVOLVED IN SCI

SCI is defined as a traumatic spinal nerve disorder that is a severe form of damage to the central nervous system, which causes the death of spinal nerve cells. Nerve cells are susceptible to various types of damage due to their limited ability to regenerate. Most SCI-induced spinal disorders, along with physiological, biochemical, and structural disorders, are destructive and irreversible. SCI is characterized by a primary lesion, which is followed by secondary damage.[27] The primary lesion is due to mechanical damage caused by axonal rupture, trauma, and death of nerve cells, which also includes bruising and damage to blood vessels. In contrast, secondary injury is an indirect result of the primary injury that begins with trauma and refers to oxidative stress, neural apoptosis, and glial scar formation in the vicinity of the injured

area. Primary damage directly causes tissue damage and leads to the irreversible loss of necrotic cells at the site of the lesion. Secondary damage is primarily caused by inflammatory reactions that alters cell function and cause nerve cell death. Primary and secondary damage includes free radicals, ischemic reperfusion injury, impaired axonal regeneration, and overall degradation of axonal function.[28,29]

While many mechanisms are associated with SCI, the exact cause and pathogenesis of this disease are not yet known. Many mechanisms, such as apoptotic cell death, axonal injury, ischemia, oxidative damage, and inflammation, lead to SCI. However, the most prominent of these factors is inflammation. As mentioned, many inflammatory mediators and several signaling pathways are involved in SCI. In addition, increased ROS and oxidative stress play key roles in the pathology of SCI. Given that, various inflammation and oxidative events such as the activation of microglia, alterations in the margin of neurons, and changes in synaptic regulation are major contributors of secondary damages observed in SCI.[30] Microglia are the primary innate immune cells of the CNS that are implicated in neuroinflammation. These specialized cells are rapidly activated in response to SCI. Overactivation of microglia induces the production of pro-inflammatory mediators such as IL-1β, TNF-α, and ROS, which exacerbate inflammation.[31] ROS mediates the mitogen-activated protein kinases (MAPKs) signaling pathway and induces an inflammatory response. The family of MAPKs is a group of signaling molecules that potently participate in the expression of pro-inflammatory cytokines. Hyperphosphorylation of MAPK activates the NF-κB transcription factors, and subsequently facilitates inflammatory reactions. Activation of macroglia provokes the SCI-induced neuroinflammation via the NF-κB pathway, which mediates neuroinflammation and the immune response.[32] It is worth mentioning that NF-κB is a sensitive transcription factor that plays a critical regulatory role in post-SCI inflammatory responses. Activation of this factor, which is involved in the development of SCI, enhances the expression of inflammatory factors such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and IL-1β (IL-1β), leading to increased cell death and inflammation.[33] Below we further discuss studies that have examined the mechanisms and signaling pathways involved with SCI and neuroinflammation.

A series of studies have shown that IL-1β mRNA and protein expression raise 12 h after SCI, which are primarily expressed by microglia and astrocytes. These changes have been observed in human neurons 30 min later and 5 h later in microglia. In addition, the enhanced expression of TNF-α mRNA at the protein level was observed in damaged spinal cord neurons approximately 1–3 h after the injury. Other chemokines, such as macrophage inflammatory protein-1a and b [MIP-1a and MIP-1b] and MIP-2, as well as monocyte chemotactic protein-1 [MCP-1], increased approximately 30 min to 6 h after the SCI.[34,35] It should also be noted that NF-κB can be activated by TLRs via two different pathways. These proteins are found in immune cells and are responsible for identifying the pathogen's sequence. These key safety mediators, which respond to microbial products, regulate the pathways that are implicated in NF-κB activation and the expression of genes that are involved in regulation of inflammatory cytokines.[36] The first pathway is dependent on myeloid differentiation primary response 88 (MyD88), and the second pathway is independent of MYD88 and stimulates the activation of interferon 1, as well as NF-κB. The MYD88-dependent pathway is associated with the formation of secondary injury in SCI via inflammatory reactions. NF-κB also contributes to inflammation and apoptosis after CNS damage.[37] Inhibition of NF-κB signaling prevents the expression of inflammatory cytokines and reduces the damage caused by inflammation. Of note, following a SCI, Nrf2 is upregulated and activates a series of antioxidants and cytoprotective genes such as HO-1 and nicotinamide adenine dinucleotide phosphate (NADPH), resulting in NF-κB suppression.[38] Nrf2 is known to play an important role in oxidative stress and inflammation. The activity of this factor is negatively regulated by Keap1. Under oxidative stress, Nrf2 cleaves from Keap1 and is transported to the nucleus, activating the transcription of cell-protective and antioxidant genes by binding to the antioxidant-responsive element (ARE). This binding induces endogenous enzymes such as heme oxygenase-1 (HO-1), superoxide dismutase (SOD), and NAD (P) H quinone oxidoreductase 1 (NQO1).[39] HO-1 is an important antioxidant that is regulated by NRF-2 and affects intracellular ROS levels. The degree of HO-1/Nrf2 induction assists in the overall prognosis following a SCI. As mentioned, it can improve the inflammatory response and the activation of NF-κB. Following acute SCI, the activation of NF-κB is cooperative, and in neurons, it can improve ischemia and reperfusion damage by increasing their antioxidant and anti-apoptotic abilities.[40,41] Moreover, the indoleamine-2,3-dioxygenase (IDO) subset of the kynurenine (KYN) (IDO/KYN) is a pathway with a crucial role in the pathogenesis of inflammatory disorders and cancers. Tryptophan is transformed into KYN by IDO influence. KYN is further impacted by three enzymes, kynureninase, kynurenine monooxygenase, and kynurenine aminotransferase, respectively, thereby producing anthranilic acid, 3-hydroxykynurenine, and kynurenic acid. 3-Hydroxykynurenine is further affected by kynurenine aminotransferase, leading to xanthurenic acid production and impacted by kynureninase resulting in generation of nicotinamide adenine dinucleotide (NAD).[42,43] Allison et al. assessed the levels of inflammatory cytokines, amino acids, IDO/-KYN-associated mediators, and cognitive function in patients suffering from SCI. It was indicated that inflammation was attenuated; however, no significant improvement was observed in cognitive functions.[44]

4 | CUR DELIVERY SYSTEMS FOR THE CNS

Cur shown beneficial effects in maintaining the integrity of the blood–brain barrier (BBB). Its neuroprotective effects are implicated in regulating the activity of mitochondria. Cur also is able to reduce microglial pro-inflammatory markers like TNF-α (which can induce neuroinflammation) and elevate anti-inflammatory cytokines such as IL-4.[45]

Cur has almost no reported side effects, but its poor absorption following oral administration and low water solubility are the primary challenges that limit its large-scale use as a therapeutic agent. Another obstacle to Cur delivery stems from the fact that the compound is extensively and rapidly metabolized. Additionally, Cur has a low BBB permeability. Due to its poor permeation of the BBB, many delivery

systems, such as nano delivery systems [i.e., poly lactic-co-glycolic acid (PLGA) nanoparticles, lipid-based nanoparticles, nanosuspensions, lipid-PLGA nanobubbles, nanoemulsions], ultrasound-targeted microbubbles, micelles, dendrimers, and exosomes have been designed and evaluated in an effort to improve its physicochemical properties, bioavailability, and pharmacokinetic parameters.[46] For instance, in a comparison between free Cur and Cur encapsulated in PLGA nanoparticles, it was found that the amount of Cur reaching the CNS was greater with PLGA nanoparticles.[47] Another strategy for increasing the delivery of Cur to the CNS includes nanosuspensions (NS). The NS formulation is primarily used for compounds having a low water solubility. NSs also can help target several anatomical sites in the body (e.g., the brain). In fact, it has been shown that Cur concentration increased in brain using a Tween-NS formulation.[48]

Recently, much attention has been paid to intranasal drug delivery systems. With intranasal delivery, there is no need to cross the BBB, because drugs will enter the CNS directly. As an example, a biodistribution study demonstrated that the brain concentration of Cur was greater for nanocrystals following intranasal administration than of a standard Cur suspension.[49] However, the combination of Cur and quercetin in the nanoemulsion improved the distribution of the natural compounds from the nasal cavity into the brain and resulted in greater cellular uptake, as well as enhanced chemical stability.[50,51]

Cur nanoparticles modified with g7 ligand (Cur-NPs-g7) have also been demonstrated to permeate the BBB and decrease oxidative stress, inflammation, and aggregation of amyloid-beta (Aβ). Cur-NPs-g7 also inhibited the decrease of Ikβ (NFkβ inhibitor family) that occurs concurrently with Aβ aggregation. Interestingly, another method to exploit the anti-inflammatory properties of Cur is by binding it to copper and zinc ions. When this is performed, it functions as an Aβ disaggregation activator.[52] Finally, the use of micro- and nanobubbles for the delivery of drugs to the CNS is gaining popularity. Specifically, the BBB is more permeable to Cur-loaded lipid-PLGA nanobubbles (Cur-NBs), together with low-intensity focused ultrasound (LIFU). In this way, the delivery of Cur into the deep-seated brain nuclei becomes more achievable. Of note, LIFU is considered a non-invasive drug delivery method that can protect both low-molecular-weight and macromolecular size drugs from chemical degradation and metabolism.[53]

5 | CUR CHEMICAL PROPERTIES

Cur, also known as diferuloylmethane, has an International Union of Pure and Applied Chemistry (IUPAC) name of (1E,6E)-1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. Cur is a phenolic compound with low water solubility, and its structure contains an active methylene group surrounded by diketofuncitonal groups and two phenyl rings with methoxy substituents. This molecule acts as a tautomer in biological liquids. In aqueous solutions, the major form in acidic pH is keto, while in basic aqueous solutions, enol form is dominant. Notably, it appears in an enolic form in an alcoholic background. The three main curcuminoids that are found in *Curcuma* species include Cur, demethoxy Cur, and bisdimethoxy Cur[54–57] (Figure 1).

As mentioned, Cur has low water solubility; the major part is exerted unmetabolized via feces. The minor part is metabolized and degraded rapidly in the intestinal tract.[58] Cur is transformed into more water-soluble metabolites through conjugation and reduction reactions. The liver and the intestine have been identified as the major sites of metabolism. The conjugation process is mediated by sulfotransferase or glucuroniosyl transferase enzymatic activities. Di-, tetra-, hexa-, and octa-hydro Cur are the major metabolites generated by the reductase processing. On the other hand, Cur sulfate and Cur glucuronide are the main derivatives produced via glucuronidase action. Moreover, reductase-dependent metabolites may undergo glucuronidation after the reduction process. As a result, dihydro Cur glucuronide and tetrahydro Cur glucuronide are produced.[59,60] Additionally, cleavage can happen to Cur, resulting in the generation of

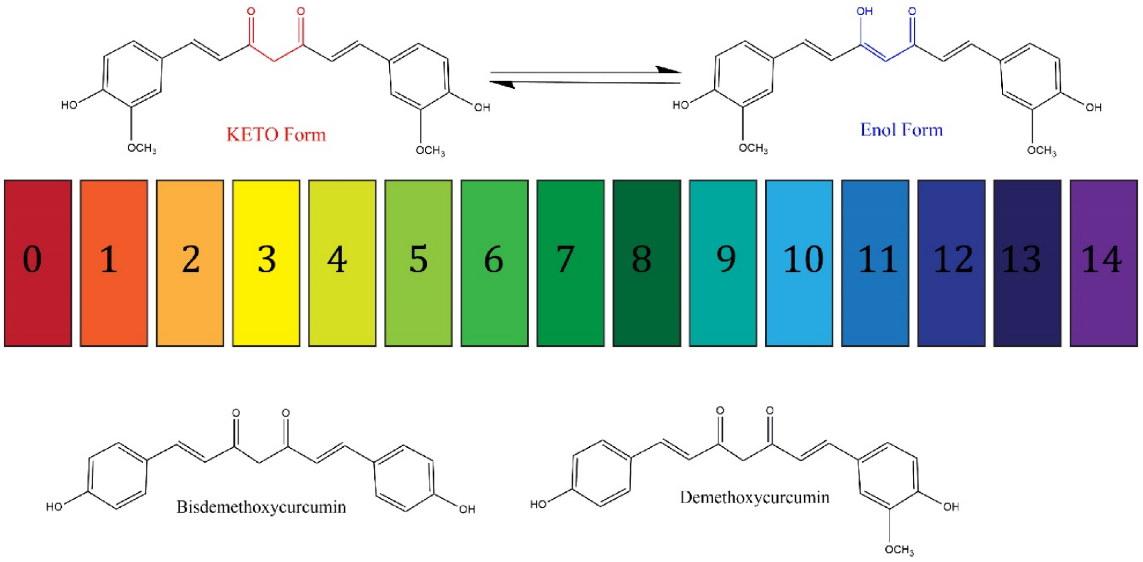

FIGURE 1 Curcumin tautomerism in biologic pH and curcuminoids.

ferulic acid, feruloyl methane, and vanilla. The last reaction is oxidation, leading to bicyclopentadione production[61] (Figure 2).

Regarding the bio-distribution of Cur derivatives in mice, it seems that Cur and tetrahydrocurcumin can reach the liver. Cur and dihydrocurcumin were also detected in the kidney. However, in the brain, Cur was the only detected compound.[62] The pharmacokinetic behavior of Cur is different when administered intraperitoneally. It required less time to reach peak levels. Moreover, faster and enhanced absorption was observed in comparison to oral dosage in rats.[63] Suresh et al. observed the pharmacokinetics of Cur, piperine, and capsaicin in rats. It appears that Cur is primarily excreted via feces and to a lesser extent in urine. Moreover, co-administration of Cur with adjuvants such as piperine positively impacted bioavailability-related factors. Cur reached maximum plasma concentrations at 6 h, which remained for about 24 h. The maximum peak in the intestine was observed in the first hour. Additionally, maximum brain levels were detected at 48 h post-administration.[64]

6 | CUR AND ITS PHARMACOLOGICAL APPLICATIONS IN SCI

6.1 | In vitro studies

Lou et al. have shown that a hybrid hydrogel of FC/FI-Cur (Fmoc-grafted chitosan/Fmoc peptide-curcumin) expedited dorsal root ganglia (DRG) neuron outgrowth. Schwann cell (SC) migration away from spheres of DRG was increased, providing a crucial association with

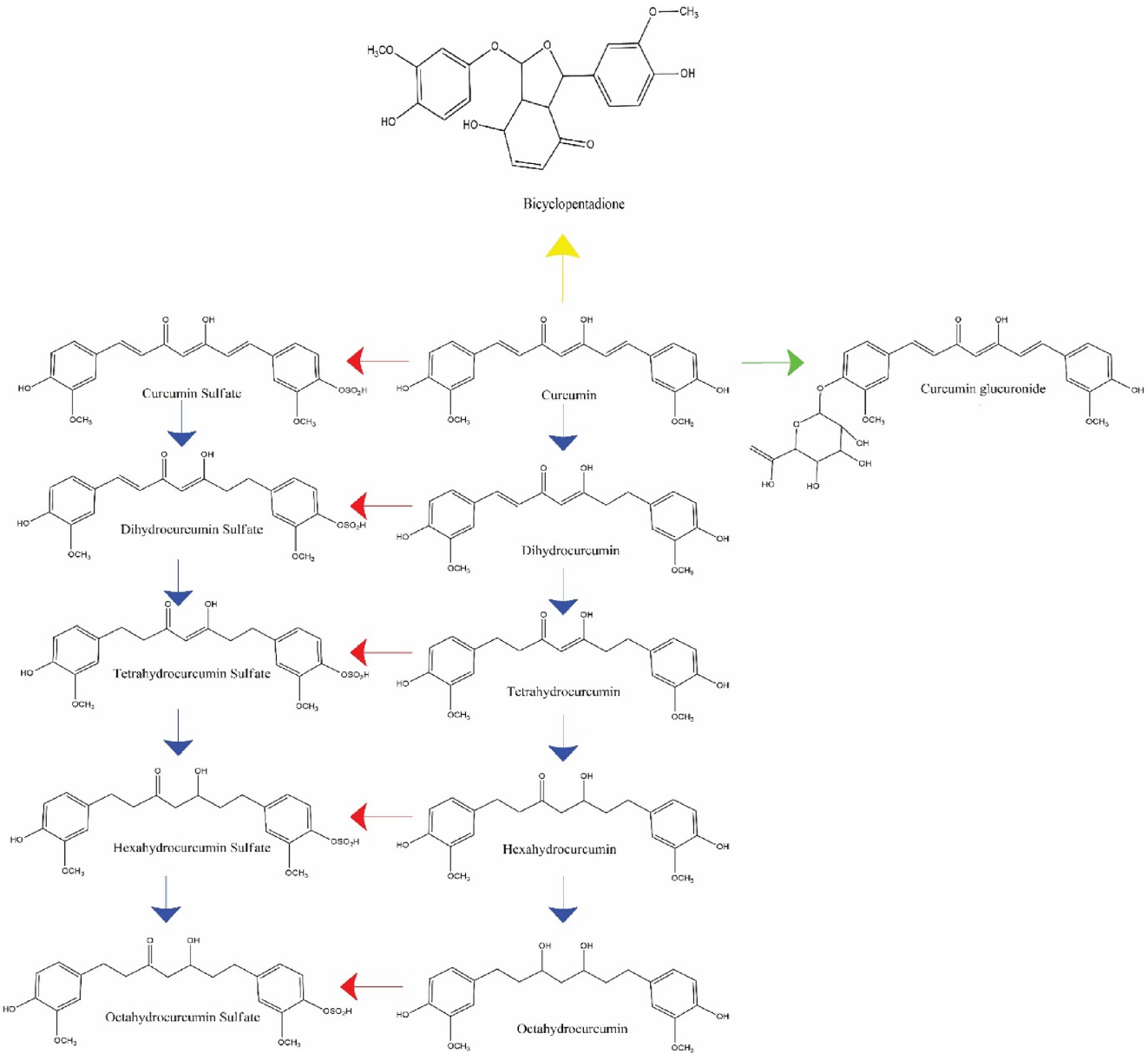

FIGURE 2 Cur metabolism in the liver. Yellow arrow, oxidase; blue arrow, reductase; green arrow, glucuronidase; and red arrow, sulfatase.

separated axons and the preparation of myelinated segments. It was suggested that the FC/FI-Cur hybrid hydrogel formulation might also be a desirable extracellular matrix for reconstruction at the lesion zone of the spinal cord. This would presumably inhibit a local inflammatory response by modulating the mRNA expression of ERK2 and AKT1 in infiltrated inflammatory cells.[65] Besides, Wanjiang et al. found that the ERK1/2, JNK, and P38 phosphorylation levels increased in apoptotic human umbilical cord-derived mesenchymal stem cells (hUC-MSCs). At the same time, Cur upregulated the ERK1/2 phosphorylation, while it could not activate P38 or JNK. As expected, the p42/44 antagonist U0126 reversed these effects. In addition, it was reported that the number of remaining human neutrophil antigen (HNA)-positive cells, as well as the score associated with motor function, were remarkably increased following transplantation therapy with hUC-MSCs and Cur 8 weeks after the SCI. These outcomes affirmed that Cur inhibited apoptosis of hUC-MSCs via the ERK1/2 signaling pathway. Combination of hUC-MSCs and Cur also ameliorated motor function deficits in rats post-SCI.[66] Gao et al. have explored the impact of Cur on the inflammatory response in lipopolysaccharide (LPS)-activated microglia. They found that Cur drastically inhibited LPS-induced inflammatory reactions through the NF-κB pathway in microglial cells, as reflected by a reduction in the content of phosphorylated-p65 (p-p65), as well as the pro-inflammatory mediators TNF-α, IL-1β, and inducible nitric oxide synthase (iNOS). In addition, Cur reduced IkappaB kinase β (IKKβ) expression and increased miR-199b-5p in activated microglial cells. IKKβ overexpression, or knockdown of miR-199b-5p, reversed the inhibitory effect of Cur on the inflammatory response and NF-κB. Overall, these authors concluded that Cur decreased neuroinflammation induced by LPS through regulating the miR-199b-5p/IKKß/NF-kappaB axis in microglia.[67] Lin et al. evaluated that whether the anti-inflammatory properties of Cur may effect on regulation of astrocyte reactivation, and specifically focused on injury-induced RANTES (regulated on activation normal T-cell expressed and secreted) from astrocytes in acute SCI in rats. To mimic the astrocyte reactivation following SCI, primary cultured rat astrocytes were challenged with LPS, which was shown to induce a robust increase of RANTES expression. This effect was decreased by the addition of Cur at a concentration of 1 μM. Furthermore, cortical neurons cultured with astrocyte conditioned medium (ACM) containing both LPS and Cur (LPS-Cur/ACM) showed a greater level of cell viability and a reduction in cell death. This is notable, because this would have normally resulted in a decrease in the expression of RANTES when compared with ACM from astrocytes treated with LPS alone (LPS/ACM). Moreover, knockdown of RANTES expression by siRNA (siRANTES) resulted in a decrease in the expression of RANTES and release from LPS-reactivated astrocytes. In fact, ACM obtained from this culture medium (LPS-siRANTES/ACM) was less cytotoxic when compared to LPS-ACM. Therefore, it was concluded that Cur reduces the production of RANTES in reactivated astrocytes both in vitro and in vivo, which might account for the neuroprotective activity of Cur in the treatment of SCI.[68] In another study, Cur decreased the loss of neurons and apoptosis, extinguished the astrocyte activation, and greatly improved the neurologic deficits 7 days after SCI in rats. Cur appeared to improve astrocyte reactivation, which is beneficial to neuronal survival by reducing the expression of glial fibrillary acidic protein (GFAP) (Tables 1 and 2).[69]

6.2 | In vivo studies

Bang et al. have investigated the effect of Cur on spinal cord neural stem/progenitor cell (SC-NSPCs) proliferation and function in a rat SCI model. Their findings suggested that Cur increased the expression of SC-NSPCs, and decreased the lesion cavity and the activity of reactive astrogliosis. Accordingly, Cur mediated functional recovery post-SCI due to the biological properties of SC-NSPCs.[70] In another investigation, administration of Cur and NF-κB p65 siRNA suppressed the astrocyte activation by inhibition of the NF-κB signaling pathway, which reduced the expression of RANTES, CXCL10, and MCP-1 released by astrocytes. Cur and NF-κB p65 siRNA reduced the

TABLE 1 Clinical interventions of curcumin on SCI.

Study design	Disease	Intervention		Number of patients		Treatment duration	Results	Adverse effects	Ref
		Case	Control	Case	Control				
Patients who referred to an outpatient Clinic of Rehabilitation in Ilam city, Iran in 2013–2015	SCI	Curcumin (110 mg/kg/day)	Placebo	$N = 50$	$N = 50$	6 month	(1) ↑ Femoral neck and hip BMD (2) No remarkable difference in lumbar spine BMD (3) ↓ BALP, sCTx, PINP and osteocalcin	-	102
Randomized, parallel-group, controlled clinical trial	SCI	Curcumin 400 mg (AOR Inflanox) PO three times a day	-	$N = 12$	$N = 8$	12 weeks	(1) ↓ Inflammation (2) ↓ IL-2, IL-6, IL-1β, TNF-α, and IFN-γ (3) ↓ Depression	-	103

Abbreviations: BALP, bone alkaline phosphatase; BMD, bone mineral density; PINP, procollagen Type I N-terminal propeptide; PO, oral administration; SCI, spinal cord injury; sCTx, carboxy-terminal telopeptide of Type I collagen; TNF-α, tumor necrosis factor alpha.

TABLE 2 In vivo interventions of curcumin on SCI.

Study design	Disease	Intervention		Number of animals		Treatment duration	Results	Adverse effects	Ref.
		Case	Control	Case	Control				
Male SD	SCI (based on Allen's weight-drop SCI trauma method)	Curcumin (i.m.)	DMSO (i.m.)	$n = 50$	$n = 50$	Within 30 min after injury	(1) ↓ Apoptosis in neurons (2) ↓ Tissue structure damage (3) ↑ Functional recovery (↑ BBB score) (4) ↓ TNF-α, IL-6, IL-1β (5) ↑ MBP (6) ↓ Spinal cord edema		72
Male SD (autophagy assessment)	SCI (based on Allen's weight-drop SCI trauma method)	Curcumin in DMSO (60 mg/mL/kg, i.m.) weekly	DMSO (1 mL/kg, i.m.) weekly	$n = 10$	$n = 10$	3 weeks	(1) ↑ LC3-II/LC-I ratio (2) ↓ p62 expression (3) ↓ Expression of Akt and mTOR		72
Female SD	SCI	FC/FI-Cur (10% (w/v))	Normal saline (injected into the lesion area)	$n = 18$	$n = 18$	2 weeks and 2 month	(1)↑ ARG1+ cells infiltrating and highest percent of ARG1+/CD68+ → regulation of inflammatory cell phenotypes (2) ↑ Infiltration of S100+ SCs (3) ↑ Remyelination		65
Male SD	SCI	Curcumin (100 mg/kg in PBS)	PBS	$n = 16$	$n = 16$	72 h	(1) ↑ Hindlimb locomotion function (↑ BBBT score) (2) ↓ Spinal cord edema (3) ↓ Apoptotic index (4) ↑ Nrf2 activity (5) ↓ NF-κB binding activity (6) ↓TNF-α, IL-1β, and IL-6		73
Female SD	SCI	hUC-MSC transplantation + Cur (100 mg/kg/daily, i.p.)	DMSO	$n = 30$	$n = 30$	14 days	(1) ↑ BBBT score and oblique plate score (2) ↑ MEP amplitude		66
Female KM mice	SCI	Cur (50/100/200 mg/kg/day, i.v.)	Untreated	$n = 20$	$n = 20$	28 days	(1) ↓ TNF-α, IL-1β, and IL-6 (2) ↓ NO levels (3) Inhibition of IKK–IκB–NF-κB inflammatory signals through the TAK1 pathway (4) Inhibition of MKK6 and p38 MAPK phosphorylation (5) Improvement of locomotive behavior (BMS scale)		74
Male WR	SCI	Nano-curcumin (0.1 mL/twice daily, s.q.)	Nano-carrier	$n = 21$	$n = 11$	4 weeks	(1) Improvement of locomotive function (↑ BBBT score) (2) Improvement of movements coordination and advanced locomotor skills (↑ Flat beam score) (3) Improvement of self-carrying ability and range of movements (↑ MotoRater)		76

(Continues)

TABLE 2 (Continued)

Study design	Disease	Intervention		Number of animals		Treatment duration	Results	Adverse effects	Ref.
		Case	Control	Case	Control				
							(4) Spare of white matter cranially to the center of lesion (5) Spare of gray matter cranially and caudally from center of lesion (6) ↓ Area of the glial scar (cranially and caudally from the center of the lesion) (7) ↓ Protoplasmatic astrocytes (8) ↑ Axonal regeneration (9) ↓ Mrc1 and Casp3 (10) ↑ (CCL5), IL-6, IL-10, IL-11, IL12, IL13, and IFN-γ		
Male SD	SCI	Curcumin (40 mg/kg once, i.p.)	DMSO (i.p.)	$n = 4$	$n = 4$	Within 30 min after injury	(1) ↓ RANTES & iNOS mRNA expression (2) ↓ Lipid peroxidation		68
Male WR	SCI	Curcumin (200 mg/kg, i.p.)	Rice bran oil (1 mL, i.p.)	$n = 8$	$n = 8$	Immediately after injury	(1) ↓ Activity of MDA (2) ↑ Activity of GSH-Px, SOD, and CAT (3) Prevention of hemorrhage, cellular edema and neurons degeneration (4) ↑ IP and BBBT score		77
Female SD	SCI	Curcumin (300, 100, and 30 mg/kg/day, i.p.)	DMSO (i.p.)	Not mentioned	Not mentioned	7 days	(1) Improvement axonal regeneration (2) Suppression formation of glial scar (3) Inhibition glial cell proliferation, shorten neurites and ↓ GFAP+ cells and GFAP expression (4) ↓ CSPG+ cells (5) ↓ Scar area and ↓ TNF-α, IL-1β, NF-κb, TGF-β1, TGF-β2, and SOX-9		78
Male SD	SCI	Curcumin (1 μM/day, i.t.)	Vehicle (10 μL ACSF, i.t.)	$n = 20$	$n = 20$	7 days	(1) Stimulation the expression of SC-NSPCs (2) ↓ GFAP area (3) ↓ Lesion cavity area (4) Neurogenesis in perilesional area (5) Improvement motor function (↑ BBBT score)		70
Female SD	SCI	Curcumin (100 mg/kg/day, i.p.)	Normal saline (i.p.)	$n = 70$	$n = 70$	Immediately after surgery then for 7 days	(1) Inhibition of glial scar formation and ↓ volume of cystic cavity (2) ↓ Number of GFAP+ and CSPG+ cells (3) ↓ Astrocyte activity and GFAP production (4) ↓ CD11b+/CD45 macrophages cell, CD3+CD4+ T-cell and CD3+CD8+ T-cells		71

TABLE 2 (Continued)

Study design	Disease	Intervention		Number of animals		Treatment duration	Results	Adverse effects	Ref.
		Case	Control	Case	Control				
							(5) Silence SOX9 expression → ↓ deposition of extracellular CSPG (6) ↓ α-SMA expression		
Male SD	SCI	Curcumin (100 mg/kg, i.p.)	PBS (i.p.)	$n = 16$	$n = 16$	15 min after injury	(1) ↓ Labile Zn accumulation (2) ↓ IL-1β, IL-6, and TNF-α (3) Improvement locomotion function (↑ BBBT score) (4) ↓ Water content (5) ↓ AI in the spinal cord tissue		79
Male SD	SCI	Curcumin (100 mg/kg, i.p.)	PBS (i.p.)	$n = 16$	$n = 16$	15 min after injury	(1) ↓ TLR4 mRNA and TLR4 protein expression (2) ↓ NF-κB DNA-binding activity (3) ↓ TNF-α, IL-1β, and IL-6 (4) Improvement locomotion function (↑ BBBT score) (5) ↓ Water content (6) ↓ AI		80
Female BALB/c mice	SCI	Curcumin (50 mg/kg/day, i.p.)	DMSO (50 mg/kg/ml/day, i.p.)	Not mentioned	Not mentioned	7 days	(1) Inhibition STAT3 and NF-κB activation (2) ↓ GFAP expression and nestin+ GFAP+ area → inhibition glial scar formation (3) ↓ Iba1+ → inhibition microglia/macrophage activation (4) ↓ IL-1β and NO production (5) ↑ Neurofilament immunoactivity (↑ NF-200+) (6) Improvement functional recovery (↑ BMS score)		81
Male SD	Ischemic SCI	Curcumin (30 mg/kg/day, i.p.)	Saline (i.p.)	$n = 10$	$n = 10$	7 days	(1) Improvement motor function (↑ Tarlov scale) (2) ↓ mRNA and protein expression of iNOS and N-methyl-D-aspartate receptor		82
Male SD	SCI	Curcumin (40 mg/kg/day, i.p.)	DMSO (40 mg/kg/day, i.p.)	$n = 17$	$n = 17$	7 days	(1) Improvement locomotor function (↑ BBBT score) (2) ↓ Apoptosis → neuroprotection (3) GFAP expression → revocation reactive astrogliosis → improvement repair of neuronal tissue		69
Female Wister albino rats	SCI	Curcumin + DMSO (300 mg/kg/once, i.p.)	Weight drop (50 g/cm)	$n = 8$	$n = 8$	Immediately after injury	(1) ↓ MDA levels (2) No remarkable difference in inclined plane values and neurological examination		83

(Continues)

TABLE 2 (Continued)

Study design	Disease	Intervention		Number of animals		Treatment duration	Results	Adverse effects	Ref.
		Case	Control	Case	Control				
							(3) No remarkable difference in large/medium-diameter myelinated axons (4) Pathologic changes in small-diameter myelinated axons (5) Protective effect on mitochondria		
Female SD	SCI-hyperglycemia	Curcumin (200 mg/kg/day, i.p.)	Not mentioned	$n = 32$	$n = 32$	56 days	(1) ↑ SOD activity and ↓ MDA levels (2) ↓ ED-1 macrophages (3) ↓ IL-6, IL-8, and TNF-α (4) ↓ p-EPK, p-JNK, and p-p38 levels (5) ↓ Astrogliosis through STAT3 signaling pathway (6) Improvement functional recovery (↑ BBBT score) (7) ↓ Lesion volume and ↑ spared tissue		84
Male New Zealand rabbits	SCI (ischemia–reperfusion)	Curcumin (200 mg/kg/once, i.p.)	Normal saline (once, i.p.)	$n = 6$	$n = 6$	Immediately after injury	(1) Improvement neurological function (↑ Tarlov scale) (2) ↓ Caspase-3 immunoreactivity → ↓ neuronal degeneration axonal damage and infiltration of glial cell (3) ↓ MDA, AOPP, and nitrite/nitrate levels (in both plasma and tissue) (4) ↑ SOD, GSH, and CAT levels (in both plasma and tissue)		85
Male New Zealand rabbits	SCI (ischemia–reperfusion)	Curcumin (50 mg/kg, i.v.)	Normal saline (i.v.)	$n = 12$	$n = 12$	10 min before	(1) Improvement neurological function (↑ Tarlov scale) (2) ↓ Neurons apoptosis (3) ↓ MDA and ↑ SOD		86
WR	SCI	Curcumin (60 mg/kg, once a week, i.t. and 6 mg/kg/day, i.p.)	Normal saline (50 μL)	$n = 27$	$n = 34$	4 weeks	(1) Preservation of white and gray matter (mostly white matter) in carnio-central region (2) ↓ GFAP+ area (3) ↓ Protoplasmic astrocytes cranially (4) No remarkable effect on axonal sprouting (5) ↑ Irf5 and CD163 expression (6) ↑ Nt3, Vegf, Bdnf, Gap43 and ↓ Casp3 (7) ↑ IL6, IL12p70, and ↓ RANTES (8) Improvement locomotor recovery (↑ BBBT score) (9) Improvement of forelimb–hindlimb coordination (Flat Beam test)		87

TABLE 2 (Continued)

Study design	Disease	Intervention		Number of animals		Treatment duration	Results	Adverse effects	Ref.
		Case	Control	Case	Control				
							(10) Improvement weight support, endurance and hindlimb coordination (rotarod test) (11) ↓ Hyperalgesia (Plantar Test)		
Male SD	Paclitaxel-induced SCI	(PTX + CUR): PTX (2 mg/kg/day, i.p.) for 5 days then CUR (100/200 mg/kg/day, p.o.) for 10 days	PTX (2 mg/kg/day, i.p.) for 5 days then corn oil (0.5 mL, p.o.) for 10 days	$n = 7$	$n = 7$	15 days	(1) ↑ Nrf2, HO-1, and NQO1 (2) ↓ NF-κB and GFAP (3) ↓ TNF-α, IL6, and iNOS (4) ↓ Caspase-3, p53, Apaf-1, and ↑Bcl-2 and Bcl-xL (5) ↓ mRNA expression of LC3A, LC3B, and Beclin-1 (6) Treatment with cur (200 mg/kg): mild neuronal necrosis, a few glial cells, MNL infiltration and ↓ atrophied neurons and demyelination		88
Female SD	SCI	Curcumin (60 mg/kg, first ep.i. and then s.q. weekly)	DMSO alone (1 mL/kg, first ep.i. and then s.q. weekly)	$n = 7$	$n = 7$	6 weeks	(1) Improvement (↑ BBBT score) (2) Improvement body weight gain (3) Higher soleus muscle weight (4) ↑ Spared gray and white matter → ↑ tissue sparing and ↓ gliosis		89
Male SD	SCI	Tetrahydrocurcumin (80 mg/kg/day, i.p.)	Normal saline (100 μL)	$n = 8$	$n = 8$	2 weeks	(1) ↑ BBB score and ↓ water content (2) Inhibition of p65 of NF-κB, TNF-α, IL-1β, and IL-6 (3) ↓ MDA levels, and ↑ activity of SOD, GSH, and GSH-PX (4) ↓ Caspase-3 activity and expression of Bax protein (5) ↓ Expression of MMP-3, MMP-13, and COX-2 (6) ↑ p-Akt and FOXO4 expression		90
Male WR	SCI	Curcumin (6 mg/kg/day, i.p. and 60 mg/kg/weekly in situ)	Olive oil	$n = 30$	$n = 30$	28 days	(1) Improvement locomotor recovery (↑ BBBT score) (2) No remarkable difference in hyperalgesia (Plantar Test) (3) Improvement in balance on a rotating pole (Rotarod Test) (4) Improvement of forelimb–hindlimb coordination (Flat Beam Test) (5) ↑ White and gray matter sparing → ↓ cavitation volume (6) ↓ GFAP+ area and protoplasmic astrocytes		91

(Continues)

TABLE 2 (Continued)

Study design	Disease	Intervention		Number of animals		Treatment duration	Results	Adverse effects	Ref.
		Case	Control	Case	Control				
							(7) No remarkable difference in axonal sprouting (8) ↓ IL-2, TNF-α, RANTES, and MIP-1 (9) ↑ IL-6, IL-12 p70, and IL-4 (10) ↑ mRNA expression of Irf5 and Gap43 (11) ↓ mRNA expression of Gfap, NF-κB		
Male SD	SCI	Curcumin (200 mg/kg/day, i.p.)	Vehicle (i.p.)	$n = 12$	$n = 12$	7 days	(1) Improvement motor function (↑ BBBT score) (2) ↑ Spare tissue (↓ cavitation volume) (3) ↓ Immunoreactivity of the ED-1 macrophage (4) ↑ SOD activity and ↓ MDA activity		92
Male SD	SCI	Curcumin (110 mg/kg/day, i.g.)	Untreated	$n = 30$–32	$n = 30$–32	2 weeks	(1) No remarkable effect on body mass (2) ↑ Osteocalcin and OPG (3) ↓ CTX and urinary DPD (4) ↑ BMC and BMD of femur and tibial (5) ↑ Tibial BV/TV, Tb.Th, Tb.N, MAR, BFR/BS, and Ob.S/BS (6) ↓ Tibial Tb. Sp, ES/BS, and Oc.S/BS (7) Improvement of femoral diaphysis stiffness, ultimate load and energy to max force (8) ↑ Femur collagen I content and ALP activity (9) ↓ mRNA levels of RANKL, TRAP and ratio of RANKL-to-OPG in distal femurs (10) ↓ TBARS in distal femurs (11) No effect on serum levels of 25(OH)D and ↑ VDR (12) ↑ mRNA levels of Wnt3a, Lrp5, and ctnnb1 (13) ↑ β-Catenin expression		93
Male SD	SCI	Curcumin (200 mg/kg/day, i.p.)	Untreated	$n = 27$	$n = 6$	56 days	(1) Improvement motor functions (↑ BBB score) (2) Repair of injured area in tissue structure (3) ↓ Bax + cells and ↑ its intensity (4) ↑ Bcl-2 expression (5) ↓ Caspase3 + cells and GFAP+ cells (6) ↓ Pathological changes (7) Formation and growing of new myelin sheaths		75

TABLE 2 (Continued)

Study design	Disease	Intervention		Number of animals		Treatment duration	Results	Adverse effects	Ref.
		Case	Control	Case	Control				
Male SD	SCI	Curcumin (60 mg/mL/kg, i.m., sc)	DMSO	$n = 50$	$n = 50$	28 days	(1) ↓ Apoptosis (2) ↑ Remyelination (3) ↓ TNF-α, IL-6, and IL-1β (4) ↓ Caspase 3 (5) ↓ p62, Akt, and mTOR		72
Female SD	SCI	Curcumin (1 μM) with olfactory ensheathing cells	Saline	$n = 30$	$n = 30$	28 days	(1) ↑ TG2 and PSR (2) ↑ BBB score (3)↓ iNOS (4) ↑ Arg-1 (5) ↑ M2 Polarization (6) Regulating APOE/TREM2/NF-κB		95
Female SD	SCI	Curcumin 100 mg/kg, i.p. with human umbilical cord-derived mesenchymal stem cell	Vehicle	$n = 30$	$n = 30$	14 days	(1) ↓ TNF-α → apoptosis (2) Regulation ERK 1/2 (3) Improvement in hindlimb function (4) No significant change in BBB score, however BBB score was ↑		97
Female SD	SCI	Curcumin 5 μM	-	$n = 3$	$n = 3$	5 days	(1) ↑ Outgrowth of Nestin-positive neurites (2) ↑ cell viability and enhance neuronal morphology (3) ↑ $\beta 3\text{-tubulin}^{+}$ neurons (4) ↓ Overexpression of platelet-derived growth factor		98
Female SD	SCI	Curcumin 0.2 mg (micelle nano particle)	-	-	-	7–28 days	(1) ↑ Arg-1, CCR-7 → ↑ M2 polarization (2) ↓ Scar formation (3) ↑ Tuj-1 positive cells → ↑ neuronal survival (4) ↑ BBB score (5) ↑ Il-4. Il-10 → ↑ anti-inflammation		99
Female SD	SCI	Implanted curcumin hydrogel	-	$n = 18$	$n = 18$	-	(1) ↑ Neurite outgrowth (2) ↑ Neuronal degeneration (3) ↑ Schwann cell migration → ↑ neuronal remyelination		65
SD Rats	SCI	Curcumin with olfactory ensheathing cells	-	$n = 5$	$n = 4$	1–28 days	(1) ↑ IL-4 → ↓ TNF-α, iNOS, IL-1β, and IL-6 → ↓ inflammation (2) ↑ IL-4 → ↑ Arg-1, TGF-β, IL-10, and CD206 (3) ↑ IL-4 → ↑ M2 polarization (4) ↑ Neurological functions (5) ↑ Tuj-1 positive cells (6) JAK/STAT and NF-κB/SOCS Regulation		100

(Continues)

TABLE 2 (Continued)

Study design	Disease	Intervention		Number of animals		Treatment duration	Results	Adverse effects	Ref.
		Case	Control	Case	Control				
Adult Rats	SCI	Curcumin with human-induced neural and mesenchymal stem cell	-	$n = 3$	-	1–9 weeks	(1) ↓ Inflammation (2) ↑ M2 polarization (3) ↑ β3-tubulin^{+} neurons (4) ↓ Scar volume		101

Abbreviations: ACM, astrocyte-conditioned medium; ACSF, artificial cerebrospinal fluid/GFAP (astrocyte marker); AI, apoptotic index; ALP, assay of alkaline phosphatase; AOPP, advanced oxidation protein products; ARG1, specific marker for the anti-inflammatory phenotype; BALP, bone alkaline phosphatase; BBBT, Basso, Beattie, and Bresnahan test; BFR, bone formation rate; BMC, bone mineral content; BMD, bone mineral density; BMS, Basso mouse scale; BS, bone surface; BV, bone volume; CAT, catalase; CCL5, RANTES; CD68, general marker; COX, cyclooxygenase; CSPG, chondroitin sulfate proteoglycan; CSPG, chondroitin sulfate proteoglycan; CTX, collagen type I cross-linked C-telopeptide; Cur, curcumin; DMSO, dimethyl sulfoxide; DPD, deoxypyridinoline; DRG, dorsal root ganglia; ED-1, anti-CD68 antibody; ep.i., epidural injection; ERK, extracellular-regulated protein kinases; ES, eroded surface; FC, fluorenyl functionalized chitosan; FI, peptide Fmoc-RRIKVAVIKVAV (Ile-Lys-Val-Ala-Val); FOX, forkhead box; GFAP, glial fibrillary acidic protein; GSH, glutathione; GSH-Px, glutathione peroxidase; HO-1, heme oxygenase-1; HUC-MSC, human umbilical cord-derived mesenchymal stem cell; i.g., oral gavage; i.p., intraperitoneally; i.t., intrathecal injection; i.v., intravenous injection; IKK, IκB kinase; IKKβ, IkB kinase β; IL, interleukin; iNOS, inducible nitric oxide synthase; IP, inclined plane; JAK2, activation of Janus kinase 2; JNK, C-Jun N-terminal kinase; LC3, autophagy protein; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MAR, mineral apposition rate; MBP, myelin basic protein; MDA, malondialdehyde; MEP, motor-evoked potentials; MMP; matrix metalloproteinase; MNL, mononuclear leukocytes; MP, methylprednisolone; NF-κB, nuclear factor kappa B; NQO1, quinone oxidoreductase 1; Nrf2, nuclear factor erythroid 2-related factor 2; Ob.S, osteoblast surface; Oc.S, osteoclast surface; OPG, osteoprotegerin; PBS, phosphate buffer saline; PINP, procollagen Type I N-terminal propeptide; PO, oral administration; p-p65, phosphorylated-p65; PTX, paclitaxel; RANKL, receptor activator of nuclear factor kappa B ligand; SCI, spinal cord injury; s.q., subcutaneously; SC-NSPCs, spinal cord neural stem/progenitor cells; SCs, Schwann cells; sCTx, carboxy-terminal telopeptide of Type I collagen; SD, Sprague–Dawley; SOD, superoxide dismutase; SOX, sex determining region Y-box; Sp, separation; STAT3, signal transducer and activator of transcription 3; TAK1, transforming growth factor (TGF)-activated kinase 1; Tb, trabecular; Tb.N, trabecular number; TBARS, thiobarbituric acid reactive substances; TGF, transforming growth factor; Th, thickness; TNF, tumor necrosis factor; TRAP, tartrate-resistant acid phosphatase; TV, total volume; VDR, vitamin D receptor; WR, Wistar rat; α-SMA, alpha-smooth muscle actin.

TABLE 3 In vitro interventions of curcumin on SCI.

Study design	Disease	Intervention		Number of cells		Treatment duration	Results	Adverse effects	Ref.
		Case	Control	Case	Control				
DRG cells	SCI	FC/FI-Cur	FC/FI hydrogels	Not mentioned	Not mentioned	7 and 30 days	(1) Accelerate the outgrowth of neurite (2) ↑ SC migration away from DRG spheres → producing myelinated segments (3) ↑ Interactions between SCs and neurites (4) ↑ MBP mRNA expression (5) ↑ mRNA expressions of ERK2 and AKT1 (6) ↑ Survival of neurons and SCs		65
hUC-MSC	TNF-α induced apoptosis and SCI	Curcumin (4 μM)		2000 cells	2000 cells	24 h	(1) ↑ p-p42/44 expressions (2) ↑ p-Bad in ERK1/2 signaling pathway → ↓ apoptosis (in vitro and injured region after SCI) (3) No difference in p38/MAPK or JNK/MAPK		66
BV2 microglial cells	SCI	Curcumin (2, 4, and 8 μM)	Untreated	Not mentioned	Not mentioned	Not mentioned	(1) Inactivation of NF-κB → ↓ iNOS, TNF-α, IL-1β, and p-p65 (2) Downregulation of miR-199b-5p and upregulation of IKKβ (3) Regulating miR-199b5p/IKKβ/NF-κB pathway → ↓ inflammation		67
Astrocyte	LPS induced astroglial reactivation	Curcumin (1 μM)	LPS (1 μg/mL)	2×10^6 cells	2×10^6 cells	24 h	(1) ↓ iNOS mRNA and RANTES expression (with no effect on GFAP expression) (2) ↓ LDH and ↓ neurotoxicity of ACM		68
SC-NSPCs	SCI	Curcumin (0.1–30 μM)	Not mentioned	2×10^4 cells	2×10^5 cells	3 days	(1) ↑ Proliferation in 0.1–1 μM of curcumin		70
Astrocyte	SCI	Curcumin (1 μM)	Serum-free medium	3000 cells	3000 cells	24 h	(1) Inhibition NF-κb signaling pathway → MCP-1, RANTES, and CXCL10 (2) ↓ p-IKK-α, p-IKK-β, p-IκB-α, and NF-κb mRNA (3) Inhibition of TGF-β-induced SOX9 activity → inhibition CSPG secretion (4) ↓ SOX9 expression → ↓ α-SMA → ↓ fibrosis		71
Astrocyte	SCI	Curcumin (1 μM)	Untreated	10^6 cells	10^6 cells	24 h	(1) ↓ GFAP expression → inhibition astrocyte reactivation → neuronal survival (2) Morphological change: cells get smaller and longer		69

Abbreviations: ACM, astrocyte-conditioned medium; ACSF, artificial cerebrospinal fluid/GFAP (astrocyte marker); AI, apoptotic index; ALP, assay of alkaline phosphatase; AOPP, advanced oxidation protein products; ARG1, specific marker for the anti-inflammatory phenotype; BALP, bone alkaline phosphatase; BBBT, Basso, Beattie, and Bresnahan test; BFR, bone formation rate; BMC, bone mineral content; BMD, bone mineral density; BMS, Basso mouse scale; BS, bone surface; BV, bone volume; CAT, catalase; CCL5, RANTES; CD68, general marker; COX, cyclooxygenase; CSPG, chondroitin sulfate proteoglycan; CSPG, chondroitin sulfate proteoglycan; CTX, collagen type I cross-linked C-telopeptide; Cur, curcumin; DMSO, dimethyl sulfoxide; DPD, deoxypyridinoline; DRG, dorsal root ganglia; ED-1, anti-CD68 antibody; ep.i., epidural injection; ERK, extracellular-regulated protein kinases; ES, eroded surface; FC, fluorenyl functionalized chitosan; FI, peptide Fmoc-RRIKVAVIKVAV (Ile-Lys-Val-Ala-Val); FOX, forkhead box; GFAP, glial fibrillary acidic protein; GSH, glutathione; GSH-Px, glutathione peroxidase; HO-1, heme oxygenase-1; HUC-MSC, human umbilical cord-derived mesenchymal stem cell; i.g., oral gavage; i.p., intraperitoneally; i.t., intrathecal injection; i.v., intravenous injection; IKK, IκB kinase; IKKβ, IkB kinase β; IL, interleukin; iNOS, inducible nitric oxide synthase; IP, inclined plane; JAK2, activation of Janus kinase 2; JNK, C-Jun N-terminal kinase; LC3, autophagy protein; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MAR, mineral apposition rate; MBP, myelin basic protein; MDA, malondialdehyde; MEP, motor-evoked potentials; MMP; matrix metalloproteinase; MNL, mononuclear leukocytes; MP, methylprednisolone; NF-κB, nuclear factor kappa B; NQO1, quinone oxidoreductase 1; Nrf2, nuclear factor erythroid 2-related factor 2; Ob.S, osteoblast surface; Oc.S, osteoclast surface; OPG, osteoprotegerin; PBS, phosphate buffer saline; PINP, procollagen Type I N-terminal propeptide; PO, oral administration; p-p65, phosphorylated-p65; PTX, paclitaxel; RANKL, receptor activator of nuclear factor kappa B ligand; SCI, spinal cord injury; s.q., subcutaneously; SC-NSPCs, spinal cord neural stem/progenitor cells; SCs, Schwann cells; sCTx, carboxy-terminal telopeptide of Type I collagen; SD, Sprague–Dawley; SOD, superoxide dismutase; SOX, sex determining region Y-box; Sp, separation; STAT3, signal transducer and activator of transcription 3; TAK1, transforming growth factor (TGF)-activated kinase 1; Tb, trabecular; Tb.N, trabecular number; TBARS, thiobarbituric acid reactive substances; TGF, transforming growth factor; Th, thickness; TNF, tumor necrosis factor; TRAP, tartrate-resistant acid phosphatase; TV, total volume; VDR, vitamin D receptor; WR, Wistar rat; α-SMA, alpha-smooth muscle actin.

infiltration of macrophages and T-cells, which subsequently decreased inflammation in the glial scar. These authors extended their work to examine the silencing of SRY-Box Transcription Factor 9 (SOX-9). First, it is important to note that silencing of SOX-9 may reduce the deposition of chondroitin sulfate proteoglycans (CSPGs) in the extracellular matrix; whereas, its over-expression can increase the expression of CSPGs. Cur suppressed SOX-9-induced CSPG deposition, reduced α-SMA (an important biomarker of fibrosis) expression in astrocytes, altered the phenotype of astrocytes, and inhibited glial scar formation by regulating fibrosis. This study confirmed that Cur modulated both the NF-κB and SOX-9 signaling pathways and mitigated the expression of intra- and extra-cellular components of glial scar via the regulation of targets involved in both inflammation and fibrosis in SCI animal model. More importantly, this study provided a new potential treatment strategy for SCI; namely, the simultaneous inhibition of both intracellular and extracellular glial scar components (Table 3).[71]

Given the inflammation secondary to SCI, Li et al. has shown that treatment with Cur decreased apoptosis of neurons and stimulated functional recovery post-SCI, improved the integrity, re-myelination, and recovery of the spinal cord, and inhibited the overall inflammatory reaction. Cur also inhibited the Akt/mTOR signaling pathway and enhanced autophagy. Moreover, Cur significantly reduced the overproduction of astrocytes and microglia by decreasing the expression of ionized calcium-binding adaptor molecule 1 (Iba1) and GFAP in SCI rats. Cur was demonstrated to significantly reduce levels of TNF-α, IL-6, and IL-1β.[72] Others have confirmed the anti-inflammatory effects of Cur via NF-κB in the context of SCI. For example, Cur significantly reduced NF-κB activation and the production of inflammatory cytokines in injured spinal cord. Treatment with Cur also markedly improved secondary SCI, as determined by a reduction in the severity of locomotion deficits, edema of the spinal cord, and apoptosis in a rat model of SCI.[73] Zhang et al. reported that Cur significantly suppressed TNF-α, IL-1β, IL-6, and NO levels in a mouse model of SCI. The compound downregulated the phosphorylation levels of TGF-β-activated kinase 1 (TAK1) protein, leading to a reduction in both the level of MKK6 and p38 MAPKs phosphorylation, which are vital factors in the microglia-mediated inflammatory response. Moreover, Cur treatment reduced the NF-κB expression upstream regulator IKKβ, and significantly improved functional recovery in a mouse model of SCI (Figure 3).[74]

Other studies have compared the anti-inflammatory effectiveness of Cur with drugs known to decrease inflammation (e.g., methylprednisolone (MP)). For instance, the efficacy of Cur was compared with MP, and Cur was found to be more effective than MP after 14 days of treatment following SCI in a rat model. In fact, Cur provided greater anti-inflammatory effects than MP, even when MP was used for a longer treatment time. This was thought to be due to the potent reduction of GFAP and CSPG, as well as an elevation in the expression of Bcl-2.[75] In a rat model of SCI, local administration of nano-Cur immediately after SCI, and followed by intraperitoneal administration of nano-Cur for four consecutive weeks resulted in: (1) preservation of white matter tissue; (2) a significant decrease in the glial scar area; and (3) a greater amount of newly-sprouted axons.[76]

Cur enhanced antioxidant activity in the treatment of neurologic conditions, which was validated based on a reduction of tissue levels of MDA and increased levels of plasma glutathione peroxidase (GSH-Px), catalase (CAT), and superoxide dismutase (SOD), and by the preservation of the structure of various tissues in SCI animal model.[77]

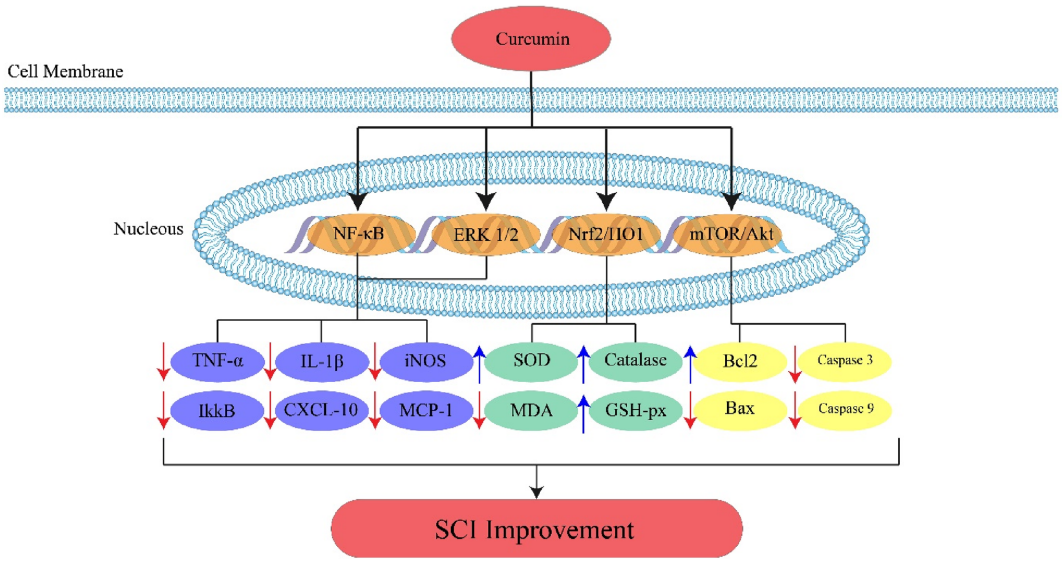

FIGURE 3 The signaling pathways that curcumin affect in SCI pathophysiology. Akt, protein kinase B; Bax, BCL2 associated X; BCL2, B-cell lymphoma 2; CXCL, C–X–C motif chemokine ligand; ERK, extracellular signal-regulated kinase; GSH-px, glutathione peroxidase; HO-1, heme oxygenase 1; IL, interleukin; iNOS, inducible nitric oxide synthatase; IkkB, IκB kinase; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; mTOR, mammalian target of rapamycin; NF-B, nuclear factor kappa b; Nrf2, nuclear factor erythroid 2-related factor 2; SOD, superoxide dimutase; TNF, tumor necrosis factor alpha.

Administration of Cur reduced the expression of intracellular GFAP through anti-inflammatory responses and inhibited the expression of TNF-α, IL-1β, and NF-κB, as well as reactive gliosis. In addition, Cur has been proven to suppress the generation of SOX-9, TGF-β1, and TGF-β2, as well as the deposition of CSPGs by inhibiting both transcription and transforming growth factors. to the compound drastically reduced glial scar volume, improved locomotor function, and increased axon growth in a rat model of SCI.[78] Ni et al. have shown that Cur downregulated the levels of inflammatory cytokines in a rat model of SCI and ameliorated hindlimb locomotion deficits, spinal cord edema, and apoptosis.[79] Overall, these studies strongly suggest that Cur has potential therapeutic effects for treatment of SCI; at least in animal models of SCI.

In another study, Cur reduced the expression levels of NF-KB, TLR4, and inflammatory cytokines related to the TLR4/NF-κB inflammatory signaling pathway. This study also showed that Cur markedly improved SCI-hind limb locomotion deficits, spinal cord edema, and apoptosis in a rat model.[80] In a mouse model of SCI, Cur treatment significantly suppressed the activation of STAT3 and NF-κB, reduced astrogliosis, decreased the expression of IL-1β and NO, together with the number of Iba1 inflammatory cells at the lesion site. Another investigation demonstrated that Cur protected residual axons and neurons and markedly improved functional recovery in a mouse model of SCI.[81]

Rat model of spinal cord ischemia, provided further knowledge on the therapeutic effects of Cur on SCI. In this model, Cur significantly improved hindlimb motor function post-injury by reducing iNOS and N-methyl-D-aspartate receptor expression.[82] In another SCI animal model, Cur reduced lipid peroxidation (LPO) within 24 h, although there was no difference in the neurological scores of injured rats when Cur-treated rats were compared to rats in the control group. However, at a minimum, Cur provided a beneficial effect by decreasing the levels of LPO and tissue damage.[83] Using a hyperglycemic rat model, Lee et al. evaluated the effects of Cur on histological alterations and functional recovery following SCI. There was an increase in activity of SOD, MDA, while ED-1 macrophage marker levels decreased. The Cur-treated group exhibited a significant decrease in levels of phosphorylated-JNK, p-p38, phosphorylated-extracellular signal-regulated kinase, IL-6, IL-8, and TNF-α when compared to rats in the control group post-SCI. Cur also reduced the expression of GFAP and lesion volume, while improving functional recovery, and resulted in a greater volume of 'spared' tissue.[84]

In rabbit model of SCI, Cur treatment significantly prevented an ischemia–reperfusion-induced increase in TNF-α and nitrite/nitrate. Additionally, this study showed that Cur maintained spinal cord tissue and GSH, CAT, and SOD levels in plasma; however, the difference was insignificant. Additional histopathological evaluation demonstrated reduced axon damage, degradation of neurons, and glial cell infiltration.[85] In the same model, Cur considerably improved neurological function, decreased MDA levels, cell apoptosis, and elevated SOD activity. Due to the fact that Cur was able to mitigate transient SCI by decreasing oxidative damage, these authors suggested that Cur should be considered as a novel therapeutic approach/intervention in treating ischemic conditions resulting from SCI.[86] Ruzicka et al. have evaluated the consequence of combination therapy of MSC and Cur on behavioral recovery and sparing of tissue, formation of a glial scar, sprouting of axons, and inflammatory reactions in a rat model of SCI. This study was designed in four groups; two groups were treated with Cur on the surface of the spinal cord immediately after induction of the SCI, and then once a week for 3 weeks. In addition to application of Cur to the surface of the spinal cord weekly, these rats also received a daily intraperitoneal injection of Cur for 28 days. The other two groups received normal saline. Seven days following the SCI, human MSCs were implanted intrathecally in one Cur and one saline group. It was found that the locomotor function significantly improved to a greater extent with both Cur and Cur + MSCs treatments when compared to the rats that only received saline. Although it should be noted that the combined treatment showed additional improvement with advanced locomotor performance. Notably, combination therapy resulted in axonal sprouting, as well as modulation of the expression of pro-regenerative factors and inflammatory responses when these same parameters were measured in rats that received either saline or single treatments. These results demonstrated that pretreatment with Cur, prior to the implantation of MSCs, exerted a synergistic therapeutic effect on experimental SCI.[87] In paclitaxel (PTX)-induced SCI, oral administration of Cur (100 and 200 mg/kg, daily in corn oil) for 10 days reduced the mRNA expression levels of NF-κB, TNF-α, IL-6, iNOS, and GFAP, whereas increasing of Nrf2, HO-1, and NQO1 levels. Furthermore, Cur inhibited the activation of apoptosis and autophagic pathways by increasing Bcl-2 and Bcl-xL, while reducing p53, caspase-3, Apaf-1, LC3A, LC3B, and beclin-1 mRNA expression levels.[88]

Additional studies in rats with experimentally-induced SCI have attempted to elucidate all mediators of inflammation and to determine precise locations in relevant signaling pathways where Cur is exerting its effects. Ormond et al. used female Sprague–Dawley rats that underwent a T9-10 laminectomy and spinal cord contusion using a classic weight-drop technique. Thirty minutes following the contusion, and weekly thereafter, percutaneous epidural injection of Cur (60 mg/kg/mL body weight in dimethyl sulfoxide), or dimethyl sulfoxide (1 mL/kg body weight), was performed at the site of injury. The recovery from the SCI was monitored weekly and utilized a scoring method to assess hindlimb motor function. Histopathological analysis of spinal cords and measurement of soleus muscle weight was determined 6 weeks postcontusion immediately following animal sacrifice. Cur-treated rats had improved motor function compared with controls starting from week 1. Additionally, there was significant improvement in body weight gain, which correlated with improved Basso, Beattie, and Bresnahan test (BBBT) scores. Notably, Cur-treated rats exhibited greater soleus muscle weight than controls. Histopathological analyses confirmed increased neural element mass and a reduction in gliosis at the site of the contusion in the Cur-treated rats when compared to the control rats.[89]

It has been reported that tetrahydroCur exhibits hypoglycemic, anticancer, hypolipidemic, anti-depressant and anti-metastasis pharmacological effects. It is worth mentioning that the antioxidative,

hypoglycemic, and hypolipidemic properties of tetrahydroCur is superior to those of Cur. In an experimentally-induced rat model of SCI, tetrahydroCur increased the average BBBT scores and decreased both water accumulation in the spinal cord, as well as the levels of inflammatory factors. Oxidative stress and apoptosis (caspase-3 activity and Bcl-xL) were also attenuated in tetrahydroCur-treated SCI rats. The compound significantly decreased the gene expression of MMP-3 and MMP-13, as well as cyclooxygenase-2, promoted the phosphorylation of Akt, and increased the expression of forkhead box (FOX)O4. Thus, it was concluded that tetrahydroCur has a protective effect against SCI and inhibited oxidative stress by regulating FOXO4.[90] Cur treatment was shown to improve behavioral recovery in the first week after experimentally-induced SCI as documented by improved BBBT and plantar scores. BBBT and plantar scores represent locomotor and sensory performance, respectively. Cur treatment decreased glial scar formation by decreasing the NF-κB activity and the levels of IL-2, and MIP1α, as well as RANTES production. Hence, these results reveal that Cur has a significant anti-inflammatory effect towards the treatment of SCI, particularly when it is administered immediately after the SCI.[91]

Kim et al. investigated the effects of Cur on histological alterations and functional recovery following SCI in an experimental rat model. BBBT scores were significantly higher in rats receiving (200 mg/kg, i.p.). Cur also reduced the levels of MDA, the number of macrophages, and cavity volume, while increasing the SOD activity at 1 or 2 weeks after the SCI, which improved early functional recovery.[92]

In SCI- induced sublesional bone loss rats, administration of Cur (110 mg/kg body mass/day, via oral gavage) for 2 weeks prevented the loss of bone mass in both tibiae and femurs. Additionally, bone microstructure was preserved, which included trabecular bone volume fraction, trabecular number, as well as trabecular thickness in the proximal tibiae. It was found that the mechanical properties of the femoral midshaft was maintained in Cur-treated rats. Interestingly, as it pertains to oxidative stress, serum and femoral levels of thiobarbituric acid reactive substances were reduced in Cur-treated rats due to the antioxidant properties of Cur. Cur-treated rats had increased mRNA and protein expression of vitamin D receptor (VDR) and upregulated protein expression of β-catenin in distal femurs, as well as increased mRNA levels of Wnt3a, Lrp5, and ctnnb1. Thus, Cur treatment decreased oxidative stress, activated VDR, and enhanced the Wnt/β-catenin pathway, which might partially explain its beneficial effects against sublesional bone loss after SCI in rats.[93]

In a dual in vivo and in vitro study conducted in 2022, the effects of Cur nanoparticles and bovine serum albumin were assessed on SCI. It was found that Cur could increase the ROS scavenging rate after SCI and reduce inflammatory cytokines. Moreover, Cur was shown to increase neurite length in PC12 cells and elevate the levels of β3-tubulin+ neurons. The agent could reduce scar formation and improve neurological behavior after SCI. Cur increased the polarization of M2 macrophages, while reducing M1 macrophages, leading to a reduction in inflammation via regulating the NF-κB pathway.[94] In another in vivo study, Cur at a dose of 60 mg/mL/kg mitigated neuronal loss and necrosis via reducing the levels of caspase-3 and simultaneously increasing the BBBT score. Cur reduced the levels of TNF-α, IL-6, and IL-1β, suggesting an improvement in inflammation after SCI induction. The expressions of p62, Akt, and mTOR signaling pathway were also reduced.[72]

In a 2023 study on a SCI rat model, Jiang et al. investigated the effects of transplantation of Cur-activated olfactory unsheathing cells to the compound enhanced and potentiated the activation of olfactory ensheathing cells, which was determined by the elevation of TG2 and PSR levels. Cur complex showed an increase in the BBBT score, indicating an improvement in neurological function following Cur transplantation. Moreover, Cur complex decreased the iNOS expression, while simultaneously increasing Arg-1 levels, suggesting the modulation of microglia polarization and suppression of inflammation. Furthermore, it was elucidated that Cur could increase the polarization of microglia into the M2 phenotype, by assessing the CD206 and CD86 levels. Favorable effects of Cur on SCI were implicated in regulating the APOE/TREM2/NF-κB signaling pathways.[95] In addition, Cur was shown to increase the rate and speed of angiogenesis, which was evaluated by increased VEGF-A and PDGF-AA levels, through the regulation of the PI3K/Akt pathway.[96]

Another novel approach to treat SCI is the use of hUC-MSC transplantation, but the main drawback of this treatment is the lack of stability and cell survival of stem cell transplantation due to several factors. In Wanjiang et al. study, administration of Cur enhanced hUC-MSC cell survival in a dose-dependent manner. Cur improved motor function within an 8-week period after SCI induction, reduced the TNF-α levels and apoptosis rate via regulating the ERK 1/2 signaling pathway, while there was no significant effect on the BBBT score.[97]

Another novel therapeutic approach for SCI treatment is the use of human induced neural progenitor cells (imps). Administration of Cur increased the outgrowth of Nestin-positive neurites from iNPCs, while simultaneously reducing apoptosis and neuronal cell loss in a dual in vitro and in vivo experiment. It was confirmed that Cur could improve cell viability and enhance neuronal morphology could the compound induced neuroprotection by assessing the levels of β3-tubulin+ neurons and also suppressed the overexpression of platelet-derived growth factor. Complex of Cur and iNPCs could be a possible therapeutic option for SCI and SCI scar coverage.[98] In another experiment conducted in 2023, investigators aimed to improve the Cur stability and bioavailability via loading Cur into a micelle nanoparticle in SCI rat model. Cur attenuated inflammation by inducing the polarization of microglia into the M2 phenotype, which was assessed by the levels of Arg-1 and CCR-7. Nevertheless, it was acclaimed that this anti-inflammatory response could reduce scar development and increase neuronal regeneration (which was measured by Tuj-1-positive neuronal cell count), nerve remyelination, and BBBT score. Moreover, the levels of IL-4 and IL-10 were increased after Cur administration.[99] In a dual in vitro and in vivo experiment in SCI animal model, specific complex of Cur improved neurite outgrowth, neuronal degeneration, and neuronal remyelination (which was assessed by Schwann cell migration).[65] In a recently published study in 2024, Guo et al. declared the notion that IL-4 could be the

main factor for M2 polarization following Cur administration. The compound increased the level of IL-4, leading to a reduction of inflammatory cytokines such as TNF-α, iNOS, IL-1β, and IL-6, while increasing the levels and expression of Arg-1, TGF-β, IL-10, and CD206. Besides, it was asserted that a Cur complex with olfactory ensheathing cells could improve neurological functions after SCI. The number and morphology of Tuj1+ cells were improved. These effects were mediated via the JAK/STAT and NF-κB/SOCS signaling pathways.[100] Cur improved the beneficial effects of human neural stem cells derived from induced pluripotent stem cells in SCI, while it did not significantly alter the BBBT score. Cur increased β3-tubulin+ neurons and induced M2 polarization, resulting in anti-inflammatory effects.[101]

7 | CONCLUSION

SCI is a neurodegenerative disease with a significant negative effect on the quality of life in affected patients. The appearance of different symptoms are related to primary and secondary SCI. Many therapeutic interventions have been investigated to relieve the symptoms associated with SCI. For example, conventional medications, as well as natural compounds, have been evaluated to identify precise therapeutic strategies/targets to treat the symptoms associated with SCI. As was discussed in this review, many in vitro and in vivo studies have attempted to clarify the potential therapeutic roles of Cur in treatment of SCI. Literature review suggest that Cur can slow the development of SCI by affecting different signaling pathways including the Nrf2, NF-κB, TGF-β, and mTOR pathways. In addition, findings from in vitro investigations have demonstrated that Cur can suppress inflammation by inhibiting the iNOS, TGF-β, and NF-κB signaling pathways, leading to the downregulation of MCP-1, RANTES, and CXCL10. Animal models of SCI exhibit that Cur reduces apoptosis, gliosis, and levels of proinflammatory cytokines such as TNF-α, IL-6, and IL-1β. This is important, since enhancing the production of anti-inflammatory cytokines and the levels of enzymes such as SOD, GPx, GST, CAT, Nrf2, HO-1, and NQO1 can ameliorate the inflammation that accompanies SCI. In general, these Cur-induced alterations in cytokine and enzyme levels result in increased tissue sparing and improvement in Tarlov, or BBBT scores. These provide improved neurologic function and the attenuation of clinical symptoms of SCI. There are few controlled clinical trials about the possible impact of Cur on SCI. For example, Hatefi et al. evaluated the effect of Cur on osteoporotic function, based on biomarkers of bone turnover and densitometry (i.e., bone mineral density), in 100 patients with SCI. In this study, patients and control group received Cur (110/mg/kg/day) and placebo for 6 months, respectively. Cur significantly reduced the progression of osteoporosis and biomarkers of bone turnover in individuals with SCI.[102] In another clinical study by Alisson and his colleagues, curcumin at the dose of 400 mg/kg PO (InflanNox or AOR InflanNox), taken three times daily, reduced inflammatory cytokines such as IL-2, IL-6, IL-1β, TNF-α, and IFN-γ, which represented its anti-inflammatory effects. Cur was elucidated to improve depression after SCI.[103] In another single-center, open-label pilot trial, the effects of theracurcumin at a dose of 90 mg, administered twice daily for 6 months, were evaluated in ALS patients. Although the results have not yet been published, the preliminary findings indicate a promising potential for this compound in treating another neurodegenerative disease. Moreover, in a randomized, parallel, double-blind clinical trial, curcumin at the dose of 500 mg PO administered twice a day for 24 months was shown to improve free relapsing time and the number of relapses per year in patients with MS, which shows another promising effects of Cur in NDs.[104] These clinical trials provide relevant information about the therapeutic potential of Cur in patients who suffer from SCI; however, more clinical studies are required to identify its precise mechanism of action, efficacy, optimum dosage, appropriate route of administration, and any long-term adverse reactions that could potentially occur. The present review encompassed the most recent findings about subject matter, and elaborated in details on the effects of Cur on SCI via regulating numerous signaling and pathophysiological pathways. On top of that, we reviewed all of the protective mechanisms of curcumin treatment in SCI such as inflammation reduction, anti-oxidant activity, apoptosis enhancement, microglia polarization, angiogenesis improvement, and scar formation attenuation to fully establish all of the beneficial aspects of curcumin on SCI. In conclusion, we suggest that Cur certainly has an important role in regulating inflammatory signaling pathways and might represent a viable treatment option for managing the symptoms of SCI, most likely as adjunctive therapy to synthetically-derived, conventional medications.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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