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The Role of Resveratrol on Spinal Cord Injury: from Bench to Bedside

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Abstract

Spinal cord injury (SCI) is a severe and disabling injury of the central nervous system, with complex pathological mechanisms leading to sensory and motor dysfunction. Pathological processes, such as oxidative stress, inflammatory response, apoptosis, and glial scarring are important factors that aggravate SCI. Therefore, the inhibition of these pathological processes may contribute to the treatment of SCI. Currently, the pathogenesis of SCI remains under investigation as SCI treatment has not progressed considerably. Resveratrol, a natural polyphenol with anti-inflammatory and antioxidant properties, is considered a potential therapeutic drug for various diseases and plays a beneficial role in nerve damage. Preclinical studies have confirmed that signaling pathways are closely related to the pathological processes in SCI, and resveratrol is believed to exert therapeutic effects in SCI by activating the related signaling pathways. Based on current research on the pathways of resveratrol and its role in SCI, resveratrol may be a potentially effective treatment for SCI. This review summarizes the role of resveratrol in promoting the recovery of nerve function by regulating oxidative stress, inflammation, apoptosis, and glial scar formation in SCI through various mechanisms and pathways, as well as the deficiency of resveratrol in SCI research and the current and anticipated research trends of resveratrol. In addition, this review provides a background for further studies on the molecular mechanisms of SCI and the development of potential therapeutic agents. This information could also help clinicians understand the known mechanisms of action of resveratrol and provide better treatment options for patients with SCI.

Keywords Spinal cord injury (SCI) · Resveratrol · Inflammatory response · Glial scar · Drug delivery system

Abbreviations

SCI	Spinal cord injury
Bcl-2	B-cell lymphoma-2
ERK	Extracellular signal-regulated protein kinase
IKK	IκB kinase
JNK	Jun N-terminal kinase
MyD88	Myeloid differentiation primary response gene 88
PI3K	Phosphoinositide 3-kinase
SIRT1	Sirtuin 1
TLRs	Toll-like receptors
TRIF	TIR-domain-containing adapter-inducing interferon-β
TBI	Traumatic brain injury
SAH	Subarachnoid hemorrhage
ROS	Reactive oxygen
HIF-1α	Hypoxia-inducing factor 1-α
CNS	Central nervous system
iNOS	Inducible nitric oxide synthase
MAPK	Mitogen-activated protein kinase
AMPK	Adenylate activated protein excitation
mTOR	Mammalian target of rapamycin
LPS	Lipopolysaccharide
LPO	Lipid peroxidase
GSH	Glutathione
SOD	Superoxide dismutase,
PC	Protein carbonyl,
GSK-3β	Glycogen synthase kinase-3β,
ULK1	Unc-51-like autophagy activating kinase 1,
Nrf2	Nuclear factor erythrocyte 2 related factor 2,
PMMSN	Manganese-doped silicon dioxide nanomedical system,
BSCB	Blood-spinal barrier

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Introduction

Spinal cord injury (SCI) is a severe and disabling neurological disorder that often results in the loss of sensory and motor functions, paralysis, and death [1]. Due to the weak capacity for autonomic nerve repair after SCI and the rapid emergence of various pathological processes, tissue repair, and functional reconstruction of the injured spinal cord are challenging [2, 3]. Because SCI often results in permanent disability and reduced quality of life, it imposes a considerable financial burden on society and patients, including medical expenses and lost productivity [4]. Current treatments for SCI mainly include surgical and conservative symptomatic treatments. Although these treatments can alleviate the related clinical symptoms to a certain extent, the recovery of neurological function after an injury is extremely long and difficult. Therefore, there is an urgent need to identify effective drugs that can control and improve these conditions. However, drug development is inseparable from the complexity of the pathological processes in SCI. Therefore, the development and discovery of new drugs and surgical methods for the intervention and treatment of SCI should be considered from the perspective of inhibiting the pathological progression of SCI to improve neurological recovery and patient prognosis.

Resveratrol is a small molecule natural polyphenol with antioxidant properties [5, 6]. Owing to its exciting pharmacological potential, it has gradually attracted the attention of researchers [7, 8]. Resveratrol has been reported to have anti-inflammatory and anti-apoptotic biological activities and has been shown to provide neuroprotective effects in different experimental models of acute nervous system injury [9–12]. For example, resveratrol can improve the histopathological and behavioral outcomes in stroke [13, 14], traumatic brain injury (TBI) [15], subarachnoid hemorrhage (SAH) [16], SCI [17, 18], and other central nervous system (CNS) injuries. In recent years, traditional Chinese medicine has gathered considerable attention in the field of SCI treatment and has been shown to be effective in the prevention and treatment of SCI [19, 20]. The potential therapeutic effects of resveratrol in SCI treatment were confirmed using behavioral scores and histopathological changes [21]. Other studies have shown that resveratrol plays a role in various pathophysiological processes in SCI [22, 23] and can be used as a therapeutic agent to improve patient prognosis [24]. Therefore, resveratrol may be an important target for future therapeutic research on SCI. However, the anti-SCI effects of resveratrol remain to be specifically reviewed. Therefore, we review the current research on the mechanism of action of resveratrol in the treatment of SCI, including its role in the pathological processes of SCI (oxidative stress, neuro-inflammation, autophagy and apoptosis) and its potential value in clinical practice. This review also focuses on the new ideas and prospects of the future clinical application of resveratrol in combination with the latest research achievements and technologies in life science and medicine.

Biological Functions of Resveratrol

As an ingredient of traditional Chinese medicine, resveratrol has been widely used to prevent or slow down the progression of many diseases, including cardiovascular disease, cancer, nervous system damage, and Alzheimer's disease and its benefits have been demonstrated through modern pharmacological research [25–27]. Resveratrol has various biological activities and pharmacological effects, including antioxidant [28], anti-inflammatory [29], and cardioprotective [30]. Resveratrol has been indicated to prevent and treat oxidative stress associated with different diseases, including type 2 diabetes [31], tissue injury [32], Parkinson's disease [33], neurodegenerative disorders [34], and metabolic syndrome [35]. The antioxidant qualities of resveratrol can be explained through its ability to either directly neutralize ROS or indirectly upregulate the expression of cellular defensive pathways and genes. Resveratrol limits free radical production, inhibits lipid peroxidation, and regulates the activity of oxidation-related enzymes. For example, resveratrol has been shown to inhibit oxidative stress and cancer growth in hypoxic rat pulmonary artery endothelial cells by inhibiting ROS production [36, 37]. In addition, resveratrol can reduce the production of oxidized low-density lipid protein cholesterol, protect vascular endothelial cells from oxidative damage caused by lipid oxides, reduce endothelial cell apoptosis, and play a protective role in cardiovascular diseases [38, 39]. In addition, in the in vivo and in vitro oxidative stress model, resveratrol has also been shown to regulate the Nrf2 pathway to relieve or prevent oxidative stress [40, 41]. The anti-inflammatory qualities of resveratrol have been shown in various animal and in vitro models and contribute to the therapeutic and alleviating effects on disease [42]. Previous studies have reported that resveratrol decreases the production of pro-inflammatory cytokine and inhibits the gene expression associated with inflammation. In addition, resveratrol shows its anti-inflammatory properties by regulating various pathway. COX is the enzyme in the rate-limiting step of the pathway that manufactures mediators of inflammation. Resveratrol has been shown to effectively inhibit the activity of NF-κB and IκB kinases to inhibit the expression of COX-2, thereby reducing the expression levels of inflammatory factors IL-1β, IL-6, and TNF-α and significantly upregulating IL-10 to prevent an inflammatory response [43–45]. In addition, resveratrol can also play an anticancer role by eliminating or reducing the

toxicity of carcinogens, inducing tumor cell differentiation and apoptosis, and inhibiting the formation of tumor blood vessels [46, 47]. However, resveratrol has been found to have anti-apoptotic effects in acute central nervous system injuries. Resveratrol can prevent the increase of hypoxia-inducing factor 1-α (HIF-1α), Bax, and caspase-3 and increase the anti-apoptotic Bcl2 levels to play an anti-apoptotic role [48]. In addition to its antioxidant, anti-inflammatory, and antitumor effects, resveratrol has antibacterial, antiviral, and immunomodulatory effects [49, 50].

Pathophysiology of SCI

The pathological process of SCI can be divided into two stages: primary and secondary. Primary injury refers to the direct injury and necrosis of spinal cord tissues and cells caused by trauma [51]. The severity of this process depends on the amount of force and is an irreversible injury process [52]. Based on the primary injury, a series of biological events (ion disorder, demyelination, axonal degeneration, excessive release of excitatory toxins, and inflammatory responses leading to massive neuronal apoptosis and glial scar formation) occur in the secondary injury, leading to progressive injury of the lesion and surrounding spinal cord tissue [53–56]. Secondary SCI begins within minutes of the primary injury and can last for weeks or months [57]. Secondary injury can be divided into three distinct but overlapping successive stages: acute, subacute, and chronic [58, 59]. Secondary injury mainly involves a series of cascade changes at the tissue, cell, and molecular levels, leading to further damage [60] (Fig. 1). The acute phase begins immediately after SCI and is primarily caused by mechanical damage, including vascular damage, ion homeostasis imbalance, oxidative stress, and free radical formation [61, 62]. The subacute phase is the continuation of acute-phase injury, including the inflammatory response, cell death, and onset of glial scar formation [63]. The chronic phase can occur days or even years after SCI and is characterized by white matter demyelination, gray matter dissolution, connective tissue deposition, reactive glial hyperplasia, and glial scar maturation [64]. We can better explore possible therapeutic measures for SCI by thoroughly understanding the mechanisms of secondary injury.

Role of Resveratrol in SCI

Secondary injury and neuronal death following SCI are synergistically mediated by several pathophysiological mechanisms, including oxidative stress, inflammation, ion imbalance, and apoptosis (Table 1). Resveratrol, a therapeutic agent, can prevent or slow these pathological changes and improve patient prognosis (Fig. 2).

Oxidative Stress

Oxidative stress occurs when pro-oxidants and antioxidants are unbalanced in living systems and plays important roles in the pathophysiology of many diseases and injuries [71]. Oxidative stress is an important SCI-related event that plays an important role in the pathophysiology of SCI and

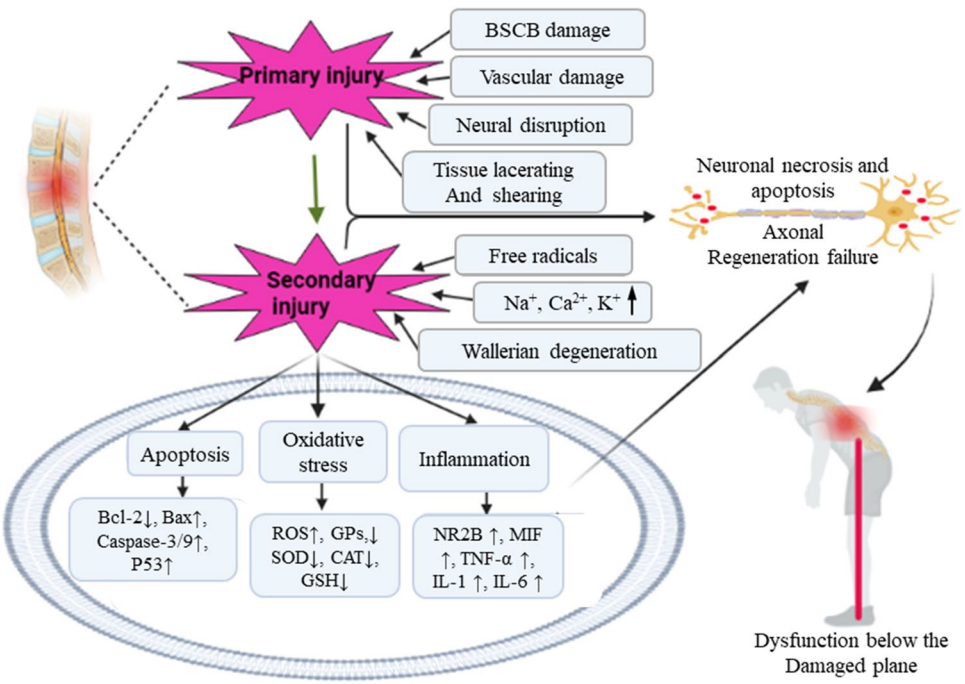

Fig. 1 Vascular changes, destruction of the blood-brain barrier, and nerve damage occur in the primary process, whereas excessive release of excitatory toxins, imbalance of ion homeostasis, oxidative stress, and free radical formation occurs in the secondary process. Both primary and secondary injuries lead to neuronal necrosis, apoptosis, glial scarring, and axonal dysplasia, resulting in dysfunction below the damaged plane in patients with SCI. BSCB, blood-spinal barrier; ROS, reactive oxygen species; SOD, superoxide dismutase; CAT, hydro-oxidase; GSH, glutathione; NR2B, aspartate receptor subunit; MIF, macrophage migration inhibitor; TNF-α, tumor necrosis factor-α

Table 1 Effects of resveratrol on various spinal cord injury models

Spinal cord injury	Experimental model	Resveratrol administration	Function	References
Contusion	Model of neuronal cell mechanical injury in vitro	Intervention in cell models with different concentrations of resveratrol (5, 10 and 20 μM)	Promoted autophagic flux by activating the SIRT1/AMPK pathway	[65]
	Allen's method, a rat model of spinal cord contusion at the T9-10 level	Intraperitoneal injection of resveratrol (100 mg/kg)	Increased the expression of SIRT1, p-AMPK, Beclin-1, LC3-B, and Bcl-2, while decreasing the expression of p62, cleaved caspase-3, caspase-9, and Bax, thereby activating autophagy, reducing apoptosis, and increasing motility, neuronal survival, and reduced lesion size	[22]
	Allen's method, a rat model of spinal cord contusion at the T9-10 level	Intravenous resveratrol (100 mg/kg)	Enhanced autophagy, reduced TNF-α and IL-1β levels, and inhibited neuroinflammation by activating the AMPK/mTOR pathway	[66]
	Spinal cord contusion model of rat at the T9-10 level	Intraperitoneal injection for 3d (200 mg/kg/day)	Protected motor neurons by enhancing blocked autophagic flux after SCI by enhancing the LKB1/AMPK/mTOR/p70s6k pathway and reducing neuronal apoptosis	[67]
	Spinal cord contusion model in rats	Intravenous resveratrol (100 mg/kg)	Increased Bcl-2 levels and lowered Bax and caspase-3 expression	[68]
Compression	Rat Rivlin-Tator compression model	A single dose of intravenous resveratrol (100 mg/kg)	Enhanced antioxidant capacity and paraoxonase-I activity	[69]
Ischemia–reperfusion injury	The vessel was clamped between the left renal artery and aortic bifurcation with a miniature aneurysm clip	Intraperitoneal injection of resveratrol (10 mg/kg)	Increased enzymatic and non-enzymatic antioxidant defenses (such as reduced glutathione, superoxide dismutase, and catalase) to reduce free radicals	[70]

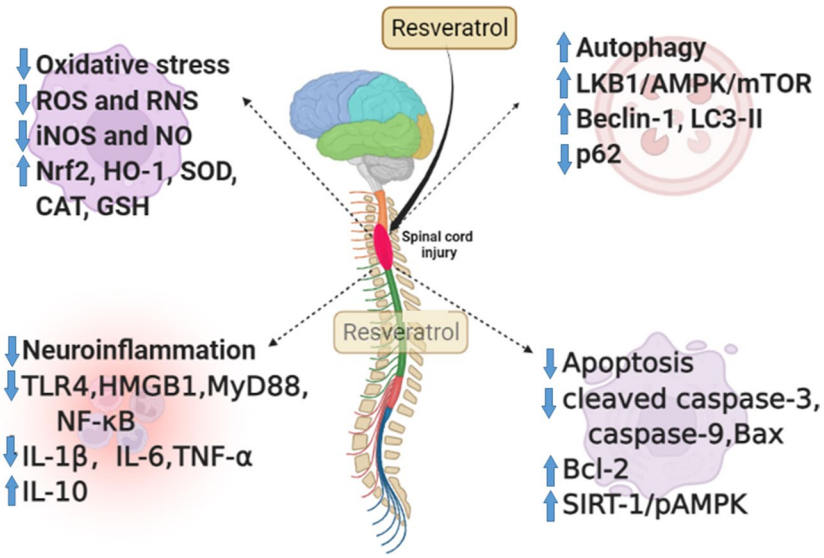

Fig. 2 Potential effects of resveratrol. Resveratrol can play a protective role in SCI through autophagy, antioxidant, anti-inflammatory, and anti-apoptotic effects. ROS, reactive oxygen species; NO, nitric oxide; Nrf2, nuclear factor erythrocyte 2 related factor 2; HO-1, heme oxygenase; SOD, superoxide dismutase; CAT, hydro-oxidase; GSH, glutathione; TLR4, toll-like receptor-4; HMGB1, high mobility group protein B; MyD88, myeloid differentiation primary response gene 88

is considered a marker of secondary injury after SCI. Spinal cord damage produces excess free radicals or reactive oxygen species (ROS), including O_2^-, H_2O_2, OH^-, and peroxynitrites. These substances attack unsaturated fats, lipids, and proteins in the spinal cord, causing oxidative damage to the spinal cord, thus accelerating SCI [72]. In addition, under oxidative stress, increased ROS levels activate the IκB kinase (IKK) complex, which is responsible for the phosphorylation of IκB, thereby allowing the degradation of the IκB proteasome and the release and translocation of NF-κB to the nucleus. Therefore, reducing oxidative stress may be an effective strategy for post-SCI therapeutic intervention.

Resveratrol, an antioxidant, plays an important role in the oxidative stress induced by SCI. Studies have shown that resveratrol induces an increase in antioxidant defense mechanisms and decreases the expression of oxidative stress markers in peripheral nerve injury [73, 74]. Xanthine oxidase is an enzyme involved in the breakdown of purine nucleotides (with the release of ROS) in animals with traumatic SCI. Early use of resveratrol after SCI induced superoxide dismutase activity, increased glutathione levels, reduced xanthine oxidase expression, and promoted the recovery of neurological function [17]. In an experimental model of SCI induced by clip compression, a single dose of resveratrol (100 mg/kg) was injected intraperitoneally 1 h after SCI, and a significant increase in total antioxidant capacity and paraoxonase-I activity was observed [69]. In another study, in a rat model of spinal cord ischemia-reperfusion injury, resveratrol treatment was found to significantly reduce rat plasma nitrite/nitrate, iNOS mRNA, and protein levels in the spinal cord and p-p38MAPK levels. Resveratrol reduces free radicals by increasing the levels of enzymes and non-enzymatic antioxidants, such as reduced glutathione, superoxide dismutase, and catalase. It is believed that resveratrol can reduce oxidative stress caused by reperfusion injury and protect against spinal cord ischemic injury by inhibiting the activation of the iNOS/p38MAPK pathway [70]. The results of these studies demonstrate that resveratrol can effectively reduce oxidative stress after SCI and promote the recovery of nerve function. Resveratrol may be an effective drug for therapeutic intervention after SCI. However, the effectiveness of its clinical application requires further confirmation.

Inflammatory Response

An inflammatory reaction is an inevitable secondary symptom after SCI that directly or indirectly determines the prognosis [75]. In secondary SCI, the activation of glial cells and the infiltration of a large number of inflammatory cells (neutrophils and macrophages) at the injury site rapidly promote the release of various inflammatory factors and interferons, accelerate neuronal death, and induce the expression of various cell adhesion and chemotactic molecules in vascular endothelial cells, thereby triggering neuro-inflammatory and neurotoxic responses [76, 77]. Their long-term presence promotes the excessive activation of motor neurons and glial cells, leading to the dysfunction of the central nervous system and the formation of scar tissue, which becomes a major obstacle in the repair of SCI [78–80]. Therefore, it is necessary to develop an effective treatment that can suppress the inflammatory response and promote SCI repair.

The significant effect of Chinese herbal extracts on SCI-induced neuro-inflammation has been increasingly recognized. Several studies have reported that resveratrol is an anti-inflammatory agent that plays an important role in the inflammatory response in various diseases via various signaling pathways [81, 82]. Other studies have found that resveratrol can reduce the inflammatory response after SCI

by inhibiting the activation of inflammasomes and inflammatory signaling pathways, thus creating a favorable environment for the recovery of neurological function [83–85]. Treatment with resveratrol after SCI reduces the expression of inflammatory cytokines such as IL-1β and TNF-α [86]. In an animal experiment, intraperitoneal injection of resveratrol (100 mg/kg) immediately after SCI in Sprague–Dawley rats was found to be accompanied by the upregulation of SIRT1 expression and a decrease in NF-κB activity. This inhibition significantly reduced neutrophil infiltration and the production of inflammatory mediators [87]. Zhao et al. [88] found that resveratrol activated the SIRT-1/NF-κB signaling pathway and showed that phosphorylated AMP-activated protein kinase (AMPK) increased and p-mammalian target of rapamycin (mTOR) decreased after SCI in rats. However, intraperitoneal injection of resveratrol (100 mg/kg) 1 day after surgery improved motor function and reduced neuroinflammatory responses in rats, suggesting that resveratrol inhibits neuro-inflammation by activating the AMPK/mTOR pathway after SCI [66]. These findings suggested that resveratrol can inhibit the inflammatory response in SCI and has potential clinical implications in the treatment of SCI.

Apoptosis

Nerve cell apoptosis is an important pathophysiological change leading to spinal cord dysfunction after SCI, as well as an important mechanism of progressive aggravation of secondary SCI and irreversible changes in neuronal cells [89, 90]. Many studies have shown that apoptosis is one of the main pathological manifestations of secondary injury, and its severity directly affects the recovery of motor function in patients with SCI [91, 92]. Therefore, inhibition of neuronal apoptosis during secondary injury is the focus of SCI treatment.

Resveratrol plays an important role in the treatment of SCI and has a neuroprotective role by regulating apoptosis [93–95]. Moreover, the anti-apoptotic effects of resveratrol in SCI have been confirmed. Administration of resveratrol after SCI can inhibit nerve cell apoptosis and promote the recovery of nerve function [96]. In a study on the effect of resveratrol on functional recovery in SCI, rats treated with resveratrol immediately after contusion had significantly higher Basso, Beattie and Bresnahan (BBB) scores than the control group and significantly reduced motor neuron loss and lesion size in the spinal cord. Resveratrol is believed to promote autophagy after SCI by upregulating the SIRT1/AMPK signaling pathway, thereby inhibiting apoptosis [22]. Sirtuin 1 (SIRT1) is crucial for apoptosis regulation [97], and its expression is significantly correlated with autophagy in some diseases [98]. He et al. simulated the microenvironment of the injured spinal cord using lipopolysaccharide (LPS) in VSC4.1 spinal cord neuron cell lines and found that resveratrol promoted autophagy, upregulated SIRT1 and inhibited LPS-induced apoptosis of VSC4.1 motor neuron cells [99]. Yue et al. reached similar conclusions in their study [100]. Resveratrol activated autophagy, improved neuronal survival, reduced cell apoptosis, and promoted recovery of neurological function after SCI in rats. These studies suggest that resveratrol inhibits neuronal apoptosis after SCI by activating autophagy. Therefore, resveratrol is a promising drug for the treatment of SCI.

Glial Scars

Glial scars are mainly composed of extracellular matrix (ECM). After SCI, resident microglia and astrocytes are activated to surround the damaged tissue, resulting in the appearance of persistent glia in the injured spinal cord scar [101, 102]. The glial scar is an important barrier affecting axonal regeneration after SCI [103]. After SCI, reactive astrocytes become hypertrophic, proliferate, and migrate to the injured area, eventually forming a dense network of glial scars that act as a physical and chemical barrier preventing the repair and regeneration of damaged neural tissue [64, 104]. Therefore, reactive astroglial response inhibition prior to glial scarring offers a potential therapeutic option for promoting axonal growth and neurological recovery.

The therapeutic effect of resveratrol on the formation of glial scars after SCI has gradually been recognized. Resveratrol plays a protective role in scar formation by regulating astrocytes. After SCI, astrocytes mainly participate in scar formation through activation and proliferation. In vitro SCI studies found that intervention with resveratrol reduced the proliferation of astrocytes and the expression of GFAP at the injured site, inhibited the expression of Smad-2, Smad-3, and Smad-4, and upregulated the expression of Smad-7, thereby reducing the number of cells in the S phase to inhibit the proliferation of astrocytes [105, 106]. However, the activation and proliferation of astrocytes after SCI are complex and involve the activation of various signals (such as mTOR and Shh). mTOR activation participates in astrocyte proliferation by increasing downstream cascades and activating astrocytes [107]. mTOR inhibition can inhibit this process to reduce the formation of glial scars [108, 109]. After SCI, resveratrol treatment can inhibit scar formation by inhibiting mTOR signaling and activating Shh signaling to increase the inhibition of astrocyte activity [110]. Therefore, we speculate that resveratrol may be a favorable drug for the treatment of post-SCI glial scar formation.

Autophagy

Autophagy is an evolutionarily conserved cellular response pathway that can lead to the degradation of proteins and entire organelles in cells under stress, thus maintaining

homeostasis of tissue structure and function [111–114]. Autophagy is speculated to be a "double-edged sword" in nervous system trauma [115]. As a major contributor to cell homeostasis, autophagy constitutes a stress-adaptive pathway to promote cell survival [113, 115, 116]. However, under certain pathological conditions, it can cause cell damage and death [114, 117]. Depending on the location and severity of neurological trauma, autophagic flux may increase or decrease [116]. Therefore, increased autophagic flux may have a protective effect after mild injury, whereas its inhibition may lead to neuronal cell death after a more severe injury [116, 118]. Inhibition of autophagy is considered to be a part of the secondary injury mechanism, and its recovery may offer a potential treatment to limit the spread of SCI.

Autophagy is not a separate process in SCI, and its activation is often cross-regulated by processes such as apoptosis, inflammatory response, and glial scarring [119]. Studies have shown that resveratrol can reduce the barriers to unc-51-like autophagy-activating kinase 1 (ULK1) phosphorylation and induce autophagy activation by inhibiting the mTOR-ULK1 pathway, including apoptosis, pathological scar formation, fibroblast proliferation, and anti-inflammatory effects [106, 120, 121]. Several recent studies have shown that resveratrol enhances autophagy and reduces apoptosis following different types of experimental nervous system injuries [22, 66, 67]. Meng et al. found that after SCI, resveratrol promoted functional recovery and inhibited neuro-inflammation by activating the AMPK/mTOR pathway-mediated autophagy [66], in addition to upregulating the SIRT1/AMPK signaling pathway, promoting autophagy, inhibiting neuronal apoptosis, reducing tissue damage, and promoting motor function recovery [22]. Another study found that treatment with resveratrol promoted the recovery of motor function, reduced neuronal degeneration, and reduced apoptosis in SCI mice [122]. These studies demonstrate that autophagy plays a crucial role in the pathological process of SCI, and the regulation of autophagy may determine the progression and outcome of SCI.

Resveratrol and Related Signaling Pathways

The pathological process of SCI is complex, involving multiple cellular and molecular mechanisms. It has been demonstrated that multiple signaling pathways are related to the pathological process [123–127]. Here, we describe the signaling pathways of resveratrol involved in the SCI pathological processes identified in current studies (Fig. 3).

PI3K/Akt/mTOR Signaling Pathway

The PI3K/Akt signaling pathway is an important intracellular signal transduction pathway involved in the signal transduction of cytokines and the extracellular matrix [128]. The mammalian rapamycin target (mTOR) is a conserved serine/threonine protein kinase of the phosphoinositol 3-kinase (PI3K)-associated protein kinase family and a central controller of cell growth [129]. Many studies have found that this pathway is activated after SCI and is involved in the regulation of various pathological processes in SCI; the activation of this pathway is believed to be not conducive to the functional recovery of SCI [130–133]. Therefore, the inhibition of the mTOR signaling pathway may be a potential target for the treatment of SCI.

Several studies have confirmed that resveratrol plays a role in the pathology of SCI by inhibiting mTOR through various mechanisms. Both PI3K and Akt are upstream activators of mTOR, and resveratrol can block PI3K and Akt phosphorylation, inhibit mTOR pathway activity, alleviate glial scarring, apoptosis and inflammatory responses, and enhance autophagy [108, 125]. In a rat SCI model, the rats were treated with an intraperitoneal injection of resveratrol after SCI. Resveratrol inhibited the phosphorylation of PI3K, Akt, and mTOR; inhibited the mTOR-ULK1 pathway; increased autophagic flux; activated autophagy; improved the Bcl2/Bax ratio; and decreased caspase-3 expression level inhibited neuronal apoptosis [134]. Other studies have shown that resveratrol can inhibit the proliferation of pathological scar fibroblasts by reducing the expression of mTOR and its downstream molecule, p70S6K [106]. In addition, studies have reported a correlation between mTOR and NF-κB pathways; the activation of the mTOR pathway can induce the activation of the NF-κB signaling pathway, thereby accelerating the inflammatory reaction process. After resveratrol treatment, the mTOR pathway is inhibited, thereby inhibiting the activation of the NF-κB pathway and the release of inflammatory cytokines [135, 136] (Fig. 3).

NF-κB Signaling Pathway

The NF-κB transcription factor family plays important roles in a variety of physiological and pathological processes. According to the activation mechanisms, the NF-κB pathway can be categorized as classical and non-classical [137, 138]. Activation of the classical NF-κB pathway is an important pathway in inflammatory responses [139, 140]. TLR is a toll-interleukin 1 receptor domain on the cell membrane that recruits junction proteins, which subsequently promote the recruitment of MyD88, phosphorylation of p38 kinase, Jun N-terminal kinase (JNK), and extracellular signal-regulated kinase (ERK) to activate NF-κB in the nucleus [141]. In addition, in another TLR signaling pathway, TLR4 forms

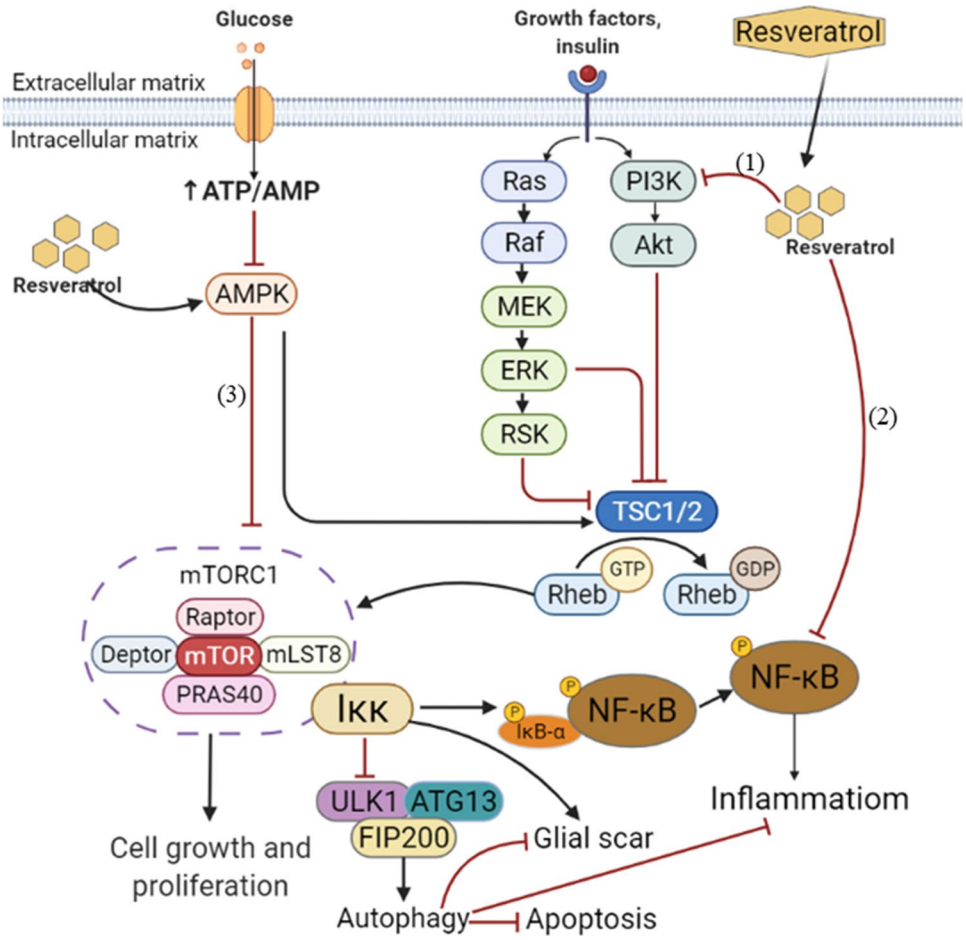

Fig. 3 Resveratrol inhibits mTOR signaling in SCI repair. (1) Resveratrol reduces the activity of PI3K and Akt and inhibits the mTOR pathway, thereby regulating protein synthesis, autophagy and apoptosis. (2) Activated mTORC1 interacts with IKK to activate NF-κB signaling to trigger inflammatory response and the formation of glial scars. Resveratrol directly inhibits the effect of NF-κB, thereby inhibiting the inflammatory response. (3) Resveratrol inhibits the downstream mTOR signaling pathway by activating AMPK phosphorylation. lKK, IκB kinase; ULK1, Unc-51-like autophagy activating kin-1; ATG3, antibody to autophagy related protein 3

signaling complexes with TIR-domain-containing adapter-inducing interferon-β (TRIF)-associated junction molecules and TRIF. It also promotes the recruitment of MyD88 and the release of IL-β and TNF-α by recruiting adaptive molecules, thereby triggering the activation of NF-κB [133]. A large number of studies have confirmed that the NF-κB signaling pathway plays an important role in the pathophysiological mechanism and repair in SCI [142–144].

Increasing evidence confirms that resveratrol is an effective inhibitor of the NF-κB pathway, which can play a variety of pharmacological effects in SCI recovery [22, 145, 146]. Resveratrol can inhibit the NF-κB pathway through multiple pathways in SCI and may enhance the expression of SIRT1 and AMPK. Activation of AMPK increases the NAD + / NADH ratio and triggers downstream processes, whereas SIRT1 acts as an anti-inflammatory NAD^+-dependent sirtuin through the direct deacetylation of NF-κB subunits such as p65 and directly interacts with RelA/p65, thereby inhibiting NF-κB transcription [147] (Fig. 4). Resveratrol has been reported to regulate autophagy and motor neuron recovery through the SIRT1-AMPK signaling pathway [22, 148]. Resveratrol pretreatment promotes autophagy by activating the SIRT1/AMPK pathway, and the increase in autophagic flux can inhibit neuronal apoptosis and promote motor function recovery [22, 65]. Other studies have shown that resveratrol can activate SIRT1 to inhibit inflammatory cytokines and improve neuronal cell survival by regulating the acetylation of NF-κB p65 after SCI [149].

Other Signaling Pathways

In addition to the effects of resveratrol on SCI through the PI3K/Akt/mTOR and NF-κB signaling pathways, resveratrol can also play a role in SCI through Wnt/β-catenin, Nrf2, Notch, and other pathways. The classical Wnt/β-catenin pathway is a highly conserved signaling cascade that plays an important regulatory role in the developing CNS [150]. Xiang et al. found that resveratrol can significantly activate Wnt3a and β-catenin levels by regulating the Wnt/β-catenin signaling pathway, inhibiting glycogen synthase kins-3β (GSK-3β), inhibiting cell apoptosis, and improve histological damage. It also promoted functional recovery and axonal regeneration after SCI. Wnt/β-catenin signaling pathway inhibitors significantly reversed the effects of resveratrol on nerve function recovery, axon regeneration and apoptosis after SCI [151]. The Notch signaling pathway is highly

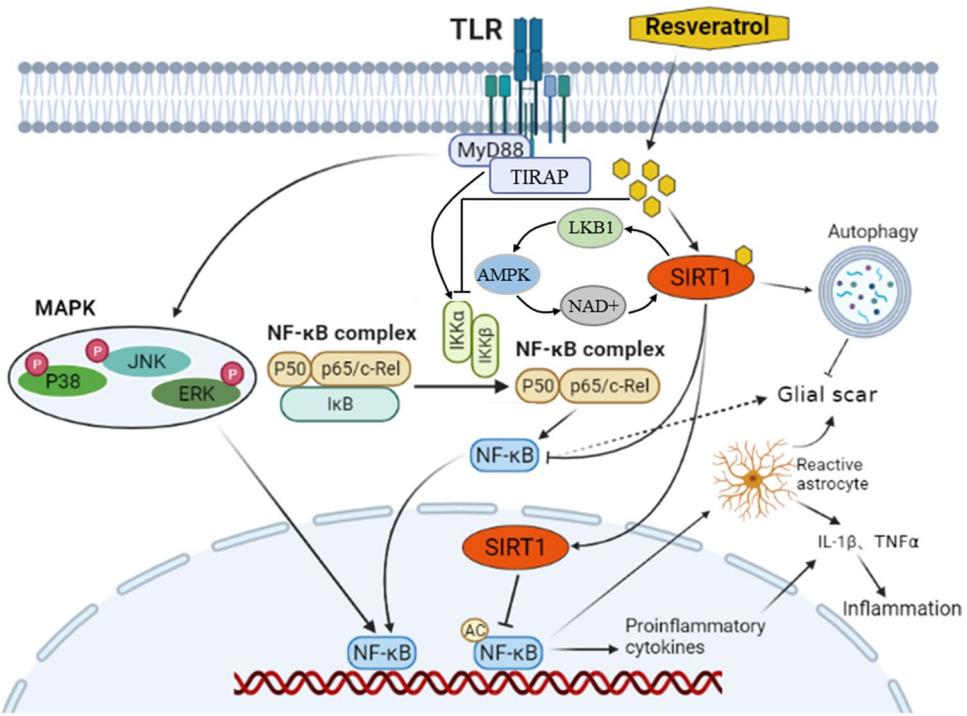

Fig. 4 The potential regulatory mechanism of resveratrol in SCI may involve the NF-κB, TLR, AMKP and MAPK signaling pathways. TLR recruits the toll-interleukin-1 receptor domain containing the adaptor protein on the cell membrane and subsequently promotes the recruitment of MyD88, which phosphorylates IKK with IκBα and IκBβ, leading to the activation of NF-κB. The NF-κB pathway can also be indirectly activated by activating the MAPK pathway. Resveratrol can inhibit IKK activity and thus inhibit the NF-κB pathway. Resveratrol may also enhance the expression of SIRT1 and AMPK. AMPK activation increases the NAD + /NADH ratio and triggers downstream processes, whereas SIRT1 acts as an anti-inflammatory NAD^+-dependent deacetylase by directly deacetylating NF-κB subunits such as p65 and directly interacts with RelA/p65 to inhibit NF-κB transcription. TLR, toll-like receptor; TIRAP, TIR functional region adaptor protein; AMPK, adenylate activated protein kinase; MAPK, mitogen-activated protein kinase; SIRT1, sirtuin 1; MyD88, myeloid differentiation primary response gene 88

conserved and involved in neuronal cell differentiation, neuro-inflammation, and axon regeneration in SCI [152]. Multiple studies have confirmed that the Notch signaling pathway plays an important role in secondary SCI recovery, including axon regeneration and neuro-inflammatory stimulation [153, 154]. The Notch pathway is an important regulator of neuro-inflammation that can regulate T cell and M1 polarization and further inhibit neuro-inflammation [155]. In a mouse SCI model, resveratrol administration inhibited neuro-inflammation and promote autophagy by inhibiting the Notch signaling pathway, thus promoting axon regeneration and nerve function recovery [156]. In addition, the Nrf2 signaling pathway is a cellular antioxidant pathway, and its expression protects cells from hypoxic damage [157]. Other studies have found that the Nrf2 signaling pathway plays an important role in SCI [158]. Damage caused by oxidative stress plays a crucial role in SCI, and cellular oxidative stress activates the Nrf2 pathway [159]. Kesherwani et al. found that resveratrol administration (50 μM) to treat a rat model of SCI significantly changed the expression of lipid peroxidase (LPO), reduced glutathione (GSH), superoxide dismutase (SOD), protein carbonyl (PC), mitochondrial ATP content, and mitochondrial Ca^{2+} content by increasing the translocation of Nrf2 in the nucleus. Thus, resveratrol plays a protective role by alleviating oxidative damage and protecting mitochondrial function [95]. These studies suggest that resveratrol regulates the recovery process after SCI through a variety of signaling pathways (Table 2).

Potential Value of Resveratrol in the Treatment of SCI

The potential mechanism of action of resveratrol is highly mature. In recent years, a large number of studies have found that the biological function of resveratrol has a significant therapeutic effect on experimental SCI. In vivo experiments showed that resveratrol administered intravenously 30 min before ischemia induction (10 mg/kg) protected neurons in gray matter by limiting white matter damage and reducing the mechanism of oxidative stress and apoptosis, thus demonstrating the protective effect of resveratrol [18, 160,

Table 2 Effects and mechanisms of resveratrol and related signaling pathways in spinal cord injury

Signaling pathway	Mechanism	Effects	References
PI3K/Akt/mTOR	p-PI3K↓, p-Akt↓ → mTOR-ULK1↓ → Bcl-2↑, caspase-3↓	Activate autophagy and inhibit apoptosis of nerve cells	[108, 125]
NF-κB	SIRT1↑, AMPK↑ → NF-κB↓ → IL-β↓, TNF-α↓	Promote autophagy, inhibit inflammation, inhibit neuronal apoptosis, and promote the recovery of motor function	[22, 65, 149]
Wnt/β-catenin	Inhibition of Wnt/β-catenin activation	Inhibit cell apoptosis, promote axon regeneration and nerve function recovery	[151]
Nrf2	Activate Nrf2	Inhibit oxidative stress	[95]
Notch	Inhibition of Notch activation	Inhibit neuro-inflammation, promote axon regeneration and nerve function recovery	[156]

161]. In a subsequent study, a clinically relevant model of traumatic SCI in rodents was used to study the intraperitoneal administration of resveratrol immediately after injury (100 mg/kg), which was found to reduce oxidative stress and nerve cell apoptosis and promote nerve function recovery by enhancing autophagy. Resveratrol inhibits lipid peroxidation and increases superoxide dismutase [21, 74, 122]. Other mechanistic studies involving in vitro and transverse models of SCI confirmed the therapeutic potential of resveratrol in improving SCI-related comorbidities. For example, resveratrol improved mitochondrial morphological changes by activating the Nrf2 pathway and inhibiting the expression of iron death-related proteins and ions in vitro, thus promoting functional recovery after SCI [162]. Resveratrol plays anti-inflammatory and antioxidant roles in secondary SCI. Resveratrol can regulate the expression of injury-related factors by inhibiting inflammatory signaling pathways and reducing the materialization of inflammatory responses through its anti-inflammatory properties, impeding astrocyte-mediated inflammatory responses and reducing the formation of glial scars, thereby promoting SCI repair [81, 163]. In addition, resveratrol regulates the AMPK/mTOR signaling pathway to improve neuroprotective function after SCI [66]. However, current research on the use of resveratrol as an SCI treatment strategy has mainly been carried out in rodent hypoxic-ischemic or contusion SCI models. These findings provide some guidance for future clinical research. However, its specific role in clinical treatment should be elucidated in future studies.

Future Expectations

The efficacy and mechanism of resveratrol therapy in SCI have been widely discussed. There is an urgent need to determine how resveratrol can be linked to the corresponding leading-edge therapeutic approaches in SCI. We described several ways in which resveratrol can be used in the hope of stimulating new ideas and research.

Drug Delivery Systems

Resveratrol has some limitations, such as a short biological half-life, extensive first-pass metabolism, chemical instability, and poor water solubility. A drug delivery system is a technical system that regulates the spatial, temporal, and dose distributions of drugs in an organism. Their purpose is to deliver the drug to the injured site and release it continuously to enhance the efficiency of drug administration, improve therapeutic effects, and reduce side effects [164]. Several nanomaterials, such as chitosan, liposomes, and polymer nanoparticles, can encapsulate resveratrol and increase its solubility in water to improve the efficiency of use [165]. Jiang et al. designed a plasma-complex-functionalized biodegradable manganese-doped silicon dioxide nanodrug system (PMMSN) with silica nanoparticles with an excellent ability to cross the blood-brain/blood-spine barrier at its core [166]. The system is loaded with resveratrol, which effectively reduces the size of resveratrol particles through the spatial limiting effect of nanoscale pores, disperses insoluble drugs in an amorphous form, and delivers more resveratrol to the spinal cord through the blood-spinal barrier (BSCB). In the SCI environment, ROS can be cleared by the slow release and long cycle effects of the drug, while alleviating neurotoxicity. It also reduces inflammation and plays a neuroprotective role. In vivo experiments further confirmed that the PMMSN-resveratrol nanoparticles effectively aggregated at the lesion site under external stimulation, promoted the transformation of M2 macrophages, and reduced the recruitment of M1 macrophages, thus effectively treating SCI by limiting the inflammatory response [167]. In addition, Li et al. designed chitosan-modified hollow manganese dioxide nanoparticles (CM) to deliver resveratrol and help it pass through the BSCBS. In vitro experiments at the cellular level have shown that CM-resveratrol can treat SCI by reducing oxidative stress, inflammation, and neuronal apoptosis [168]. Exosomes are lipid-bound extracellular vesicles with good lipid solubility and can easily cross the blood-brain barrier [169, 170]. Exosomes can carry drugs and deliver them to damaged sites, thereby improving drug solubility and

stability [171]. Yue et al. wrapped resveratrol in exosomes and verified in vivo that exosomes enhanced the stability of resveratrol and helped it cross the blood-brain barrier, thus maintaining local drug concentration in the spinal cord of rats after SCI. This resulted in a greater degree of enhanced neuronal survival and increased autophagy while reducing apoptosis [100]. It is important to note that recovery from SCI is typically a chronic process that can be controlled by the long-term administration of drugs, which is made possible by the drug delivery systems.

Current and Future Trends in Resveratrol Research

Basic research on resveratrol is well established; however, large multicenter clinical trials are lacking, and the exact effective or optimal dose, safety (side effects), and feasibility have not been determined. Future studies should focus on large-scale clinical and pharmacological studies to further explore the specific mechanism of resveratrol in SCI and strive to find sufficient medical evidence for the use of resveratrol in SCI.

Conclusion

Preclinical studies have shown that resveratrol has a significant therapeutic effect in SCI. It plays an antioxidant role, regulates the autophagy signaling pathway, protects the BSCB, alleviates apoptosis after injury, and alleviates glial scar formation via various mechanisms. It can also downregulate the expression of injury-related factors and inhibit inflammatory pathways to inhibit or relieve inflammatory responses, thus playing a neuroprotective role and promoting the recovery of nerve function after SCI. The beneficial effects of resveratrol have been demonstrated in a variety of animal models. However, due to the lack of sufficient clinical trial evidence, several questions need to be evaluated in greater depth before transitioning to clinical practice. First, most current research on resveratrol in the field of SCI is still at the cellular or rodent stage. Second, although we have a basic understanding of the relationship between resveratrol and SCI, the specific mechanism of action of resveratrol in SCI remains unclear. Finally, the clinical relevance of the previous findings in animal models of SCI remains unclear. However, with large-sample studies, multi-center clinical trials, targeted controlled release, and other pharmaceutical technologies, resveratrol is expected to become a new generation of drugs to treat SCI.

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Declarations

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