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Resveratrol Can Attenuate Astrocyte Activation to Treat Spinal Cord Injury by Inhibiting Inflammatory Responses

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Abstract

Several preclinical and clinical studies have attempted to elucidate the pathophysiological mechanism associated with spinal cord injury. However, investigations have been unable to define the precise related mechanisms, and this has led to the lack of effective therapeutic agents for the condition. Neuroinflammation is one of the predominant processes that hinder spinal cord injury recovery. Resveratrol is a compound that has several biological features, such as antioxidation, antibacterial, and antiinflammation. Herein, we reviewed preclinical and clinical studies to delineate the role of toll-like receptors, nod-like receptors, and astrocytes in neuroinflammation. In particular, the alteration of astrocytes in SCI causes glial scar formation that impedes spinal cord injury recovery. Therefore, to improve injury recovery would be to prevent the occurrence of this process. Resveratrol is safe and effective in the significant modulation of neuroinflammatory factors, particularly those mediated by astrocytes. Thus, its potential ability to enhance the injury recovery process and ameliorate spinal cord injury.

Keywords Resveratrol · Spinal cord injury · Inflammation · Astrocyte · Glial scars

Introduction

When any part of the spinal cord is injured, it causes either permanent loss or reduction of physical function below the damaged area [1]. According to present data, the annual incidence of spinal cord injury (SCI) is approximately 54 cases per million people in the United States, or about 17,810 new SCI cases each year [2]. SCI profoundly imperils the physiological systems, such as cardiovascular and immune systems [3]. The clinical complications of SCI include urinary tract infections, autonomic dysreflexia, sudden hypertension, and other symptoms caused by neuroinflammation [4–7]. Although SCI is a severe condition, its complete remedy is still lacking [8] because of the complex injury mechanisms. Neuroinflammation is not the only basis of secondary SCI but also one of the main reasons underlying the impediment process to SCI repair [9].

Neuroinflammatory responses in the secondary SCI can induce a series of cellular and molecular events, including activation of microglia/astrocyte, infiltration of macrophages from peripheral blood [10], imbalance of proinflammatory and antiinflammatory responses, abnormal mitochondrial activity, oxidative stress [11], abnormal protein aggregation, and free radical toxicity. Inflammasomes are closely related to neuroinflammation [12]. Inflammasomes are large multiprotein complexes that mediate neuroinflammatory responses [13]. Classical inflammasomes are composed of pattern-recognition receptors (PRRs), the adaptor protein known as apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC), and the effector protein, pro-caspase-1 [14–16]. Pyrin domain-containing related nod-like receptor protein family (NLRP) is a sensor of inflammasomes [17]. The damage-associated molecular patterns (DAMPs) and adenosine triphosphate (ATP) triggers the NLRP2. Moreover, the human astrocytes express the NLRP2 [18]. Activated NLRP2 recruits ASC and pro-caspase-1. During the

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recruitment process, the complex oligomerizes and assembles to NLRP2 inflammasome. After central nervous system (CNS) injury, especially SCI, ATP released by apoptosis–activated astrocytes lead to inflammatory responses and induces the assembly of the NLRP2 inflammasomes. NLRP2 inflammasome cleaves the pro-caspase-1 and secretes caspase-1, which triggers interleukin-1β (IL-1β) to produce mature IL-1β.

Nuclear factor kappa-B (NF-κB), a typical pro-inflammatory signaling pathway, is closely related to the inflammatory response. In secondary SCI, neuroinflammation triggers the activation of the NF-κB signaling pathway through the classical pathway. The activated NF-κB signaling pathway expresses immature IL-1β, with caspase-1 modifying it to mature IL-1β and contributing to inflammatory responses. Presently, some glucocorticoids are commonly used in the clinic to prevent this mechanism of neuroinflammation caused by secondary SCI. However, long-term clinical use of these agents diminishes their effectiveness, coupled with significant side effects [19]. Therefore, modern interventional agents having minimal to no side effects concomitant with favorable therapeutic effects are needed.

Resveratrol (RSV), as a component of traditional Chinese medicine, is a natural polyphenol and is present in grapes, berries, peanuts, and wine. It has characteristics of antiproliferation, antiangiogenesis, antiinflammation, and antioxidation [20–22]. RSV can scavenge the generation of free radicals, inhibit lipid peroxidation, and regulate the activities of oxidation-related enzymes. Studies have shown that RSV can regulate the F1 subunit of ATP synthase [23] and reactive oxygen species (ROS) levels [24]. ATP is closely associated with the activation process of NLRP2 in astrocytes. In addition, RSV can effectively inhibit the activation of the NF-κB signaling pathway by suppressing the activity of inhibitor protein, κB kinase (Iκκ) [25]. RSV can also reduce ATP production and ROS levels to hinder the formation of NLRP2 inflammasome in astrocytes. Further, RSV can inhibit the production of pro-IL-1β by repressing the NF-κB signaling pathway. These inhibitory effects can reduce the occurrence and development of inflammatory response after SCI and accelerate the repair process.

Inflammatory Response After SCI

SCI neuroinflammatory response is relatively complex and encompasses the interaction between the nervous and immune systems. The activation of inflammasomes and inflammatory signaling pathways is a vital factor that causes the over-activation of astrocytes. In addition, some risk-related factors can bind to receptors on astrocytes and lead to their activation.

The Mechanism of Inflammatory Response

Inflammation is a defensive response to stimuli characterized by redness, swelling, fever, and pain. Generally, inflammation is beneficial for the human body; however, over-inflammation can damage tissues of the body to aggravate the disease. Inflammation in the brain and spinal cord is neuroinflammation. The definition of neuroinflammation is broad, as it includes two complex fields: nervous and immune systems [26]. Neuroinflammatory response mediates the expressions of cytokines, chemokines, secondary messengers, and ROS. Most of these factors come from microglia and astrocyte in the CNS. In the wake of CNS injury, the primary stage of neuroinflammation has a positive effect. During this stage, the inflammatory response triggers the immune response to play a protective role. When neuroinflammation develops to the second stage (i.e., chronic stage), instigation of cells of the CNS arises, resulting in aggravated inflammatory factors that impact the process of injury repair. Several neurodegenerative diseases (like Alzheimer's disease, Parkinson's disease, traumatic brain injury (TBI), and secondary SCI) have a close association with the chronic developmental stage of neuroinflammation [27, 28].

In a physiological state, microglia, a type of permanent immune cell in the brain, is an ineffective phenotype [27]. There are some risk signal factors in the microenvironment under pathological conditions. DAMP is a risk-related factor released by cells or tissues after receiving external stimuli. The non-self-factors or pathogenic microorganisms in the microenvironment are the pathogen-associated molecular patterns (PAMPs). PRRs are responsible for sensing PAMPs and DAMPs [29]. The main subfamilies of PRRs include toll-like receptors (TLRs), nod-like receptors (NLRs), RIG-like receptors (RLRs), AIM2-like receptors (ALRs), and C-type lectin receptors. NLRs form inflammasomes [29, 30]. The three known NLRs in the CNS are NLRP1, NLRP2, and NLRP3 [31–33]. Once PRRs on the microglia detect either DAMPs or PAMPs, microglia immediately switch to activated phenotype, phagocytized injury-related factors, and forms elements that affect astrocytes and neurons, leading to neuroinflammation. In addition, astrocytes and neurons can identify some DAMPs and PAMPs to mediate neuroinflammation. These neuroinflammatory responses could further transmit to the immune system and promote tissue repair. In most cases, these inflammatory responses are transient and would disappear once infection or injury is repaired [26].

The persistent neuroinflammatory response is an indication of physiological mechanisms not being controlled. This leads to the over-activation of glial cells and neurons that produces neurotoxic factors, which aggravates the

disease state. The accumulation of signal and endogenous factors (such as inflammasome polymers) can cause a persistent neuroinflammatory response. Infectious signaling factors (such as Gram-negative bacteria, viral double-stranded RNA, and bacterial lipopolysaccharide) are identified by TLRs, with endogenous signaling factors (including IL-1, tumor necrosis factor (TNF), and ATP) detected by NLRs in the PRR family. Presently, most CNS cells express TLRs. TLRs pronounced entirely in the microglia enhance its abilities to monitor the microenvironment. Astrocytes and neurons also express TLRs. Under pathological conditions, astrocytes may upregulate TLR3 [34], TLR2, and TLR4 [34, 35] expressions. These recognized PRRs stimulate the activation of the signal transduction pathway by regulating transcription and posttranscription processes. Notably, TLRs either recruit adapter protein MyD88 or send signals through the TRIF-dependent pathway, leading to transcription of downstream κB kinase and mitogen-activated protein kinase (MAPK). Activated downstream kinases regulate various inflammatory signaling pathways, including NF-κB and activator protein 1 (AP-1). These inflammatory signaling pathways highly express the precursors of interleukin and interferon (such as pro-IL-1) to exacerbate the occurrence of inflammatory response. These factors need further processing and modification to play their role, and caspase-1 is significant in this process. Activated inflammasomes express caspase-1, and NLRs play a vital role as the upstream factors of inflammasomes assembly and activation. NLRs recognize DAMPs and recruits ASC and pro-caspase-1 to further assemble into inflammasomes. Caspase-1 combines with precursors of interleukin and interferon to co-express inflammatory factors [36]. Both TLRs and NLRs cooperate to control immune response dysfunction (Fig. 1). This immune response is usually a feed-forward loop, i.e., the ultimate expressed inflammatory factors are delivered back to the initial recognition receptor as risk signal factors. This further aggravates the process of inflammatory responses. Although some inflammatory responses have beneficial effects and are closely related to the tissue repair process, uncontrolled inflammatory reactions can trigger secondary damage and hinder this repair process.

Astrocyte Activation and Inflammasome Formation

Astrocytes are abundant and complex in the mammalian brain, accounting for about 19%–40% of human brain cells [37]. Mature astrocytes have complex structures that interact with synapses to support neurons. CNS injury causes activation of astrocytes. Reactive astrocytes show alterations of morphology and metabolism, including cellular hypertrophy and upregulated expressions of glial fibrillary acidic protein (GFAP) and Nestin.

DAMPs stimulate human astrocytes to generate NLRP2 inflammasomes, which further induces inflammatory responses to form caspase-1 and IL-1β. In addition, NLRP2 inflammasome is significantly involved in immune response and disease occurrence. Therefore, NLRP2 inflammasome, as the core of inflammatory response, may provide a new target for the treatment of various inflammatory diseases. ATP is a representative of DAMP released from injured or dead cells after tissue trauma and can stimulate the activation of

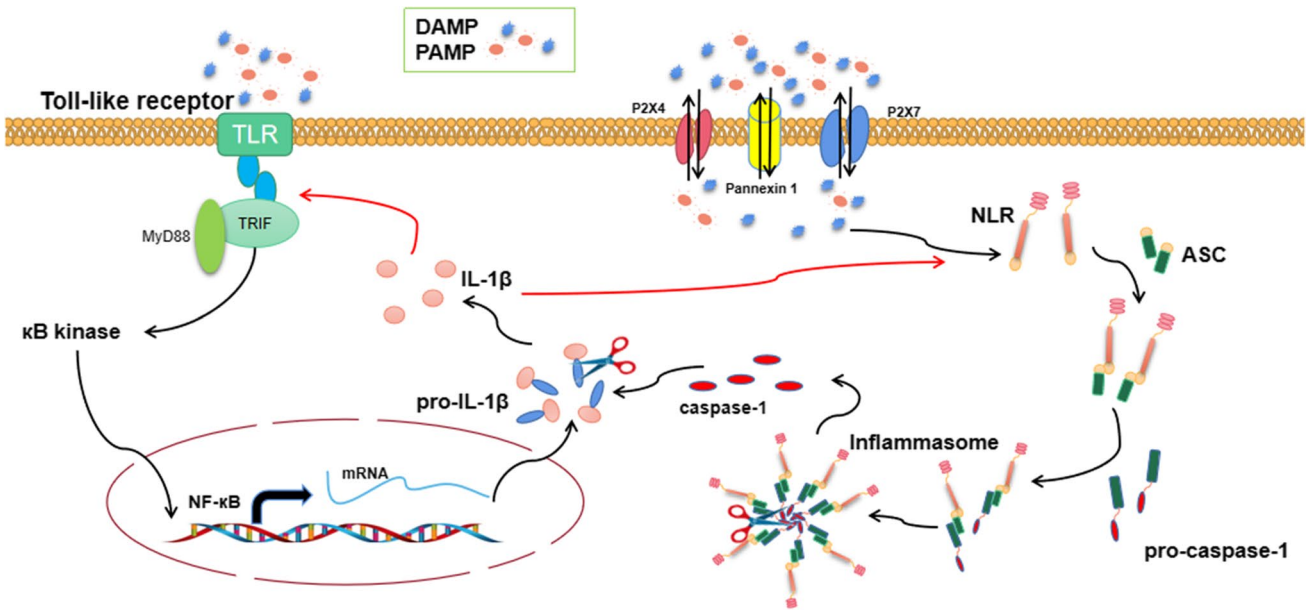

Fig. 1 Combined TLRs and NLRs regulate inflammation

inflammasomes [36]. Studies have demonstrated the activation of several NLRs family proteins to be closely associated with the P2X7 receptor and Pannexin 1 channel [38]. Recombinant purinergic receptor P2X, ligand-gated ion channel 7 (P2X7), and Pannexin 1 of membrane proteins are ATP gating proteins [39]. A recent study evidenced that the interaction between NLRP2 inflammasome in astrocytes and P2X7 receptor and pannexin-1 channel protein on the cell membrane can accelerate inflammatory response process and promote caspase-1 expression [32, 36]. In addition, the P2X4 receptor may interact with these two gating proteins and control ATP to stimulate cells [40]. However, there is limited information regarding the expression and stress response of NLRP2 inflammasome in astrocytes after tissue trauma. The activation of NLRP2 inflammasome in astrocytes is related to P2X4/P2X7/Pannexin 1 channel; nonetheless, the specific molecular mechanism remains to be clarified.

After SCI, reactive astrocytes not only express NLRP2 inflammasomes but also migrate and gather at the center of the lesion, which helps repair the damaged tissue. However, excessive cell accumulation can cause scar formation and eventually create a glial scar. A glial scar can inhibit axonal regeneration and intricate injury recovery. Studies have shown that reactive astrocytes in glial scars secrete chondroitin and keratin sulfate proteoglycans, which are involved in inhibiting axonal regeneration [41]. Also, signal transducer and activator of transcription-3 (STAT3) was found in reactive astrocytes after SCI and participated in cell migration and aggregation processes [42].

In the wake of SCI, astrocytes change from primitive state to reactive state to scar-forming astrocytes, which is usually irreversible (Fig. 2). Among them, neuroinflammation caused by reactive astrocytes is beneficial to injury recovery to a certain extent. However, glial scars affect injury recovery. Thus, after SCI, inhibiting the occurrence and development of reactive astrocytes before glial scar formation can influence the injury recovery process.

RSV Can Attenuate Neuroinflammation

Several studies have reported the immense potential of RSV in the treatment of inflammatory diseases. RSV can act on multiple signaling pathways to inhibit inflammatory responses. For instance, RSV degrades intracellular and extracellular risk-related factors and inhibits κB kinase activity. In the wake of SCI, RSV mitigates inflammatory responses by inhibiting the activations of inflammasomes and NF-κB, thereby creating a conducive microenvironment for axonal recovery.

The Biological Functions of RSV

In recent years, RSV has gained the attention of scientists due to its beneficial outcomes in infectious, neurodegenerative, metabolic, and autoimmune diseases, while relieving aging and prolonging life (Table 1). RSV can reduce the concentration of low-density lipoprotein and inhibit cyclooxygenase activity on the cardiovascular system [59, 60]. More so, RSV can reduce oxidative stress via its regulation of ROS [61]. For instance, He LN et al. [62] showed that RSV could inhibit the oxidative stress of rat pulmonary artery endothelial cells under hypoxia by blocking hypoxia-inducible factor 1α (HIF-1α)/Nicotinamide Adenine Dinucleotide Phosphate Oxidase 4 (NOX4)/ROS signaling pathway. More so, RSV inhibited cancer growth by scavenging free radicals on the cell surface. Specifically, RSV induced the death of human ovarian cancer cells by inhibiting Notch1/phosphatase and tensin homolog deleted on chromosome ten (PTEN)/protein kinase B (Akt) signaling pathway mediated by ROS [63].

Concerning neuroinflammatory responses, RSV can prevent these reactions by inhibiting the activation of the

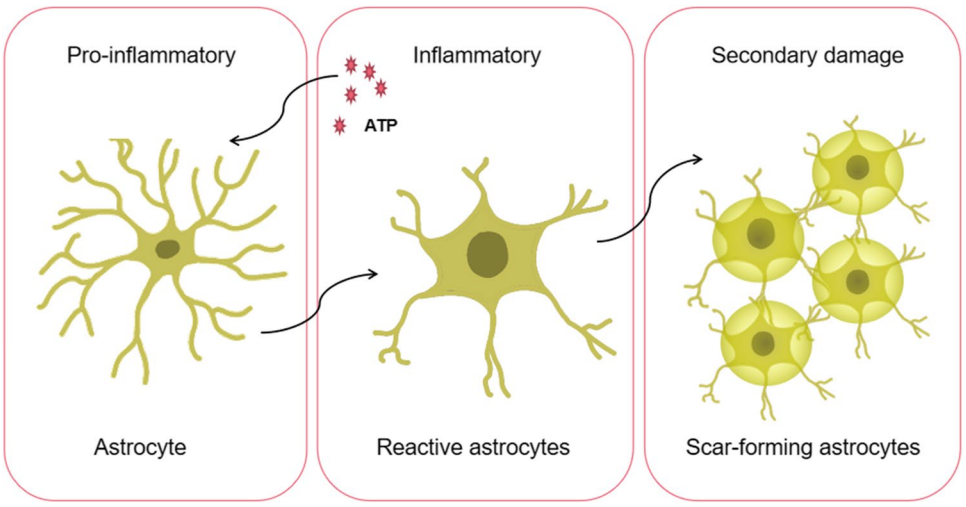

Fig. 2 The alteration of astrocytes from primitive state to reactive state to scar-forming astrocytes after SCI

inflammatory signaling pathway, such as NF-κB, or reducing the formation of inflammatory factors. Some studies have analyzed the interaction between RSV and vital enzymes, including Iκκ, cyclooxygenase 2 (COX-2), and TNF receptor-associated factor-associated NF-κB activator binding kinase 1 (TBK1), in the TLR4 pathway [64], which showed the molecular mechanism of RSV in regulating inflammation. Also, studies have revealed that RSV could inhibit inflammation by regulating several inflammatory pathways: TLR4/NF-κB/STAT3, TLR4/Akt/ forkhead box protein O1 (FoxO1), nuclear factor erythroid 2-related factor 2 (Nrf2)/TLR4/NF-κB, and sirtuin1 (Sirt-1)/FoxO1 [65–68]. All these studies evidence RSV potential as an interventional agent for the treatment of inflammatory-associated diseases.

Studies are currently exploring the positive role of RSV in bacterial infections. For instance, Al Azzaz J et al. [69] found RSV to promote heterogeneous phagocytosis and enhance the clearance of two invasive bacteria (*Salmonella typhimurium* and invasive *Escherichia coli*). Similarly, RSV has extensive antiviral activities, mainly in Epstein-Barr virus (EBV), HIV infections, and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV)) [70–72]. In particular, RSV suppressed nucleocapsid (N) protein expression, leading to the inhibition of MERS-CoV infection. While the biological absorption rate of RSV in clinical trials has been low, the biological efficacy of RSV derivatives and nano-scale RSV are immensely high [73], implying that RSV effectiveness in the clinical setting may be pronounced following modification.

RSV Attenuates Inflammatory Responses of Diseases

The occurrence of inflammation further induces various diseases, including atherosclerosis, rheumatism, rash, Alzheimer's disease, tumor, and various secondary symptoms [74–76]. RSV has diverse biological effects and is less toxic to the body [77]. It has been employed in various medical conditions, such as inflammatory bowel disease (IBD), nervous system inflammation, eye inflammation, and gynecological inflammation (Table 2).

The antiinflammatory effects of RSV have been attributed to the cascade effects of disparate mechanisms, which lead to the inhibition of both the inducer and intermediate enzyme that mediate the occurrence of inflammatory responses and eventually hindering the production of inflammatory factors. Generally, DAMPs and PAMPs trigger inflammation. RSV curtails DAMPs by scavenging reactive substances and ROS through its antioxidative action [94, 95], while it reduces PAMPs via its antibacterial effect [96, 97], thereby decreasing the incidence of inflammatory responses. Additionally, TLRs and pro-inflammatory cytokines, such as TNF and IL-1, trigger the classical pathway that instigates p65 activation [98]. Noteworthy is that RelA regulates the expression of pro-inflammatory and cell survival genes, and its

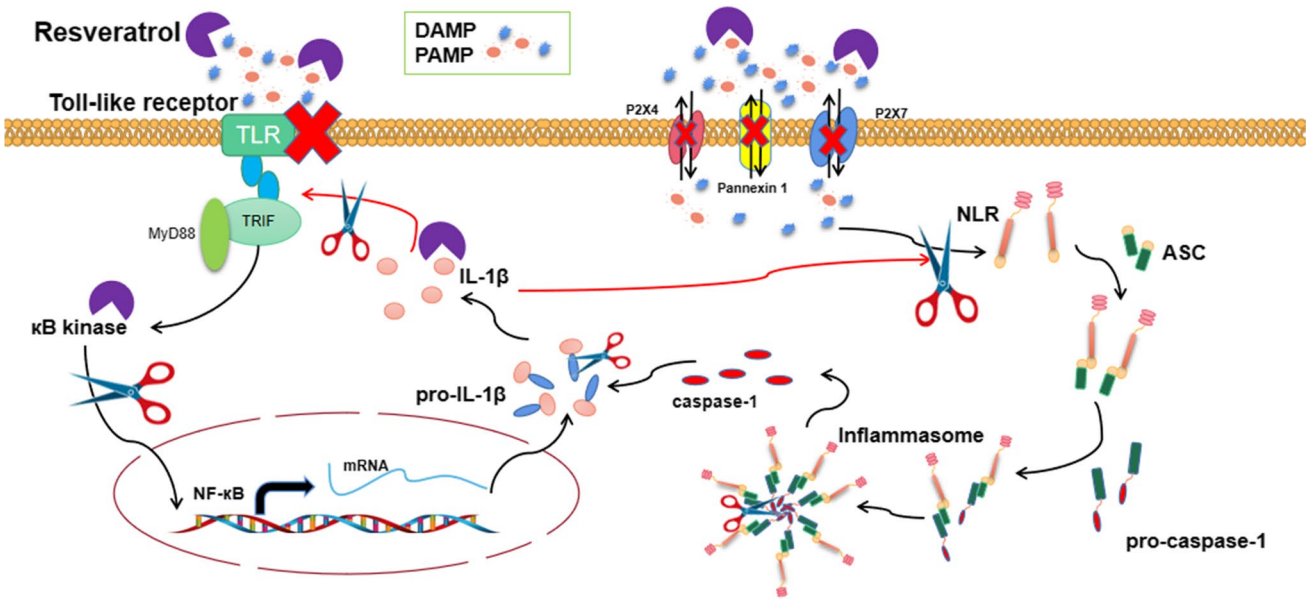

Fig. 3 RSV inhibits the inflammatory response through multiple pathways. RSV hinders assembly and stimulation of TLRs by oxidizing degradation of risk factors associated with the activation of inflammatory responses, DAMPs and PAMPs, such as ATP and ROS. Furthermore, the inhibition of DAMPs and PAMPs prevents the activation of P2X4, P2X7, and Pannexin 1, thereby indirectly inhibiting the activation of inflammasomes, NLRP2. In addition, RAV is an inhibitor of κB kinase activation, which blocks the NF-κB signaling pathway by suppressing p65 activation. RSV significantly reduces the inflammatory response and repress astrocyte activation through the above-mentioned mechanisms

Table 1 Application of RSV in various diseases

Disease categories	Diseases	Species	Routes and doses	Results	Biological functions of RSV	References
Autoimmune diseases	Type 1 diabetes (T1D)	Humans (N=13)	Oral/ RSV capsules (1 g/d)	RSV showed strong antidiabetic and antioxidant effects by significantly decreasing fasting blood sugar (FBS) and hemoglobin A1c (HbA1c) in patients with T1D.	Antidiabetic Antioxidant	[43]
	Systemic lupus erythematosus (SLE)	BALB/c inbred strain of mice (N=100; pristane-induced SLE murine model)	Intraperitoneal injection/ RSV (25 mg/kg; 50 mg/kg) and bio-enhancer piperine (2.5 mg/kg; 5 mg/kg)	The combination of RSV and piperine significantly reduced the expression of related factors of SEL, but did not affect the level of antibodies.	Antioxidant Anti-inflammatory	[44]
	Inflammatory bowel diseases (IBD)	C57BL/6 WT and Nrf2$^{-/-}$mice (induced by dextran sulfate sodium); Human colon cancer LS174T and Caco2 cells	Intraperitoneal injection/ Imine RSV Analog 2-Methoxyl-3,6-Dihydroxyl-IRA (C33); RSV (200 mg/kg)	The derivative C33 modified by RSV showed stronger anti-inflammatory effect, and effectively improved IBD by activating Nrf2 signaling pathway *in-vivo* and *in-vitro*.	Anti-inflammatory	[45]
	Autoimmune encephalomyelitis (AE)	C57BL/6 mice	Intraperitoneal injection/ RSV (10 mg/kg; 25 mg/kg; 50 mg/kg)	RSV reduced oxidative stress and inflammation in EAE mice to protect the integrity of blood-brain barrier.	Antioxidant Anti-inflammatory	[46]
Neurodegenerative diseases	Alzheimer disease (AD)	Human umbilical cord-derived mesenchymal stem cells (hUC-MSCs); Tg2576 Swedish transgenic AD mice	Passage 3 hUC-MSCs were cultured in media with 2.5 μM RSV, and intravenously delivered the suspension of hUC-MSCs to AD mice (1×106 cells/ 200μl saline solution)	RSV-treated hUC-MSCs showed a significant neuroinflammatory inhibitory effect that inhibited MAPKs, p38, and other signal pathways in AD mice by interacting with astrocytes and microglia.	Antioxidant Anti-inflammatory	[47]
	Parkinson disease (PD)	Mice (N=24; induced by neurotoxin MPTP)/ Human neuroblastoma cell line SH-SY5Y	Intragastric administration of RSV (50 mg/kg) for mice/ SH-SY5Y were cultured in media with 500 mM MPTP and 50 mM RSV	RSV promoted the expression of miR-129, increased the number of TH+ cells, and inhibited the expression of MALAT1 and SNCA by regulated MALAT1/miR-129/SNCA signaling pathway, thus protecting neurons and preventing PD.	Neuroprotective	[48]
	Amyotrophic lateral sclerosis (ALS)	ALS-MSCs (BM-MSCs derived from ALS patients)	BM-MSCs were cultured in media with 1 μM RSV for 12 hours	RSV activates SIRT1/AMPK signaling pathway of ALS-MSCs to improve the functional recovery effect of ALS-MSCs.	Neuroprotective Anti-inflammatory Anti-apoptosis	[49]
Cancer	Lung cancer (LC)	Human small-cell LC (SCLC) H446 cell line	H446 cells were cultured in media with RSV (40 μg/ml)	RSV inhibited the survival of human SCLC H446 cells, and promoted apoptosis by inhibiting PI3K/Akt/c-Myc signaling pathway.	Anticancer Antioxidant	[50]
	Pancreatic cancer (PC)	Human pancreatic stellate cells (PSCs)/ KPC mice	PSCs were cultured in media with 50 μM RSV/ KPC mice were treated with 50 mg/kg RSV	RSV blocked the interaction between PSCs and PC cells, and thus inhibited malignant proliferation of PC cells by inhibiting the activation of hypoxia-induced PSCs.	Anticancer Antioxidant	[51]
	Colon cancer	Human colon cancer cell lines SW480 and SW620/ BalB/c (nu/nu) mice	SW480 and SW620 cells transfected with siAKT1 were established in EMT model by using epidermal growth factor. (50 ng/ml)/ Tail vein injection EMT to BalB/c (nu/nu) mice/ Intragastric administration of RSV for mice (150 mg/kg)	RSV inhibited malignant colon cancer by reversing Epithelial-Mesenchymal Transition (EMT) via the AKT/GSK-3β/Snail signaling pathway.	Anticancer Antioxidant	[52]
	Breast cancer	MDA231 cells/ Nude mice	MDA231 cells were cultured in media with RSV/ MDA231 cells were transplanted into the fat pad of nude mice breast/ Intraperitoneal injection of RSV (100 mg/kg)	RSV inhibited malignant MDA-MB-231 human breast cancer by reversing Epithelial-Mesenchymal Transition (EMT) via the TGF-β1 signaling pathway.	Anticancer Antioxidant	[53]

Table 1 (continued)

Disease categories	Diseases	Species	Routes and doses	Results	Biological functions of RSV	References
Cardiovascular diseases	Atherosclerosis (AS)	$ApoE^{-/-}$mice/ $CD4^+$T cells(from the spleen of C57BL/6 mice)	Intragastric administration of RSV (5 mg/kg) for mice/ $CD4^+$T cells were cultured in media with RSV (20, 40, 80 μM)	RSV effectively alleviated AS caused by HFD, concomitant with LPS in $ApoE^{-/-}$mice/ RSV inhibited the activation of $CD4^+$T cells.	Antioxidant Anti-inflammatory	[54]
	Hypertension	Spontaneously hypertensive rats (SHRs)	Intragastric administration of RSV (50 mg/kg) for rats	RSV attenuated the development of high blood pressure in SHRs by inhibiting the expression of Giα proteins.	Antioxidant	[55]
	Myocardial ischemia	C57BL/6J mice	Intragastric administration of RSV (320 mg/kg) for mice	RSV protected mouse heart injury induced by ischemia *in-vivo*, and NRCM injury induced by hypoxia *in-vitro* by regulating Sirt1/p53-mediated cell senescence, and inhibiting NLRP3 inflammasome activation.	Antioxidant Anti-inflammatory Anti-apoptosis	[56]
Infectious disease	*Helicobacter pylori*	clinical *H. pylori*l *G. mellonella* larvae	*H. pylori* strains were cultured in media with RSV (100 μL)/ *G. mellonella* larvae were injected with 10 μL of *H. pylori*	RSV derivatives significantly reduced the colony movement ability and biofilm formation of *H. pylori*.	Antimicrobial	[57]
	Staphylococcus aureus	*S. aureus*/ A549 human lung epithelial cells (ATCC CCL 185)	*S. aureus* strains were cultured in media with RSV/ ATCC CCL 185 were cultured in media with treated strain of *S. aureus*	RSV effectively inhibited the expression of Hla and alleviated the cell damage of ATCC CCL 185 co-cultured by bacteria.	Anti-apoptosis	[58]

activation promotes the assembly of inhibitors of NF-κB (IκB). The activation of the NF-κB signaling pathway typically occurs after Iκκ phosphorylates IκB [99]. RSV acts on the intermediate enzyme of the NF-κB signaling pathway to block the transmission of information by the inflammatory pathway. All these functions of RSV aid repress the instigation and development of inflammation. Moreover, studies have shown that RSV could improve autophagy [93] when inflammation occurs.

RSV Curtails Inflammasome Formation After Nervous System Injury

The inflammasome is a multiprotein complex that plays a vital role in the immune system. In general, the recognition of PRRs with PAMPs or DAMPs is the first step in triggering the development of neuroinflammation. Identified PAMPs or DAMPs by PRRs of the inflammasome leads to the recruitment and activation of caspase-1. Activated Caspase-1 can modify the precursor substances of IL-1 or IL-18 to form cytokines that cause an inflammatory response. Significant mitigation of the recognition of risk-related factors and PRRs can decrease inflammasome formation. Therefore, to obviate inflammation is to block the initial recognition mechanism.

The above evidence shows that the development of inflammatory responses requires the cooperation of TLRs with NLRs. The activation of TLRs can stimulate the NF-κB inflammatory signaling pathway, and NLRs activation can trigger inflammasomes. TLRs are present in a variety of cells and are often associated with inflammatory responses. Presently, there are ten different TLRs (TLR1-10) in human cells and twelve in mice [100]. Ahmad SF et al. [101] indicated that RSV could reduce the expression of TLRs/NF-κB/COX-related factors and improve the deterioration of neuroimmune diseases. In this study, RSV effectively downregulated the expressions of TLR2, TLR3, and TLR4. The inhibition of TLR2, TLR3, and TLR4 is a treatment strategy for various nervous system diseases, including neuroinflammation. For instance, Kwilasz AJ et al. [102] showed TLR2/TLR4 antagonists to effectively alleviate neuroinflammation and memory decline caused by experimental autoimmune diseases. The suppression of TLRs expression affects the activation of inflammatory pathways and the secretion of related cytokines, thereby curtailing the inflammatory response. Previous studies have shown RSV to repress the expression of NLRP3 inflammasome [56, 103]. However, the study did not show RSV to directly act on inflammasome, but rather through an indirect effect. The activation of inflammasome was caused by NLRs recognizing risk signaling factors. Therefore, a vital step in inflammatory signaling pathways and inflammasome activation may be the recognition of PRRs with risk-related factors. The discerning

Table 2 Application of RSV in the treatment of inflammatory diseases

Diseases	Species	Routes and doses	Results	References
Lung inflammation (PM-induced)	C57BL/6J mice	Mice were exposed to ambient PM, and treated with RSV (50 mg/kg; 100 mg/kg)	RSV inhibited the activation of NLRP3 inflammasomes, and the expression of related inflammatory factors, which improved lung inflammation and fibrosis	[78]
Skeletal muscle inflammation (obesity-induced)	C57/BL6 mice	Mice were fed with normal chow die (NCD) and high fat diet (HFD)-supplemented with 0.4% RSV (4 g/kg)	RSV improved inflammation by reducing macrophage recruitment, increasing M2 polar cell count, inducing Treg cell ratio, reducing M1 polar cell number, and downregulating the expression of pro-inflammatory cytokines	[79]
Secondary damage after SCI	Sprague Dawley rats/ PC-12 cells	SCI rats received RSV treatment via intraperitoneal injection (200 mg/kg)/ PC-12 cells were cultured in media with RSV (10 μM ~ 50 μM)	RSV inhibited NF-κB and p38MAPK signaling pathways, inhibited inflammatory responses, and upregulated miR-132 expression to improve polysaccharide-induced cell damage	[80]
Asthma-induced airway inflammation and remodeling	Sprague Dawley rats	Asthma rats received RSV via intraperitoneal injection (10 μmol/l; 50 μmol/l)	RSV reduced asthma-induced airway inflammation by inhibiting HMGB1/TLR4/NF-κB pathway	[81]
Non-alcoholic steatohepatitis (high-fat diet-induced)	Sprague Dawley rats	Rats were fed high-fat diet (HFD) with RSV (100 mg/kg)	RSV maintained intestinal barrier integrity, stability of intestinal microbial community, and inhibited intestinal inflammation to alleviate chronic steatohepatitis.	[82]
Diabetic nephropathy	HBZY-1 cells (the rat glomerular mesangial cell line)	HBZY-1 cells were cultured in media with RSV (5 μM; 10 μM; 20 μM)	RSV inhibited proliferation, accumulation of extracellular matrix, and cellular inflammation of lipopolysaccharide-induced HBZY-1 cells by blocking SphK1/S1P2/NF-κB signaling pathway.	[83]
Polycystic ovary syndrome (PCOS)	Humans	PCOS patients received 800 mg/day of RSV orally	RSV inhibited the expression of NF-κB signaling pathway-related factors, and reduced endoplasmic reticulum stress to inhibit the occurrence of inflammatory reactions, thereby exerting therapeutic effects on PCOS patients.	[84]
Radiation-induced brain injury	Wistar rats	Rats of radiation-induced brain injury received RSV by intraperitoneal injection (100 mg/kg; 250 mg/kg)	RSV significantly reduced oxidative stress response, and expressions of inflammation/ apoptosis-related factors to protect brain tissues	[85]
Spontaneous Ulcerative Colitis	Winnie mice	Winnie mice were treated with β-lactoglobulin-RSV nanoparticles (50 mg/kg)	The stability and solubility of RSV encapsulated in β -lactoglobulin nanospheres were enhanced, and the incidence of colonic inflammation was significantly reduced.	[86]

Table 2 (continued)

Diseases	Species	Routes and doses	Results	References
Skin inflammation (PM-induced)	Normal human epidermal keratinocytes	Cells were cultured in media with various concentrations of PM and RSV (0; 0.01 μM; 0.1 μM; 1 μM; 10 μM; 50 μM; 100 μM)	RSV alleviated inflammatory response in human keratinocytes by inhibiting the expression of pro-inflammatory factors, and PM-induced oxidative stress.	[87]
Age-related macular degeneration	ARPE-19 human retina pigment epithelial cells	Cells were cultured in media with RSV (10 μM)	RSV downregulated the expression of inflammatory and apoptotic factors, and other cytokines, thus inducing autophagy, promoting survival, and anti-inflammatory stimuli of ARPE-19 cells.	[88]
Retinal inflammation (diabetes-induced)	Human retinal vascular endothelial cells (HRVECs)	HRVECs were cultured in media with high glucose and RSV (1 μmol/L; 10 μmol/L)	RSVS inhibited the infectious metabolic memory and increased HRVECs viability by activating the SIRT1/ AMPK signaling pathway.	[89]
Cirrhotic inflammation (neurological sequelae)	CD-1 mice	Cirrhotic-induced mice received daily RSV through oral gavage (10 mg/kg)	RSV significantly reduced inflammatory signaling factors, effectively relieved cell damage caused by oxidative stress, and upregulated the expression of tight junction protein in CCl4-induced cirrhotic mice.	[90]
Experimental autoimmune encephalomyelitis (EAE)	C57BL/6 mice	EAE-induced C57BL/6 mice received RSV via intraperitoneal injection (100 mg/kg)	RSV attenuated neuroinflammatory in EAE by regulating key miRNAs involved in cell cycle progression and apoptosis in activated encephalitogenic T-cells.	[91]
Neonatal hypoxic-ischemic brain injury (HIBI)	Pups (from timed-pregnant ICR mice)	HIBI-induced mice received RSV via by intraperitoneal injection (100 mg/kg)	RSV reduced neuroinflammatory responses in neonatal HIBI by activating SIRT1 to inhibit HMGB1/TLR4/MyD88/NF-κB signaling pathway.	[92]
Neuropathic pain	Sprague Dawley rats	Rats constructed for neuropathic pain were treated with RSV by intraperitoneal injection (300 ug/day)	RSV reduced neuroinflammation and neuropathic pain in rats by inhibiting autophagy via downregulating the TREM2 signaling pathway.	[93]

of these injury factors by PRRs may further promote the inflammatory response that could lead to injury aggravation [104]. Also, RSV can directly act on these risk-related factors, resulting in the downregulated expression of these factors and significantly hindering the assembly process of inflammasomes (Fig. 3).

RSV Can Improve the Repair of SCI by Inhibiting Inflammatory Responses

The occurrence of inflammatory response is an inevitable secondary symptom of SCI. However, neuroinflammation has a two-way effect on SCI repair: positive inflammatory response is beneficial to tissue regeneration, while negative inflammatory response inhibits the injury repair process. In secondary SCI, the activation of glial cells and subsequent release of inflammatory factors and interferon accelerate neuronal death and induce vascular endothelial cells to express various cell adhesion and chemotactic molecules that attract more inflammatory factors [105]. The intensification of inflammatory response is the primary cause of secondary SCI and is also a considerable hindrance in the SCI repair process. Chronic inflammation instigates the over-activation of motor neuronal and glial cells that leads to CNS dysfunction and form scar tissue, which impedes the process of SCI repair. Hence, improving the immune microenvironment of the spinal cord during secondary SCI is one of the prime treatment goals [106]. It is, therefore, necessary to find an effective treatment that can inhibit the inflammatory response and promote SCI repair. Studies at the cellular level have shown extracellular vesicles of mesenchymal stromal cells filled with at the injured area of the spinal cord to significantly alleviate inflammatory response and inhibit glial scar formation [107]. Also, another study at the molecular level showed progranulin deficiency to promote neuroinflammation and apoptosis and aggravate SCI [108].

Currently, increased attention is being afforded to the considerable impact of Chinese medicinal extracts for neuroinflammation management induced by SCI. In particular, the antiinflammatory and antioxidative effects of RSV play an immense role in secondary SCI. Prior studies have shown RSV to hinder inflammatory response in SCI by repressing and triggering the NF-κB inflammatory signaling pathway and Sirt-1 signaling pathway, respectively [109]. Moreover, Menghay et al. [110] showed that RSV could regulate adenosine 5′-monophosphate-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) signaling pathway to improve neuroprotective functions after SCI. Another study also demonstrated that RSV promoted autophagy and recovery of motor neurons by regulating the Sirt-1/AMPK signaling pathway after SCI [111]. In recent years, study outcomes concerning the employment of RSV have been encouraging and have boosted its position as a potential interventional agent for alleviation of secondary SCI.

Conclusion

SCI is a neurological disease that is difficult to treat, and chronic neuroinflammation and glial scar formation aggravate its recovery process. Current investigations are predominantly focusing on the treatment of neuroinflammation. In the wake of SCI, astrocyte-mediated neuroinflammation occurs within a short time. Transient inflammatory response is conducive to injury recovery. However, excessive neuroinflammation provokes cells to secrete detrimental factors that promote the over-activation of reactive astrocytes and further transforms to scar-forming astrocytes. The formation of glial scar complicates SCI recuperation. Therefore, it is imperative to find novel treatment strategies that suppress this process and promote injury repair.

In recent years, biological functions (such as antiinflammation and antioxidation) of RSV have had significant treatment effects on SCI. Specifically, RSV can downregulate the expression of injury-related factors, prevent cells that inhibit the inflammatory pathway, and reduce the materialization of inflammatory reactions. Although the antiinflammatory effect of RSV has been evident in experiments, its specific action mechanism is yet to be clarified. Nonetheless, RSV can minimize the activity of inflammatory factors through its antioxidant effect, and inhibit inflammatory signaling pathways through its antiinflammatory properties, thereby hindering astrocyte-mediated inflammatory response, curtailing glial scar formation, and promoting SCI repair. Studies addressing the precise mechanism of this process would provide the molecular basis for RSV employment in treating SCI. Recent completed clinical trial investigations have shown the significant effects of RSV [112–114]. For example, clinical studies have evinced the effectiveness of high-dose RSV with no serious adverse effects [115, 116]. Although these studies did show the efficacy of RSV, more clinical investigations are needed for a better understanding of its safety in the clinical setting (Tab. 1 and 2).

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Data Availability I confirm that I have included a citation for available data in my reference section.

Declarations

Ethics Approval Not applicable.

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