REVIEW ARTICLE | Iranian Biomedical Journal 30 (2 & 3): 97-124 March & May 2026

Resveratrol in Combination Therapy: Mechanisms and Limitations of Resveratrol in Cancer, Regeneration, and Chronic Disease

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OPEN ACCESS

Article type: Review Article
Received: September 9, 2025
Revised: January 7, 2026
Accepted: January 31, 2026
Published online: February 2, 2026

How to cite:
Noori E, Rezaei R, Valiyari S, Rekabgardan M, Mohammadi P, Soleymani F, Sharif E, Jafari Z, Rezaee D, Hajighasemi F, Shams F. Resveratrol in Combination Therapy: Mechanisms and Limitations of Resveratrol in Cancer, Regeneration, and Chronic Disease. *Iran. Biomed. J.* 2026; 30(2 & 3): 97-124.

ABSTRACT

Resveratrol (RSV), a nonflavonoid polyphenol phytoalexin, has considerable therapeutic potential for managing chronic and acute diseases due to its anti-inflammatory, anti-cancer, antimicrobial, and antioxidant properties. It can help protect cells from free radical damage and modulate signaling pathways in the body to promote overall health. RSV can also facilitate the therapeutic effects of mesenchymal stem cells by increasing their self-renewal, survival, anti-aging effects, and lineage commitment. However, the natural form of RSV has limitations, such as poor intestinal absorption and low bioavailability. This review focuses on the potential of RSV to explore its effects and mechanisms of action in cancer, regenerative medicine, and chronic disease. It also discusses how RSV can protect normal tissue against genomic instability and presents findings from combination therapies involving RSV and nanoparticle-based agents. Overall, this review highlights the latest developments regarding RSV as a promising compound, emphasizing the potential to overcome its limitations.
DOI: 10.61882/ibj.5210

Keywords: Nanoparticles, Regenerative medicine, Resveratrol

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[DOI: 10.61882/ibj.5210]

1. INTRODUCTION

Resveratrol (RSV) is a natural polyphenol found in certain plants, such as red wine grapes, peanuts, berry fruits, and various human foods. It possesses high antioxidant potential and exhibits various health benefits, including anti-inflammatory, antimicrobial, anti-angiogenic, anti-carcinogenic, immunomodulatory, anti-diabetic, vasorelaxant, phytoestrogenic, cardio-protective, and neuroprotective effects. Since RSV can affect different biological targets and produce various biological effects, it is considered a multi-target drug, similar to other natural products. RSV has been the subject of much research in recent years due to its potential health benefits. It has shown promise in cancer research by demonstrating the ability to prevent mutations and induce phase II hepatic enzymes that detoxify carcinogens, such as cytochrome P450 (CYP) enzymes. Additionally, it has been found to stimulate apoptosis of tumor cells, which can help to reduce tumor growth. Research has suggested that the P53 tumor suppressor protein could be a potential target for the apoptosis process, which involves different phosphorylation enzymes and Bcl proteins[1]. In various trials, RSV has been found to activate the suppressor of *Rad 9* gene, which induces the death of tumor cells. RSV has particularly demonstrated a reduction in lung and breast cancer at micromolar concentrations in both in vitro and in vivo studies. It can also inhibit metastasis and angiogenesis by reducing inflammatory cytokines in oral cancer cells, primarily by targeting tumor-related macrophages. In summary, RSV has been shown to affect all three phases of cancer development (initiation, promotion, and progression), which suppress final steps such as angiogenesis and metastasis. The multiple therapeutic properties of RSV, particularly its anti-tumor capacity, continue to interest researchers. While RSV has previously been considered preventive against cancer development due to its antioxidant nature, recent research has also revealed its dose-dependent cytotoxic properties, which can make it a useful chemopreventive and therapeutic agent[2]. Given its anti-tumor properties and low toxicity even at high doses, RSV has the potential to serve as an excellent starting point for the development of new compounds.

RSV is poorly water-soluble, which makes this compound difficult for the body to absorb orally. While complexing it with cyclodextrins or forming salts can improve its solubility, it does not increase its bioavailability. The short half-life of RSV, due to its rapid metabolism, can be attributed to free hydroxyl groups that facilitate conjugation with glucuronic acid and sulfation via 3′-phosphoadenosine 5′-phosphosulfate. Despite these inevitable limitations, studies on RSV have attracted significant attention in recent years, with many publications in the last five years alone[3]. While the clinical benefits of RSV are still being studied, most of the research conducted so far has focused on potential therapeutic applications. Based on the pharmacological properties of RSV and other flavonoids, they have a crucial effect in the treatment of multi-targeted diseases such as metabolic syndrome, neurodegenerative diseases (NDs), cardiovascular diseases (CVDs), cancer, wound healing, and infertility. This review focuses on the potential of RSV to explore its effects and mechanisms of action in cancer, regenerative medicine, and chronic disease (Fig. S1).

2. SOURCE, STRUCTURE, AND EXTRACTION

RSV, also known as 3,5,4′-trihydroxystilbene, is a naturally occurring polyphenol characterized by its stilbene structure[3]. It was initially identified in 1940 by Takaoka from the root of Veratrum grandiflorum, which has a rich historical presence dating back over 2000 years in medicinal formulations like Darakchasava or Manakka[4]. Its fundamental structure comprises two phenolic rings linked by a double styrene bond and constitutes the 3,5,4′-trihydroxystilbene with a molecular weight of 228.25 g/mol. Notably, this double bond gives rise to both cis- and trans-isomeric forms of RSV, with the trans-isomer prevailing due to its superior steric stability (Fig. 1A)[5]. The realm of RSV extends beyond its natural occurrence, with numerous synthetic and natural analogs, as well as various adducts, derivatives, and conjugates, including glucosides[6]. RSV is a type of stilbene that has two hydroxyl groups on one of its phenyls and another hydroxyl group on its second benzene ring. Although RSV and its analogs typically have the *E*-configuration, which is characterized by a specific pattern of signals in an H NMR analysis, phenyl groups that are connected by an ethylene unit can exist in both the *Z* and *E* configurations. In this light, Grau et al. showed that increasing the bioavailability and cytotoxic capacity of RSV by preparing derivatives through the alkylation of hydroxyl groups (compounds 2, 4, and 5) or acylation (compounds 6 and 7) (Fig. 1B)[7].

RSV synthesis diminishes progressively during grape maturation, rendering mature fruits more susceptible to *Botrytis cinerea* infection. RSV and its counterparts, which function as a phytoalexin, belong to a class of compounds characterized by their low molecular weight and ability to impede the advancement of specific infections. The accumulation of these phytoalexins in plants serves as a mechanism to combat parasites and withstand unfavorable conditions such as fungal attacks, ultraviolet (UV) radiation, chemical stressors, and other environmental adversities. Over 70 plant species produce RSV in response to such stressors. The concentration of RSV in plants varies depending on several factors, notably weather conditions and fungal

[DOI: 10.61882/ibj.5210]

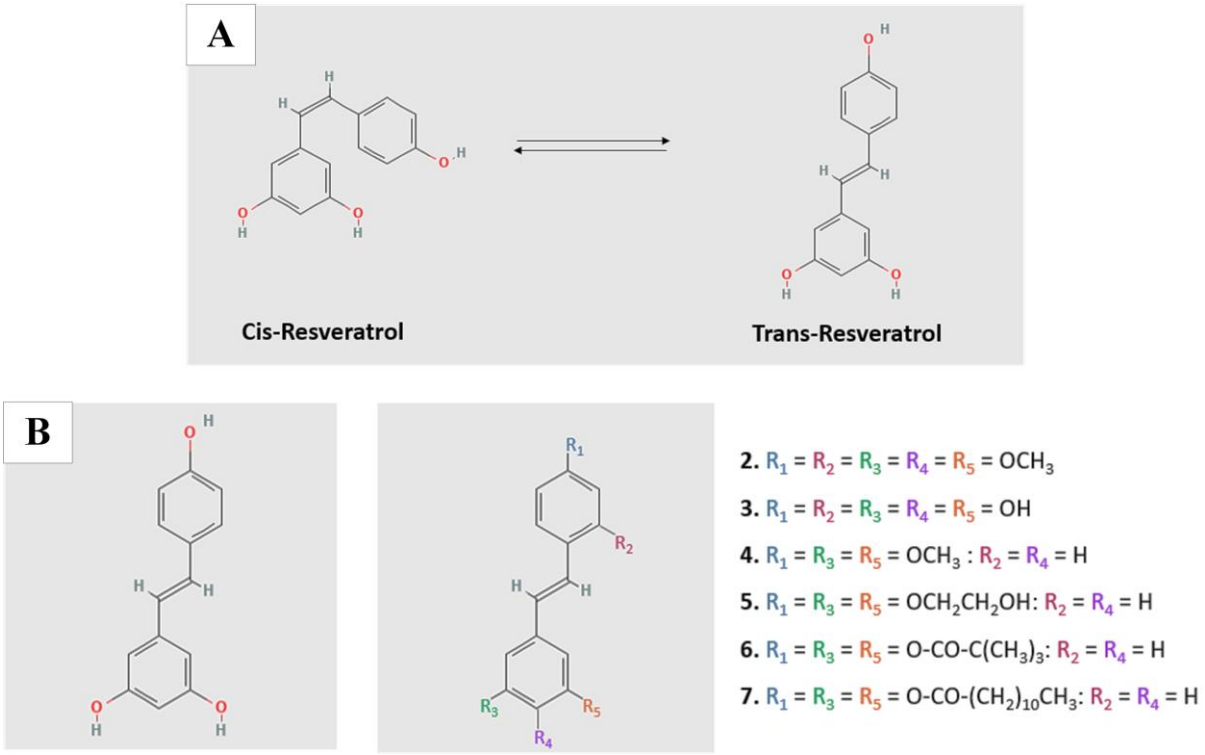

Fig. 1. Chemical structures and derivatives of RSV. Chemical structures of (A) trans-RSV and cis-RSV and (B) RSV and its analogs.

presence[8]. RSV is naturally present in select fruits consumed in the human diet, including blueberries, blackberries, and peanuts. However, red wine remains the primary dietary source of RSV in the Mediterranean region. Within grapes, RSV predominantly resides in the skin, seeds, petioles, and woody parts, making red wine richer in RSV compared to white wine due to the maceration process during red wine production, which facilitates its extraction via alcohol formation[9].

3. METABOLISM AND BIOAVAILABILITY

After use, RSV is readily absorbed through the intestinal epithelium. However, before it reaches systemic circulation, the compound undergoes extensive pre-systemic metabolism in the enterocytes (the gut lining) and subsequently in the liver. RSV undergoes phase II conjugation, where liver enzymes attach sulfates or glucuronides to its hydroxyl groups. The resulting water-soluble metabolites are rapidly excreted by the kidneys, leaving little active RSV in circulation. This process results in the formation of RSV sulfates and glucuronides. The Phase II metabolism of RSV or its metabolites predominantly occurs in the liver, with enterohepatic transport via bile, which potentially results in cyclical reintroduction into the small intestine. Moreover, RSV can induce its own metabolism by enhancing the activity of phase II hepatic detoxifying enzymes. RSV undergoes extensive metabolism, yielding conjugated sulfates, glucuronides, and up to five distinct metabolites excreted in urine, which may retain some biological activity. However, the nature and quantity of these metabolites exhibit inter-individual variability[10]. The metabolic fate of RSV is not uniform across individuals. Genetic polymorphisms in metabolizing enzymes, differences in gut microbiota composition, and dietary context contribute to significant inter-individual variability in the profile and quantity of metabolites produced. This variability is a critical factor in human studies and may account for the differing physiological responses observed. Notably, cis-metabolites have been detected in human urine samples, primarily as cis-RSV-4′-sulfate, cis-RSV-3-O-glucuronide, and cis-RSV-4′-O-glucuronide. While most research focuses on the trans-isomer due to the instability of the cis-isomer, both isomers appear to elicit differing biological effects (Fig. 2)[11].

An important mechanism influencing RSV pharmacokinetics is enterohepatic recirculation. Conjugated metabolites excreted from the liver into the bile are released into the small intestine. Here, gut bacterial enzymes (particularly β-glucuronidases) can hydrolyze the glucuronide and sulfate moieties, releasing free RSV back into the lumen for potential reabsorption. This cycle can prolong the residence time of RSV-derived compounds in the body and may lead to

[DOI: 10.61882/ibj.5210]

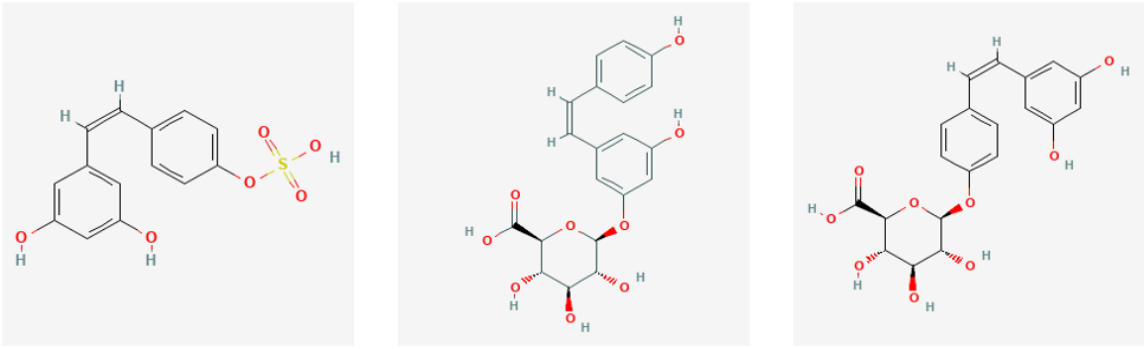

Fig. 2. Metabolites detected in human urine samples.

secondary peaks in plasma concentration. Evidence suggests that RSV sulfate and glucuronide conjugates retain certain biological activities, including antioxidant and anti-inflammatory properties. Moreover, these metabolites may act as a circulating reservoir, with enzymes in target tissues (e.g., liver, endothelium) capable of reconverting them back to the active aglycone, delivering RSV precisely where it might be needed[12]. Although RSV possesses lipophilic characteristics that lead to high absorption, its bioavailability varies depending on the consumption method and accompanying food[13]. Based on the low bioavailability of RSV, in vivo studies have demonstrated efficacy that may be attributed to the metabolite reconversion in target organs like the liver, as well as enterohepatic recirculation and the activity of its metabolites[7,14]. Early human studies on RSV absorption and bioavailability have utilized single oral doses of 25 mg. Despite employing susceptible methods, detecting non-metabolized RSV in circulating plasma proved challenging. Estimated maximal concentrations of <10 ng/mL are calculated to occur approximately 0.5–2 hours post-dose, while total metabolite concentrations are significantly higher, indicating low oral bioavailability of free RSV but considerable metabolite bioavailability[15].

4. BIOACTIVITIES OF RSV

4.1. Antioxidant activity and signaling pathways

RSV functions as an antioxidant through multiple interconnected pathways, including (1) direct free radical scavenging: the chemical structure of RSV allows it to directly donate hydrogen atoms or electrons to neutralize reactive oxygen species (ROS) and reactive nitrogen species (RNS); (2) upregulation of endogenous antioxidant defenses (indirect antioxidant): RSV activates key cellular signaling pathways that enhance the expression of the body's own antioxidant enzymes, particularly Nrf2 (nuclear factor erythroid 2-related factor); (3) pathway activation: RSV activates the transcription factor Nrf2, which translocates to the nucleus and binds to the antioxidant response element (ARE). Additionally, RSV activates the deacetylase SIRT1, which is involved in mitochondrial biogenesis, energy metabolism, and stress resistance, indirectly reducing oxidative stress; (4) chelation of pro-oxidant metal ions: RSV can chelate transition metal ions, like copper (Cu^{2+}) and iron (Fe^{2+}). These ions are potent catalysts in the Fenton reaction, which generates highly damaging hydroxyl radicals. By sequestering them, RSV prevents the generation of these damaging radicals; (5) modulation of pro-oxidant enzymes: RSV inhibits the activity of enzymes that generate ROS, such as NADPH oxidases (NOX) and xanthine oxidase (XO); (6) protection of mitochondrial function: RSV improves mitochondrial efficiency, reduces electron leakage from the electron transport chain (ETC), and promotes mitochondrial biogenesis (via SIRT1/PGC-1α). In this light, oxidative damage underlies the pathogenesis of numerous significant diseases, including diabetes mellitus (DM), CVDs, neurodegenerative conditions, and cancer, and also contributes to the aging process[16]. As a result, considerable attention has been directed toward identifying natural antioxidants that could potentially aid in treating these ailments. For instance, some studies have demonstrated the antioxidant activity of RSV within isolated rat brain mitochondria, where it inhibits mitochondrial respiration and complex III activity by competing with coenzyme Q[17,18]. This mechanism not only scavenges unpaired electrons but also inhibits free radical generation from mitochondrial complexes.

In vitro studies have reported RSV concentrations higher than achievable through red wine consumption. Therefore, it is crucial to ascertain if the low plasma concentrations of free RSV are sufficient to exert antioxidant effects. Notably, nutritionally relevant concentrations of RSV have been shown to reduce H_2O_2

[DOI: 10.61882/ibj.5210]

levels in MCF-7 cells by inducing the expression of antioxidant genes, such as catalase and manganese superoxide dismutase (SOD1), through the PTEN and protein kinase B (PKB) signaling pathway[19]. The interaction of RSV with MAPK pathways also offers insights into its diverse beneficial effects. RSV has been implicated in cardioprotection through its modulation of MAPK pathways.

Studies have shown that in porcine coronary arteries, RSV inhibits the activation of p38, JNK1, and ERK1/2 induced by endothelin-1 (ET-1), a mediator of CVDs[20,21]. It also prevents the translocation of phosphorylated ERK1/2 to the nucleus. Additionally, RSV targets the ERK signaling pathway to mitigate angiotensin II (Ang II)-induced proliferation and ET-1 gene expression in rat aortic smooth muscle cells. Inhibition of MEK, an ERK kinase, by RSV has been found to hinder cardiac fibroblast mitogenic signaling, proliferation, and differentiation into myofibroblasts, thereby mitigating cardiac fibrosis[21]. Anti-cancer properties of RSV are partly attributed to its activation of the p53 protein and suppression of NF-κB and AP-1 through the inhibition of signaling cascades. It induces apoptosis and activates p53 in various cell types, mediated by the ERK and p38 pathways[22]. Moreover, RSV inhibits AP-1 activity induced by tumor promoters like 12-myristate 13-acetate (PMA) and UV light-C by suppressing all three MAPK pathways. In vivo, topical application of RSV inhibits 12-O tetradecanoylphorbol-13-acetate (TPA)-induced COX-2 expression by inhibiting AP-1 activity and ERK phosphorylation. Additionally, RSV suppresses induced COX-2 activity in human breast epithelial cells through the protein kinase C (PKC) signal transduction pathway, thereby preventing PKC translocation to the membrane and suppressing the expression of c-Jun, a component of the AP-1 dimer[22]. RSV also modulates the Wnt signaling pathway at multiple levels, impacting the nuclear translocation and expression of β-catenin, GSK-3β expression, and upstream mediators like SIRT1 and TGF-β. It regulates Wnt signaling to enhance apoptosis and inhibit cancer cell viability and proliferation[23]. RSV decreases fibrosis and promotes β-cell formation through Wnt pathway modulation. Additionally, RSV exhibits immunomodulatory effects by inhibiting the Wnt signaling pathway to decrease inflammatory cytokine concentrations. Its neuroprotective effects result from a combination of antioxidant and anti-inflammatory properties, while it improves bone condition by enhancing mineralization and reducing fractures. Furthermore, RSV protects against ischemia-reperfusion injury by inhibiting the Wnt signaling pathway to mitigate apoptosis[22].

4.2. Modulation of the immune system

RSV significantly influences the immune system by fine-tuning its responses, rather than simply boosting or suppressing it. Its effects are largely achieved by modulating specific immune cell populations and dampening chronic inflammatory pathways, which are particularly relevant for conditions such as cancer, autoimmune diseases, and chronic inflammation. RSV can act as an immunomodulator by regulating immune cells, the synthesis of inflammatory cytokines, and immune-related gene expression. Like most compounds, RSV affects the immune system, which is dose-dependent. At low doses, the compound acts as an immune system inducer, and at higher doses, as an immunosuppressor. This property can be utilized in the therapy and prevention of immune diseases for different reasons, such as inducing the immune system in pathogenic diseases and immunomodulation in autoimmune diseases, by adjusting the dose. RSV can immunomodulate via interaction with immune cells, including macrophages, natural killer (NK) cells, T cells, and B cells.

Macrophages, derived from monocytes, play a crucial role in coordinating innate and adaptive immunity. These diverse cells possess various pattern recognition receptors, including toll-like receptors (TLRs), C-type lectin receptors (CLRs), cytoplasmic nucleotide oligomerization domain (NOD)-like receptors (NLRs), and gene I-like receptors (RIG-I), which enable them to detect pathogen-associated molecular patterns (PAMPs). By producing anti-inflammatory cytokines and inhibiting TLR-mediated inflammatory pathways, macrophages regulate immune responses. RSV regulates the expression of TLR-4, impacting TLR-mediated inflammatory responses and chronic diseases associated with TLR activation, such as obesity, type 2 diabetes (T2DM), fatty liver disease, Crohn's disease, rheumatoid arthritis, CVDs, and neurodegenerative disorders. It also exerts an anti-inflammatory action by interacting with tumor necrosis factor receptor-associated factor 6 (TRAF6), mitogen-activated protein kinase (MAPK), and PKB pathways in macrophages[24]. Additionally, it modulates the immune system response by affecting cellular levels of prostaglandin E2 (PGE2) and upregulates the secretion of chemokines, including COX-2, in inflammatory diseases[25].

NK cells make up around 15% of circulating lymphocytes and are crucial for defending against pathogens and cancer. They express various PRRs and release cytokines and cytotoxic granules to kill target cells. Evidence has demonstrated that RSV can be an anti-tumor component or adjuvant in immunotherapy by acting on NK cells[26]. RSV can improve the cytotoxicity of NK cells through Akt- and

[DOI: 10.61882/ibj.5210]

mTORC2-mediated c-Myb upregulation[26]. In a study aimed at decreasing side effects, researchers used melatonin and RSV in rats with DM. The results indicated that this treatment could diminish the side effects of DM on the activity of NK cells[27]. In viral diseases, NK cells play a significant role in viral clearance in the body, while their uncontrolled activity leads to inflammation and damage to the host tissue. Therefore, providing conditions to control inflammation can be essential. In this regard, RSV was examined for its ability to reduce NK activity in BALB/c mice infected with respiratory syncytial virus. The results showed that targeting NK cells helped reduce airway inflammation and hyper-responsiveness caused by RSV.

Dendritic cells (DCs) are professional antigen-presenting cells (APCs) that play a crucial role in fighting pathogens and maintaining tolerance to self and harmless antigens. They capture pathogens and use signals to guide immune responses and regulate T-cell activity. RSV inhibits the expression of CD80, CD86, and MHC class II molecules, suppressing DC maturation and decreasing their ability to stimulate naive $CD4^+$ T cells. RSV has multiple molecular targets that enhance its immunosuppressive effects during DC differentiation. Incubation with RSV leads to the development of "alternatively" differentiated DCs, which are unresponsive to maturation stimuli and exhibit increased ILT-3 and ILT-4 transcripts[28] and secrete more interleukin (IL)-10. Regarding the effect of RSV in balancing between pro-inflammation and anti-inflammation of DCs, in vitro results revealed that RSV pretreatment regulates maturation and function of DCs to enhance the recovery of acute lung injury.

B cells produce antibodies, release cytokines, act as secondary APCs, and have regulatory and pathogenic functions. Regulatory B cells (Bregs) are a rare subpopulation with suppressor functions, constituting less than 10% of total B cells in circulation. They primarily use IL-10 for regulation and to prevent inflammation by inhibiting Th1 cell activation, maintaining the Treg cell population, and controlling Th17 proliferation. Low doses of RSV have been shown to induce anti-tumor effects and interfere with cancer escape mediated by tB-regs[29].

5. THERAPEUTIC ACTIVITY OF RSV

The application of natural molecules such as RSV, devoid of developing resistance and delivering therapeutic effects without side effects, remains a primary objective in the fight against diseases. Hence, the therapeutic effectiveness of RSV has been determined in cancer, neurological disorders, CVDs, DM, wound healing, and metabolic disorders. Figure 3 depicts a summary of the effects of RSV in the treatment of various disorders.

5.1. Neurodegenerative diseases

Considering the ceaseless growth of the elderly population, the incidence of NDs has significantly increased. Therefore, the costs of preventive measures and therapeutic interventions across the world are expected to be trillions of dollars. In brain aging, certain alterations can increase the susceptibility to developing diseases such as Alzheimer's, Parkinson's, and stroke. Biomarkers such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) are important in the early detection of brain aging and in slowing the progression of NDs. RSV can cross the blood-brain barrier (BBB), making it useful for therapeutic actions. RSV also modulates intracellular signaling, resulting in neuron survival, and inhibits beta-amyloid (Aβ) protein aggregation[30]. Researchers have analyzed the neuroprotective function of RSV in counteracting the pro-inflammatory stimuli in RSV-treated microglia that are incubated with lipopolysaccharide (LPS). In addition, RSV could play a protective role in preventing or decreasing neuron death due to its antioxidant feature. Interestingly, long-term exposure to LPS actually led to lower production of the inflammatory molecules nitric oxide (NO) and TNF-α in RSV-treated microglia. This occurred because RSV's anti-inflammatory properties prevented the breakdown of IκB the protein that normally keeps the inflammatory switch turned off. As a result, the overall inflammatory response was diminished[30]. Every therapeutic strategy could be able to postpone the start of the disease or decrease the consequences and signs in patients. Recently, trying to revive neuroprotective pathways against stress injuries (like oxidative stress) has been seriously considered. Scientists explored that e 17β-estradiol (E2)/estrogen receptor β (ERβ) could induce the accumulation of neuroglobin (NGB) in the cytosol of neuronal cells, resulting in improved mitochondrial function, subsequently suppressing apoptosis and improving neuron survival. This pathway could protect both cancer and neural cells against injuries via ROS. Hence, a low concentration of RSV regulates the ERβ/NGB axis, and neuronal cell resilience against oxidative stress decreases the triggering of the apoptotic cascade[30].

5.1.1. Brain tumors

Gliomas are aggressive, malignant brain neoplasms that are often associated with late diagnosis. The origin of gliomas is an irregular proliferation of glial cells cells (responsible for neuron protection) or the spine. Glioblastoma multiforme (GBM) and anaplastic

[DOI: 10.61882/ibj.5210]

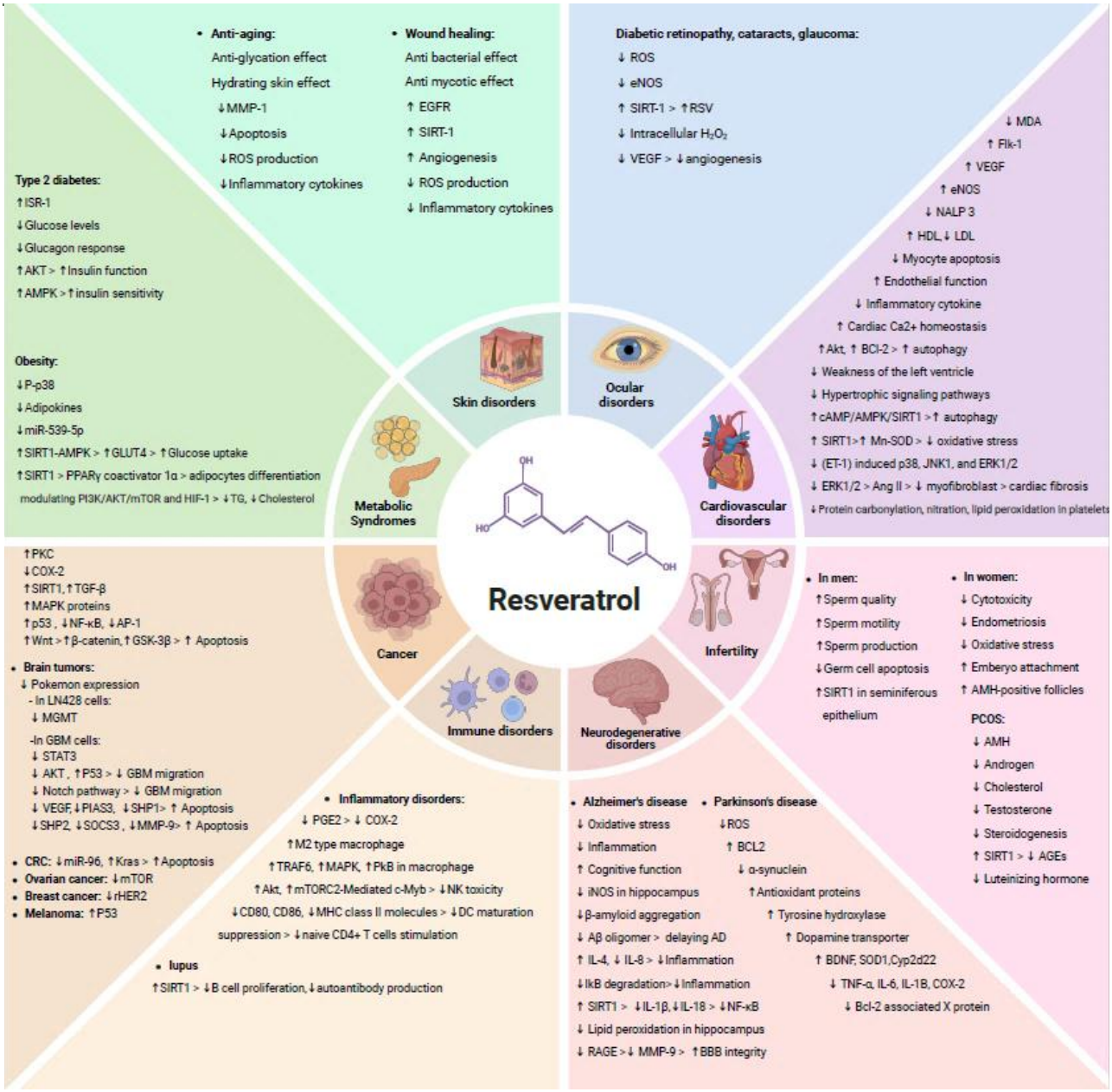

Fig. 3. Effects of RSV in the treatment of different diseases.

astrocytoma are the most common primary brain tumor in adults. Gliomas are diffuse without boundaries within the brain tissue. In very optimistic conditions, the average survival of GBM patients is two years with therapeutic interventions. To date, therapeutic strategies have included surgical resection, radiotherapy, and chemotherapy applied against brain tumors. Among chemotherapeutic agents, temozolomide (TMZ) and Avastin, both approved by the FDA, are associated with side effects. TMZ is an alkylating agent that causes toxicity by methylating the O6 position of guanine. Erythroid myeloid oncogenic factor (POK) is an anti-apoptosis and proto-oncoprotein factor that regulates the expression of many genes and is one of the most critical contributing factors in tumorigenesis. Western blot analysis reported that POK is expressed in U87MG, T98G, U251, and primary glioblastoma cells. Results showed that RSV could decrease POK expression. Additionally, RSV could induce cell senescence associated with β-galactosidase activity and apoptosis in U87MG cells[31]. Previously, researchers have examined a chemotherapy combining TMZ with RSV to enhance

[DOI: 10.61882/ibj.5210]

the chemosensitivity of glioblastoma cells to TMZ. RSV and TMZ showed anti-proliferation and anti-migration activity by inhibiting STAT3 signaling and reducing MGMT levels in LN428 cells in GBM tumors and elevating the sensitivity of LN428 to TMZ. Furthermore, RSV and TMZ can induce apoptosis by regulating factors such as vascular endothelial growth factor (VEGF), PIAS3, SHP1, SHP2, SOCS3, and matrix metalloproteinase (MMP)-9. According to the poor physicochemical properties of RSV, scientists designed a system involving PEGylated liposomes (RES-L) coated with transferrin receptors (Tf-RES-L), which were overexpressed in GBM cells. Intriguingly, this system prolonged drug release and increased its solubility and stability. In a study on rats, researchers encapsulated RSV in nanoparticles (NPs) (Pep-PP@Res) and targeted it with IL-13Rα2, a common marker expressed in GBM cells. Fluorescent confocal microscopy analysis showed an increased half-life of Pep-PP@Res in the cytoplasm compared to free RSV, along with improved anti-cancer properties. However, Pep-PP@Res showed little toxicity for normal healthy brain cells[32].

5.1.2. Alzheimer's disease (AD)

AD is the most common form of dementia and one of the most prevalent degenerative disorders. Nowadays, AD is becoming a significant socioeconomic problem in societies worldwide[33]. Patients with AD suffer from a gradual decrease in cognitive abilities and treatment. The main cause of the onset and progression of AD is an inflammatory response that leads to the formation of amyloid plaque and tau tangles. Other contributing factors include the accumulation of amyloid-β (Aβ) plaques, loss of acetylcholine (ACh), free radicals, and oxidative stress in the early stages of the disease. Some effective medications that could mitigate symptoms are acetylcholinesterase (AChE) inhibitors (such as donepezil, galantamine, and rivastigmine). These medications improve AD symptoms by enhancing cholinergic transmission. However, even the most effective medications have side effects. Therefore, pharmaceutical agents with neuroprotective features are required to improve patients' life expectancy without adverse effects[34]. Scientists have applied a high-fat diet (HFD, 60% kcal from fat) to induce different aspects of AD neuropathology in wild-type mice and exacerbate the condition in 5XFAD mice. Their findings demonstrated that RSV can counteract the adverse neurodegenerative effects of HFD by moderating the inordinate activity of the proteasome and immunoproteasome caused by metabolic stress[35]. RSV ameliorates learning impairment and attenuates cognitive deficits in Tg256 mice by minimizing the formation of Aβ oligomers, causing a delay in the onset of AD. Moreover, RSV interferes with some epigenetic modifications involved in central nervous system function, which may have hereditary implications. Previous research has developed a system in which red blood cells are surface-modified with both rabies virus glycoprotein (RVG29) and triphenylphosphine (TPP) cations, which serve as antioxidant agents. Later, researchers encapsulated RSV and targeted the mitochondria of neuron cells. They showed that RSV could alleviate AD symptoms by inhibiting Aβ-related mitochondrial oxidative stress both in vitro and in vivo. Also, RSV protects neurons by attenuating high levels of lipid peroxidation in the hippocampus, resulting in protecting neurons against oxidative stress. Notably, the combination of RSV and vitamin E could increase cortical neuron density[34].

5.1.3. Parkinson's disease (PD)

PD is the second most prevalent ND after AD. Aging is the most important risk factor for this slowly progressive disorder[36]. In PD, dopaminergic neurons decline in the substantia nigra, resulting in a diminished release of dopamine. Gastrointestinal dysfunction, caused by gut microbiota disturbance, is one of the common consequences of this condition in patients. PD is characterized by some behavioral abnormalities, such as bradykinesia, postural instability, resting tremors, rigidity, and a few neuropsychiatric symptoms, such as depression, cognitive dysfunctions, and dementia. Additionally, patients with PD suffer from sleep disorders, bladder disorders, orthostatic hypotension, and anosmia. The accumulation of Lewy bodies (including α-synuclein aggregates) is the main pathological trait of PD. The overexpression of α-synuclein is significantly implicated in the pathology of the disease. Some common drugs, such as levodopa and dopamine agonists, are used to alleviate PD symptoms with some side effects. L-DOPA (L-3,4-dihydroxyphenylalanine) could alleviate PD symptoms. However, its long-term consumption may cause adverse effects. RSV could palliate dyskinesia caused by L-DOPA as well as PD pathologies through various pathways. Indeed, RSV decreases ROS, resulting in reduced oxidative stress. Findings indicated that RSV could be used as a promising therapeutic intervention due to its anti-inflammatory and antioxidant attributes. Likewise, RSV stimulates autophagy pathways to remove misfolded proteins and dysfunctional organelles[36]. It also reduces the expression of some inflammatory cytokines, such as TNF-α, IL-6, and IL-1β in epithelial cells. By decreasing TNF-α and COX-2, RSV may help reduce neurodegeneration caused by free radicals. Moreover, RSV could improve neuroprotective

[DOI: 10.61882/ibj.5210]

effects by increasing the expression of BDNF, SOD1, and Cyp2d22. Nevertheless, a significant problem in using RSV is poor bioavailability in the brain, which limits its therapeutic potential. To overcome this challenge, researchers have designed a system consisting of RSV and PLGA NPs conjugated with lactoferrin (LF) to enhance the penetration of RSV to the brain. Results showed that LF-RSV-PLGA-NPs internalization into SH-SY5Y and human brain microvascular endothelial cells was more efficient than using free RSV. Furthermore, it has been demonstrated that LF increases the accumulation of LF-RSV-PLGA-NPs in the brain. Intriguingly, treatment with RSV in the PD mouse model induced by MPTP (1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine) could decrease α-synuclein expression at both transcriptional and translational levels[37].

5.2. Metabolic syndrome

Metabolic syndrome includes hypertension, high blood glucose levels, central obesity, and abnormal triglyceride and cholesterol levels, increasing the risk of CVD and T2D. Metabolic syndrome is a global problem linked to non-communicable diseases like T2DM, CVD, and cognitive deficits[38]. Therefore, control of these parameters can affect the occurrence of metabolic diseases. RSV has various mechanisms through which it improves symptoms of metabolic syndrome and related disorders. Its antioxidant activity results in the upregulation of endogenous antioxidant defenses. The antioxidant activity of RSV in metabolic syndrome is multifaceted and extensive. It extends beyond simple radical scavenging to orchestrate a systemic antioxidant response by activating master regulatory pathways like Nrf2 and SIRT1. This process helps mitigate the root cause of oxidative stress in various tissues, such as adipose, liver, vascular, and muscle tissues, thereby improving insulin sensitivity, endothelial function, and lipid metabolism. One important target of RSV is the SIRT1 protein, which helps control conditions like obesity and CVD. RSV activates SIRT1, which activates peroxisome proliferator-activated receptor (PPAR) γ coactivator 1α to control mitochondrial biogenesis and promote the differentiation of white-to-brown adipocytes in adipocytes. Another mechanism for inhibition of lipogenesis in white adipose tissue by RSV includes the activation of AMPK/SIRT1 proteins and inhibition of phosphorylation of p38 proteins in adipocytes[19] and upregulation of miR-539-5p[39]. However, investigations in humans have revealed that RSV supplementation could not have a significant effect on body adiposity or body weight, even though it can reduce the size of adipocytes. Research has indicated conflicting results in patients with metabolic syndrome, with a reduction in fat mass, while others report no effects[40]. Similarly, RSV could not change fat mass or body weight in patients with non-alcoholic fatty liver disease (NAFLD) or T2D. RSV activates insulin receptor substrate-1 and Akt as the insulin-signaling components and decreases the expression of adipokines. Clinical trials have been conducted to investigate the effects of RSV on glucose homeostasis in individuals with different degrees of glucose alteration, from normoglycemia to T2D. In nondiabetic individuals, some studies showed no changes in insulin sensitivity or glucose levels after RSV supplementation at doses between 75 and 2000 mg[41]. However, other research found that a 150-mg dose of RSV for 30 days led to decreased glucose levels, improved insulin resistance, and suppressed glucagon response in obese non-diabetic individuals[42]. In patients with T2D, supplementing with RSV did not enhance insulin sensitivity, possibly due to interaction with metformin. Meanwhile, in a study investigating the hepatic steatosis model of HepG2 cells, it was observed that the combination of RSV and metformin reduced hepatic steatosis by causing autophagy through the cAMP/AMPK/SIRT1 signaling pathway[43]. Furthermore, curcumin (CUR) and RSV revealed a synergistic effect on reducing triglycerides, cholesterol, and lipid accumulation in HepG2 cells, and this effect was related to modulating PI3K/AKT/mTOR and HIF-1 signaling pathways. Finally, RSV supplementation has been found to reduce triglyceride levels in obese rodents and inhibit fatty acid synthesis in rat hepatocytes[44].

5.3. Diabetes mellitus

DM is an ever-increasing global epidemic affecting about 10.5% of adults worldwide. This disease is a metabolic disorder and is associated with serious complications in multiple organs/tissues, which lead to high economic costs. The prevalence of DM as a major challenge to society and health has reached an alarming level. DM is characterized by persistent hyperglycemia, defects in insulin secretion and/or action, and metabolic syndromes such as obesity, hypertension, and dyslipidemia. According to the recent classification, DM is divided into T1DM, T2DM, gestational DM, and special types of DM. Among them, T1DM and T2DM account for more than 90% of all cases. In T1DM, autoimmune destruction of pancreatic β-cells causes a deficiency in insulin secretion. In contrast, T2DM is a multifactorial disorder that impairs insulin secretion and action[45]. Improving lifestyle through exercise and dietary modification is very effective in preventing and delaying T2DM[45]. The serious and long-term complications of DM include CVDs, diabetic nephropathy, diabetic neuropathy, and diabetic eye

[DOI: 10.61882/ibj.5210]

disease. Therefore, management of DM is a serious task to improve the quality of life of patients with DM and prevent complications. Cardiovascular complications are the main cause of death among these patients. Given the concerning side effects and the increasing number of people with DM, discovering safe and efficient drugs is an essential and unmet need. RSV, with antioxidant, anti-inflammatory, and hypoglycemic effects, prevents DM and its cardiovascular complications and also improves glucose homeostasis. The anti-DM properties of RSV are exerted through the following molecular mechanisms: the activation of the SIRT1-AMPK signaling pathway, induction of autophagy, regulation of lipid metabolism, and promotion of glucose transporter 4 (GLUT4) expression. These processes enhance glucose uptake and metabolism, protect pancreatic beta-cells, and improve insulin resistance. RSV also exerts its cardiovascular/antioxidant effects via SIRT1, activating FOXO1, manganese SOD1, FOXO3a, and PI3K/Akt pathways. Adenosine 5-monophosphate-activated protein kinase (AMPK) is a molecule involved in the regulation of energy metabolism. RSV can activate AMPK/SIRT1 and regulate insulin secretion in pancreatic β-cells, lipid metabolism, and insulin sensitivity[45]. In addition, RSV enhances glucose uptake in skeletal muscle cells by increasing the expression of GLUT4 and translocation of GLUT4 via phosphorylation of AMPK and the PI3K-Akt pathway[46].

5.4. Cardiovascular disease

CVD causes morbidity and mortality all around the world, especially in developed countries. Heart failure has been increasing in recent years and has become one of the leading health and medical problems. CVD, as a metabolic disease, includes several heart and blood vessel disorders such as cerebrovascular, atherosclerosis, coronary artery disease, deep vein thrombosis, congenital heart diseases, high blood pressure, peripheral artery disease, and stroke. RSV is exerted through molecular mechanisms such as cardiac $Ca2^{+}$ homeostasis, hypertrophic signaling pathways, and myocyte apoptosis. Its application in the treatment of CVD is due to its remarkable antioxidant and anti-inflammatory properties and its ability to upregulate endothelial nitric oxide synthase (eNOS). As a multitarget natural substance, RSV can reduce ROS, decrease inflammation, and improve left ventricular function and endothelial performance. Oxidative stress plays a crucial role in the development of CVDs; hence, antioxidants can be used in their management. RSV protects heart muscle cells from inflammatory damage through two main mechanisms. First, it fine-tunes inflammatory signaling molecules (cytokines) to prevent excessive immune responses. Second, it blocks the activation of key inflammatory protein complexes, particularly nucleotide-binding Leucine-rich repeat receptor pyrin domain-containing 3 (NLRP3; formerly known as NALP3), which is a major driver of tissue-destroying inflammation. Beyond this, RSV offers additional cardiovascular benefits by improving cholesterol balance, it boosts protective HDL while simultaneously lowering harmful LDL[18]. Also, the potential benefit of RSV in cardioprotection is the improvement of endothelial function and NO-mediated vasodilation through upregulating eNOS. NO, produced via the eNOS enzymatic reaction, can inhibit atherosclerosis by reducing platelet accumulation and modulating immune cell activity, including that of leukocytes. However, further studies are needed to conduct a more detailed investigation into the efficacy of this remarkable composition. RSV confronts oxidative stress via SIRT1 activation by the stimulation of the antioxidant enzyme manganese-superoxide dismutase, hence suppressing oxidative stress and preventing cardiomyocyte cell death[47].

5.5. Ocular diseases

Today, ocular diseases are increasing due to population growth, aging, and lifestyle changes. Eye diseases such as diabetic retinopathy (DR) and age-related macular degeneration (AMD) are increasing throughout the world. A study conducted in 2019 in Europe estimated that diabetic eye disease could affect between 6.4 million and 8.6 million people by 2050[48]. The inflammatory reactions, oxidative stress, and apoptosis are the main causes of age-related ocular disorders, including cataracts, glaucoma, and diabetic retinopathy[49]. RSV shows potential in the prevention and treatment of these age-related ocular disorders[49]. Various approaches are used to treat DR, including anti-VEGF monoclonal antibodies such as ranibizumab and aflibercept. Although these drugs are approved by the FDA, they have several side effects, including delayed wound healing, hypertension, and cataract formation[48]. As a result, efforts are underway to develop new treatment strategies that can mitigate these disadvantages. RSV via SIRT1 provides additional protection against retinopathy, particularly in cases of DR[50]. Several in vitro studies have reported that RSV has an antioxidant effect and can reduce the generation of intracellular ROS in the management of AMD and DR[51]. For example, when human retinal pigment epithelial cells (ARPE-19) were treated with RSV, a significant downregulation of VEGF expression occurred. The retina is particularly susceptible to ROS because of its exposure to light and high-energy demands. RSV may protect ocular tissues against ROS due to its antioxidant properties and reduce intracellular

[DOI: 10.61882/ibj.5210]

H_2O_2 via its action on mitochondrial enzymatic pathways. One of the factors involved in retinal and choroidal neovascularization is VEGF-activated eNOS; hence, treatment with RSV reduces eNOS mRNA expression in eye tissue compared to control[48].

5.6. Infertility

RSV demonstrates potential therapeutic effects in women with ovarian issues and conditions like polycystic ovary syndrome (PCOS), endometriosis, and fibroids. It may also improve testicular function and sperm quality[52]. Animal studies have suggested that RSV could treat both male and female infertility, but few human trials have been conducted. PCOS is described by enlarged ovaries, hyperandrogenism, and ovulation disorders. RSV, studied in rats, inhibits cholesterol production and steroidogenesis by blocking the mevalonate pathway and reducing androgen production. It also improves ovarian health in a rat model of PCOS by decreasing the levels of testosterone, luteinizing hormone, and anti-Müllerian hormone levels[53]. Recently, a systematic review has revealed that RSV can treat PCOS by reducing testosterone levels in women. This review analyzed four randomized clinical trials involving 218 women, indicating that RSV significantly decreases testosterone, luteinizing hormone, and dehydroepiandrosterone sulfate levels compared to a placebo[54]. Additionally, RSV, a compound with various effects on the human endometrium, has been found to promote embryo attachment and inhibit endometriosis progression[55], and modulate angiogenesis. However, the anti-inflammatory actions of RSV could hinder embryo implantation by accelerating the downregulation of the retinoic acid pathway, thus influencing senescence and gene expression related to decidualization. It may also inhibit decidual senescence and deacetylation[56], potentially affecting endometrial receptivity. Therefore, more detailed studies should be conducted to understand the effect of RSV on endometrium and embryo implantation. Male infertility can be caused by abnormal semen parameters or azoospermia[57]. Various nutritional and medical interventions have been used to treat male infertility, but management remains challenging due to conflicting evidence. In animal models, RSV has demonstrated positive effects on the hypothalamic-pituitary-gonad axis, testosterone levels, sperm production, and sperm motility. Studies have shown that RSV decreases germ cell apoptosis and improves mitochondrial activity, DNA integrity, and sperm parameters. In this regard, a study evaluated the effects of a multivitamin supplement containing 150 mg of RSV on semen parameters. The results revealed improvements in sperm motility and concentration after 3 and 6 months of treatment[52]. Another study investigated male rats with T1DM to evaluate the effects of RSV on sperm DNA integrity and reproductive outcomes. While DM caused damage to male reproductive organs and reduced fertility rates, RSV treatment improved these parameters. Similarly, the study utilized RSV and L-carnitine, both strong antioxidants, on testicular tissue and sex hormone levels in rats treated with busulfan, an alkylating agent used in chemotherapy. The results exhibited that RSV and L-carnitine improved various aspects of testicular health, including weight, volume, tissue structure, and hormone levels[58]. However, daily treatment with RSV from puberty improved all qualitative sperm parameters and restored the morphological integrity and expression of SIRT1 in the seminiferous epithelium[59].

5.7. Skin protection

5.7.1. RSV in skin wound healing

Skin wound healing is a complex and regulated process that involves four phases: hemostasis, inflammation, proliferation, and remodeling. Any impairment during these phases can lead to chronic wounds, which affect individuals' social and personal lives worldwide. Several factors, including inadequate vascularization, infections, and prolonged immune responses, contribute to chronic, non-healing wounds. RSV, with anti-inflammatory, antioxidant, angiogenic, and antibacterial effects, improves wound healing by regulating repair-related processes in the skin[60]. RSV, through cellular pathways controlled by the epidermal growth factor receptor (EGFR), activates SIRT-1 and infiltration. In addition to its antioxidant effects, RSV has been shown to have various benefits, including antimycotic, cardiovascular protective, anti-tumor, immunomodulatory, anti-obesity, anti-T2D, and neuro-protection[61].

5.7.2. Photoprotective and anti-aging properties of RSV

The accumulation of glycated proteins and long-term exposure to UV irradiation are related to aging and age-related diseases. Glycation affects elastic fibers and collagen, leading to post-translational modification of proteins and promoting angiogenesis, which contributes to age-related skin damage. The absence or lack of enzymes that eliminate glycosylated products and activate inflammatory and oxidative pathways is a crucial mechanism of damage to the skin. RSV and its derivatives are novel natural products known for their anti-glycation activity, which is effective only with continuous dosing. UV irradiation compels ROS production, which subsequently activates factors contributing to skin aging. These factors include MMP-

[DOI: 10.61882/ibj.5210]

1, IL-6, and IL-8, as well as apoptosis pathways. Research has shown that RSV and RSV-enriched foodstuffs with antioxidant properties decrease UVB-induced ROS production, as well as the levels of MMP-1 and inflammatory cytokines. Also, RSV and its derivatives significantly increase the viability of human skin cells through their anti-apoptotic effects. An earlier study has shown that solubilizing excipients and lipid NPs, including bisurfactant and β-cyclodextrin, increases the penetration and effectiveness of RSV. This binary system increases the loading and release efficiency of RSV and improves the signs of aging. Igielska-Kalwat et al. showed that RSV hydrates the deeper layers of the skin and prevents water loss by changing intercellular fluid dynamics[14]. Due to the water-insoluble nature and low bioavailability of RSV, there is a crucial need to design novel drug delivery carriers or chemical changes in the structure of RSV. These delivery systems include hydrogels, biological scaffolds, dermalix, nanovesicles, and wafers, all of which improve systemic and topical applications of RSV[60].

5.8. Antimicrobial activity

An early and necessary step in the treatment of damaged skin is to prevent wound infections. Microbial pathogens, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*, are the main cause of skin infection. Antimicrobial agents, such as antibiotics, are required in the wound healing process[61]. The presence of opportunistic bacteria is the most common reason for the chronicity of wounds. Studies have shown that RSV, with its antimicrobial activity, could treat antibiotic resistance and vaginal infection[62]. Also, RSV can mitigate acne lesions caused by *Propionibacterium acnes*[61]. Drug resistance is increasing over time due to inappropriate use. Therefore, the comprehensive investigation of natural drugs with fewer side effects is a fundamental unfulfilled need to solve the problem of drug resistance. Studies have shown that RSV fights microbial agents by destroying cell walls, inhibiting DNA synthesis, and interfering with metabolic activity and energy production[61]. RSV, compared to polyphenols such as dihydroquercetin and dihydromyricetin, has a favorable efficiency in wound healing and regeneration of damaged skin, which can be used alone or in combination with other common antimicrobials[61]. RSV is notably more effective against fungi than bacteria and provides an antifungal effect at lower minimum inhibitory concentrations. Another significant property of RSV is its anti-virulence capability, which disarms microbial agents with the help of the immune system of the host. RSV performs anti-virulence properties through interference with biofilm formation, motility, toxin secretion, quorum sensing, adhesion, and colonization. Research has also shown that RSV has an antiparasitic effect against *Trypanosoma cruzi*, *Setaria cervi*, and *Leishmania amazonensis* through antipromastigote and antiamastigote activity, decreased mitochondrial capacity, and inhibited differentiation[63]. In vitro experiments have demonstrated that RSV is effective against respiratory viruses, such as rhinovirus, influenza, and coronavirus, by hindering the translation of viral proteins, blocking replication, translocation of viral ribonucleoproteins, and preventing the release of new viruses[63,64]. Also, an in vivo survey showed that RSV decreased viral pulmonary titers in mice infected with influenza A[64].

5.9. Anti-cancer activity

Cancer is a serious public health problem all around the world, causing about 10 million deaths in 2020, with numbers increasing over time[65]. According to the World Health Organization report, cancer is considered the second leading cause of mortality all around the world, contributing to nearly 1 in 6 deaths. Despite significant advances in pharmaceuticals and technology in recent years, cancer remains a global problem. Drug resistance and side effects are the most serious problems of chemotherapy and radiotherapy in the treatment of cancer. Therefore, there is an urgent need to investigate and develop novel and more effective therapeutic agents. RSV and its derivatives, found in a wide range of plants, have been used to treat different types of cancer since 1997. RSV is considered to be a wonderful multitarget anti-cancer agent that interferes with cellular mechanisms involved in the initiation and progression of cancer. These mechanisms include cell growth, apoptosis, angiogenesis, signaling pathways, receptor tyrosine kinases, and metastasis. RSV, as a preventive and therapeutic agent when combined with other chemotherapeutic drugs, is effective against many cancers, including lung, ovarian, pancreatic, breast, colon, and prostate[66]. In vivo studies have shown that RSV administration restrains colorectal tumors (the third most common cause of cancer-related mortality) through the upregulation of miR-96 and downregulation of KRAS. Also, an in vitro study has reported that RSV suppresses the growth of Caco-2, LS174T cells, and HT-29 while inducing apoptosis in WiDr colon cancer cells[66]. Furthermore, in vitro studies have shown that the combination of RSV with Herceptin decreases human epidermal growth factor receptor 2 expression compared to treatments with Herceptin alone in breast cancer. In vivo experiments have also revealed that RSV decreases the growth of skin tumors induced by 7,12-dimethylbenz[a]anthracene (DMBA) and TPA via

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a p53-dependent apoptosis process. RSV induces autophagy in many cancers, including ovarian cancer, via the inhibition of the mTOR signaling pathway, which induces cell death. Another mechanism of action for RSV is to activate the Nrf2 transcription factor, an important antioxidant, which subsequently promotes apoptosis and inhibits cancer development[67].

6. DELIVERY SYSTEMS for RSV: NANO-FORMULATIONS, TARGETED THERAPY, AND BEYOND

In recent years, the use of nanotechnology in medicine as an effective tactic, especially in drug delivery and molecular-targeted therapy, has been very much considered[68]. Recently, nanocarriers have been used to deliver anti-cancer agents and improve drug efficiency. RSV has a variety of pharmacological applications, which is gaining popularity in cancer and inflammatory disorder treatment and prevention. Zhang et al. have shown that RSV nanodispersion exhibits enhanced water solubility, high light stability, and enhanced antioxidant activity compared to unprocessed raw RSV[69]. RSV, which has been encapsulated into various nanocarriers, such as liposomes, polymeric NPs, lipidic NPs, and inorganic NPs, can modulate drug release, increase bioavailability, water solubility, stability, and permeation across biological membranes, and provide enhanced permeation-controlled release in the tumor sites. In addition, some potential treatment agents, such as RSV and CUR, have poor bioavailability. To overcome these obstacles, a cancer cell-targeted NP was designed to deliver anti-cancer drugs to these cells. Zhang et al. have shown that NPs were modified with the hepatocellular carcinoma-specific peptide moiety (SP94) and loaded with RSV and CUR, which led to improved bioavailability. The encapsulation of these drugs increased the anti-tumor effect without causing obvious side effects on normal cells and tissues[70]. Khatun et al. have found that zinc oxide (ZnO) NPs conjugated with RSV are more effective in inducing cell death in the ovarian cancer cell line PA compared to free RSV. In vitro and in vivo studies have revealed that the ZnO-RSV nanoconjugate enhances ROS activity and anti-cancer effects through electron migration from ZnO NPs to RSV[68]. Encapsulation protects RSV against physicochemical factors such as UV light, high temperatures, oxygen, and oxidative enzymes[71]. In addition, RSV-loaded liposomes can induce apoptosis and inhibit cell growth in brain cancer. In another study, Du et al. have shown that chitosan encapsulation with RSV-ZnO improves its stability, effectiveness, and bioavailability in gestational DM. In vitro and in vivo studies have revealed that the 38 nm RSV–zinc oxide complex encapsulated in the chitosan (CS-ZnO-RS) formulation, which significantly decreases blood glucose levels, inflammation markers (IL-6 and MCP-1 [monocyte chemotactic protein-1]), and endoplasmic reticulum stress (GRP78, p-IRE1a, p-eIF2a, and p-PERK) in gestational DM[72]. Initial-stage clinical trials are currently investigating RSV nanoformulations in various cancers, such as colon cancer, adult solid tumor adenocarcinoma of the colon, and rectal adeno-carcinoma. Overall, the administration of RSV-conjugated or RSV-loaded NPs shows excellent anti-cancer potency compared to free RSV. However, the anti-cancer efficacy of RSV is often prevented by factors such as low water solubility, low bioavailability, rapid hepatic metabolism, and dose-limiting toxicity[73].

7.APPLICATION OF RSV IN REGENERATIVE MEDICINE

Nowadays, RSV stands at the forefront of regenerative medicine, an interdisciplinary field aiming to repair, replace, or regenerate damaged tissues and organs. The central challenge in this field often lies not in sourcing regenerative cells such as mesenchymal stem cells (MSCs), but rather ensuring their survival, functionality, and integration within hostile disease microenvironments. MSCs derived from diseased or aged tissues frequently exhibit impaired regenerative capacity, diminished viability, and reduced differentiation potential. RSV has emerged as a promising pharmacological preconditioning agent that can enhance the therapeutic performance of stem cells before transplantation. The regenerative potential of RSV stems from its ability to modulate multiple cellular signaling pathways, acting through a complex, synergistic network rather than targeting a single pathway. Although RSV has been studied as an effective agent in vast fields of biomedical research, this section focuses on its application in the context of regeneration and regenerative medicine, which may include tissue engineering and cell therapy. As a brief definition, ‘regenerative medicine replaces or regenerates human cells, tissue, or organs to restore or establish normal function. For example, RSV consistently promotes osteogenesis across various MSC sources. In periosteum-derived MSCs, crucial for fracture healing, RSV treatment at optimal doses significantly increased alkaline phosphatase activity and calcium deposition, key markers of bone formation. This osteogenic enhancement appears linked to the effects of RSV on mitochondrial biogenesis, with treated cells showing increased mitochondrial mass and DNA content. This metabolic shift from glycolysis to oxidative phosphorylation provides the energy necessary for producing bone matrix. Additionally, peripheral nerve repair via RSV-preconditioned adipose-derived stem cells (ADSCs) showed significantly improved

[DOI: 10.61882/ibj.5210]

therapeutic outcomes. When transplanted into rats with sciatic nerve injuries, resveratrol-treated ADSCs enhanced functional recovery, increased myelin sheath density, and improved muscle reinnervation. At the molecular level, RSV protected ADSCs from oxidative stress by modulating the Bcl-2/Bax ratio and reducing caspase-3 activation, key regulators of apoptosis[70]. Transplanted stem cells often contend with a hostile microenvironment at injury sites, characterized by inflammation, oxidative stress, and limited nutrient conditions that reduce cell survival and integration. Combined anti-inflammatory, antioxidant, and pro-survival effects of RSV help shield cells from these challenges. For instance, in neural regeneration models, RSV protected stem cells from H_2O_2-induced oxidative stress, a common challenge in injured nervous tissue[70]. From this point of view, we summarized many studies across different tissues that survey the influence of RSV on cells and the regeneration or repair of tissues, alone or in combination with pretreated cells and scaffolds (Table 1). RSV, as an antioxidant, anti-inflammatory, and cell proliferation or differentiation chemical inducer, has gained its position in the area of tissue engineering and regenerative medicine, as well as the angiogenic effect in wound healing treatment. Its ability to enhance stem cell functionality and create bioactive, multifunctional scaffolds addresses fundamental hurdles in the field. Additionally, the majority of evidence from in vitro and in vivo studies indicates a pressing need for well-designed human clinical trials to conclusively establish the safety, efficacy, and comparative advantage of RSV-reinforced regenerative therapies over existing standards of care. RSV can effectively be integrated into engineered scaffolds to create bioactive implants. Materials such as gelatin, polycaprolactone, collagen, and bacterial cellulose, along with RSV, develop anti-inflammatory, antioxidant, and pro-angiogenic properties. These combined materials create a microenvironment that scavenges harmful free radicals, stimulates blood vessel formation, and modulates the local immune response, hence accelerating tissue regeneration in applications ranging from cartilage and bone defects to chronic skin wounds[74].

8. ADVERSE EFFECTS OF RSV

The absence of debilitating or toxic side effects is a key aspect of the potential of RSV as a promising drug. Numerous in vivo and in vitro studies have utilized varying doses of RSV, making it crucial to establish the most suitable dose and method of administration. RSV has been demonstrated to induce cell death, especially in tumors, upon administration[75]. RSV has been shown to induce cell death in tumor tissues but has little effect on normal adjacent tissues. Variations in cellular targets and gene expression in cancer cells could cause differences in RSV uptake between normal and tumor cells, resulting in RSV with tumor-specific properties. According to Mukherjee et al., lower doses of RSV may offer health benefits, while higher doses can induce apoptosis and destroy tumor cells[76]. When given at doses of 1.0 gr, RSV appears to have no short-term side effects. However, in patients with NAFLD disease, side effects such as nausea, vomiting, diarrhea, and liver dysfunction may become apparent when the dosage exceeds 2.5 g per day[75]. Importantly, no significant adverse effects have been reported in long-term clinical trials. In fact, it has been established that RSV is considered to be safe and well-tolerated at dosages of up to 5 g per day, whether administered as a single dose or as part of a multi-day regimen. However, it is crucial to note that these investigations were conducted on individuals in good health, and outcomes may vary in individuals with medical conditions. The understanding of the dose-dependency and route of administration of RSV is further complicated by the fact that RSV, when taken orally, undergoes metabolic processes mediated by gut microbiota[77]. This complexity presents a challenge in distinguishing the effects is solely attributed to RSV from those caused by its metabolites. To investigate the theory regarding the inhibitory effects of RSV on the development of atherosclerosis in hypercholesterolemic rabbits, Wilson et al. conducted a study. The rabbits were given either oral RSV (1 mg/kg) or not given any treatment at all. The researchers found that the administration of RSV had no negative effects on the overall health of the rabbits, but it promoted atherosclerosis[78]. There was no difference in plasma LDL electrophoretic mobility between the two groups. However, examination of atherosclerotic plaques in both the control and RSV-treated groups revealed that the rabbits treated with RSV had a significantly larger area of their aortas occupied by atherosclerotic plaques[78]. Therefore, it can be concluded that RSV actually promotes the progression of atherosclerosis, rather than providing protection against it. This effect can be attributed to a different mechanism that is distinct from the observed differences in animal health, liver function, plasma cholesterol levels, or LDL oxidative state[78]. In a distinct investigation conducted by Ferry-Dumazet et al., the nephrotoxic effects of RSV were examined. Rodents were orally administered a dose of 3,000 mg/kg body weight of RSV for 28 days. This therapeutic intervention resulted in the development of nephrotoxicity, as indicated by elevated levels of serum blood urea nitrogen and creatinine, increased kidney weights, noticeable pathological changes in the kidneys, and an increased incidence and severity of histopathological alterations[79]. Microscopic

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Table 1. Application of RSV in tissue engineering and regenerative medicine

Tissue of interest	Intervention	Concentration/dosage	Study design	Cell target/accompany	Outcome	Ref.
	RSV	0.2 mL of 20 mg/kg/day for 7 days	Mice cranium defects	Human dental pulp stromal cells (hDPSCs)	Enhance osteogenic differentiation in oxidative stress conditions	[80]
	Polydatin, natural precursor of RSV	0.1-1.0 μM in culture medium	In vitro	hDBSCs	Differentiate DBSCs toward osteogenic lineage	[81]
	Collagen+ RSV scaffold + hASCs	N/A	Rat oral mucosal and calvarial bone defect	hASCs	Visible bone regeneration and more effective wound closure	[74]
	PLGA microsphere sintered + RSV	1-3 μM 1-7 days and 5-12.5 μM 7 -21 days	In vitro	hBM-MSCs	Modulate M1 to M2 macrophage-accelerate releasing of angiogenic factor- differentiating hBM-MSC stem to osteogenic lineage	[82]
	Apigenin + RSV+ Curcumin	10 mg/kg (gavage)	Rat calvarial defect	hDPSCs	Upregulate osteogenic-related genes in all groups, apigenin showed the best results in bone healing	[83]
	RSV-loaded albumin nanoparticles (RNP) entrapped in PCL (PCL-RNP)	N/A	In vitro	hBM-MSCs	Enhanced mineralization	[84]
	Solid lipid nanoparticles (SLNs) + RSV encapsulated in gelatin methacrylate (GelMA) hydrogel	Encapsulated at 0.02% concentration in GelMA	Rat cranial defect	BM-MSCs	Osteoconductivity, osteoinductivity, enhanced osteogenic differentiation	[85]
	RSV	5 μM, 10 μM and above	In vitro	PO-MSCs	Increasing both ALP activities and calcium deposits	[86]
	RSV + Biograft® HT (IFGL Bio Ceramics)	Oral administration 5mg/kg/day for 28 days	Rat calvarial defect	N/A	Accelerate osteoinductive effect - could be a supportive drug to induce new bone formation in the body	[87]

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Tissue of interest	Intervention	Concentration/dosage	Study design	Cell target/accompany	Outcome	Ref.
	RSV	In vitro: 10 μM In vivo: 100 mg/kg/day for 2 months (i.p,)	Mice osteoblastogenesis/ osteogenesis defective	mBM- MSCs	Upregulates Mitofilin, or Mic60, which improves mitochondrial function in stem cell senescence & improvement in osteogenic function of senescent mBM- MSCs	[88]
	RSV encapsulating in thiolated Pluronic F-127 + hyaluronic acid (HA)–acrylate+ hydrogel	Encapsulated 0.3% (*w*/*v*)	In vitro	hBM-MSCs	Osteogenic differentiation and antioxidative and anti-inflammatory actions on hBM-MSCs	[89]
	RSV + DTPF	N/A	Rat periodontal defect	mBM- MSCs and RAW264.7 cell line	Macrophage M2 polarization, osteoblast differentiation, & inhibition of osteoclast formation; enhances bone regeneration reduce osteoclast function	[90]
	Nano-hydroxyapatite (n HA)/RSV (RSV)/chitosan composite microspheres of Res	N/A	Rat femoral condyles defects in the ovariectomized osteoporotic model	rBM-MSCs and RAW264.7 cells line	Anti-inflammatory activity, enhancing adhesion, proliferation, and osteo-differentiation	[91]
	RSV	50 μM	Mouse periodontitis	N/A	Inflammation modulation after 1 week, increasing bone mass, and regeneration after 2 weeks	[92]
	RSV	N/A	In vitro periodontitis model	hPDLSCs	Modulating inflammatory response in hPDLSCs and promoting osteogenic differentiation	[93]
	Core-shell poly(ε-caprolactone)/chitosan/polyvinyl alcohol (PCL/CS/PVA+RSV	0.5%	In vitro and In vivo	pre-osteoblast cells	In vitro*:* osteogenic differentiation of pre-osteoblasts	[94]

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Tissue of interest	Intervention	Concentration/dosage	Study design	Cell target/accompany	Outcome	Ref.
	SPEEK + RSV	N/A	Zebrafish model	MG63 cell lines	Caudal fin regeneration relating to mineralization of osteoblasts in zebrafish	[95]
	PLA+ RSV	N/A	In vitro	hASCs	Antioxidant & osteogenesis properties	[96]
	RSV	10 mg/kg for 30 days	Rat calvarial defects	N/A	Improved repair of critical-sized bone defects	[97]
Cardiovascular	RSV	10 µmol/L	In vitro	mESCs	Differentiate toward cardiomyocytes and gain the beating properties	[98]
	RSV	In vitro: 1 mM-72 h In vivo: 10 mg/kg/day for 3-6 weeks (gavage)	Rat model of injured aorta	hEPC	Upgrading eNOS expression, increasing the proliferation, migration, & adhesive activities of cells, also accelerating the repair of injured arteries, increasing EPC mobilization, and improving eNOS expression	[99]
	RSV	2.5 µM for 1 h	Rat myocardium ischemic model	Rat heart multi-potent clonogenic Cancer stem cells (CSCs)	Enhancing cardiac function	[100]
	RSV	Administration of 2.5 mg/kg/day for 4 weeks	Mice AMI model	Antigen-1-positive (Sca-1+) CSCs	Increasing Sca-1+ CSCs, improving left ventricle function, capillary density, and decreasing cardiomyocyte apoptosis	[101]
	RSV	2.5 mg/kg/day for 2 weeks (gavaged)	Rat myocardium ischemic model	Adult CSCs	Improving cardiac regeneration and function via enhancing redox potential, stem cell survival, & proliferation	[102]
	RSV	Ex vivo: 5 µM for 12 h In vivo: 20 mg/kg/day for 4 weeks	Mice	mBM- MSCs &HUVEC	Improving tube formation in the HUVEC cells, MSC cells differentiation, and promotion of neovascularization of transplanted MSCs	[103]

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Tissue of interest	Intervention	Concentration/dosage	Study design	Cell target/accompany	Outcome	Ref.
	PCL+RSV	N/A	Rat abdominal aorta	ECs	Enhancing NO production, cell migration, increasing tube formation, supporting M2 macrophages, and reducing proinflammatory factors, enhancing vascular regeneration & reendothelialization	[104]
	RSV + PCL scaffold	N/A	Mice MI model	N/A	Decreasing inflammation, improving ECM secretion and blood vessel formation, improving ejection fraction and fractional shortening	[105]
	RSV + autologous ASCs	N/A	Rat T2D-induced model	Autologous Adipose stem cells (ASCs)	Improving fibrosis, hypertrophy, and apoptosis	[106]
Cartilage	RSV+ PLGA	N/A	In vitro	Cardiac Progenitor Cells (CPCs)	Expression of cartilage-related genes and deposition of specific ECM	[107]
	Porcine articular chondrocytes + RSV	50 µM for 14 days	In vitro induced osteoarthritis	Porcine articular chondrocytes	Improvement of cartilaginous ECM deposition of glycosaminoglycan	[108]
	RSV	17 µM for 14-21 days	In vitro hyperglycemic condition	Wharton's jelly of the human umbilical cord (hWJSCs)	Regulating the pro-inflammatory cytokines, increasing proteoglycans and collagen synthesis, and promoting chondrogenesis	[109]
	hBM-MSCs + RSV + hydrogel	1 µM	Rabbit osteochondral defect	hBM-MSCs	Enhancing proliferative, stemness, chondrogenic differentiation, senescence inhibition,	[110]
	RSV	1 µM	In vitro	hBM-MSCs	and hyaline cartilage regeneration Maintenance of self-renewal and stemness proliferation capacity	[111]

[DOI: 10.61882/ibj.5210]

Tissue of interest	Intervention	Concentration/dosage	Study design	Cell target/accompany	Outcome	Ref.
	Nanocrystalline HA + RSV + colloidal suspension	N/A	In vitro	hASCs	Enhancing viability, proliferation, and reduction of oxidative stress	[112]
Stem cells	RSV	5 µM	Mice periodontitis model	PDLSCs	Superior capability in stemness, self-renewal, proliferation, multipotent differentiation, immunomodulation, and rescuing bone loss	[113]
	RSV	1 µM	In vitro	hBM-MSCs	Maintenance of self-renewal and stemness proliferation capacity	[111]
	Nanocrystalline HA + RSV + colloidal suspension	N/A	In vitro	hASCs	Enhancing viability, proliferation, and reduction of oxidative stress	[112]
	RSV	5 µM	Mice periodontitis model	PDLSCs	Superior capability in stemness, self-renewal, proliferation, multipotent differentiation, immunomodulation, and rescuing bone loss	[113]
Kidney	hUC-MSCs + RSV	20 µmol/L for 12 h	Rat-induced kidney injury model	Rat renal tubular epithelial cell line hUC-MSCs	Accelerating proliferation and migration, and enhancing angiogenesis in endothelial cells	[114]
	RSV	4 mg/kg i.p. for 7 days	Mice ischemia/ reperfusion renal injury model	N/A	Does not affect renal recovery and regeneration	[115]

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Tissue of interest	Intervention	Concentration/dosage	Study design	Cell target/accompany	Outcome	Ref.
Liver	RSV	4 mg/kg/day (i.p.) for 3 and 7 days	Mice bile duct ligation (BDL) injury model	N/A	Promoting hepatocyte proliferation & reducing the mortality rate of mice, the number of Kupffer cells, and hepatic fibrosis	[116]
	RSV	6 mg/kg (i.p.)	Mice induced an acute toxic liver injury model	Mouse hepatocyte cell line	Reducing hepatocyte apoptosis, but limited in hepatocyte regeneration	[117]
	RSV + MSCs	100 mg/kg (i.p.) single dose alone and accompanied with rBM-MSCs	Rat PH model	rBM-MSC	Increasing liver regeneration	[118]
	RSV + Melatonin	RSV: 30 mg/kg/day for 7 days; melatonin: 10 mg/kg/day for 7 days	Rat PH model	N/A	Antioxidative effects and adverse influences on proliferation and apoptosis	[119]
	RSV	10 mg/kg (i.p.) for 7 days	Rat blunt hepatic trauma (BHT) model	N/A	Decreasing inflammation, improving hepatic histology, & modulation of apoptosis	[120]
	RSV	10 mg/kg/day for 60 days	Mice induced a toxic liver damage model	N/A	Ameliorating the liver injury	[121]
Muscle	RSV	0.1 or 25 μM for 3 days	In vitro	Mouse myoblast C2C12	Proliferation, myogenesis, and hypertrophy promotion	[122]
	RSV	10, 20, 40, or 60 mM for 24-48 h	In vitro	Mouse myoblast C2C12	Low doses (<40): promote cell migration, sprouting, and cell cycle arrest; High doses (>40): damaging effects on viability and oxidative capacity of muscle cells	[123]

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Tissue of interest	Intervention	Concentration/dosage	Study design	Cell target/accompany	Outcome	Ref.
Nervous system	PCL +RSV	N/A	In vitro	Rat spinal cord cells	Superior cell viability	[124]
	RSV	200 mg/kg/day (i.p.) for 10 days	Rat sciatic nerve crush model	PC-12 cells	Nerve regeneration & motor repair after a sciatic nerve crush injury	[125]
	PU+ PRP + RSV + Schwann cells	N/A	Rat sciatic nerve injury model	Primary rat Schwann cells	Creating resemblance to normal sciatic nerve, intact myelin sheath, & well-arranged fibers	[126]
	rADSCs + RSV	20 µM for 24 h	Rat sciatic nerve injury model	rADSCs	Improving H2O2- induced apoptosis and promoting sciatic nerve regeneration	[70]
	RSV	30 mg/kg/days (i.p) for 14 days after surgery	Rat spinal cord injury (SCI) model	Murine microglia BV2 cells	Inhibition of apoptosis and axonal regeneration	[127]
	PQQ+ RSV	5 µM	In vitro wound healing assay	Postnatal mice	Supporting neurite outgrowth, increasing the number of viable CGNS, and decreasing neurite length	[128]
	DPSCs +RSV + neuronal induction media	-	In vitro	DPSCs	Increasing neuro progenitor marker Nestin and anin and differentiation of neuronal cells	[129]
	hBM-MSCs + RSV + neuronal induction media	-	In vitro	hBM-MSCs	Increasing neuronal marker and neuronal differentiation of hBM-MSCs	[130]
	RSV	0.1-10 µM	In vitro	hUC-MSCs	Dose-dependent effect on self-renewal and neural differentiation	[131]
	Autografting nerves + RSV	-	Rat nerve root avulsion model	N/A	An increasing number and myelin thickness of regenerated axons and motor neurons	[132]
	RSV	250 mg/kg/day, oral administration for 3 weeks	Mice with a multiple sclerosis (MS) model	N/A	Reversing cuprizone-induced demyelination, improving motor coordination and balance, enhancing mitochondrial function, and alleviating oxidative stress	[133]

Ref.: references; N/A: not applicable

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examination of the kidneys revealed lesions. These lesions are likely attributable to the interaction between RSV (or its metabolites) and the osmotic gradients present in the renal medulla, where the compound becomes concentrated.

Administering either 1,000 or 300 mg of RSV per kg of body weight daily did not result in any observed nephrotoxic effects. The primary clinical signs of toxicity in the group receiving a dosage of 3,000 mg/kg of body weight per day included dehydration, piloerection, the presence of red material in the urine, reduced body weight gain, hyperalbuminemia, and anemia, which is due to renal impairment leading to decreased erythropoietin synthesis, and increased leukocyte counts due to inflammation of the renal pelvis[79]. RSV rapidly activates MAPK through a process that relies on MEK-1, Src, MMP, and EGFR. This activation occurs at concentrations in the nanomolar range, significantly lower than those required for genomic activity of the estrogen receptor. These concentrations can be temporarily achieved in the bloodstream after consuming red wine orally. Furthermore, studies have shown that consuming moderate amounts of RSV can prolong the lifespan of one-year-old mice. However, when mice were given high doses of RSV (1,800 mg/kg), they experienced mortality within 3 to 4 months. Studies on the steady-state pharmacokinetics and tolerability of a 2,000 mg dose of trans-RSV, taken twice daily with food, quercetin, and alcohol (ethanol), revealed that healthy individuals showed positive tolerance to trans-RSV, despite a significant occurrence of diarrhea[134].

9.CONCLUDING REMARKS AND FUTURE PERSPECTIVES

According to the beneficial effects, small molecular structure, and polyphenolic character of RSV, RSV is considered a robust antioxidant agent with the ability to bind to organic compounds present in many organisms. This ability to interact with biological molecules provides RSV with multiple biological activities, including protective effects against tumor processes, improvements in cardiovascular health, benefits for metabolic syndrome, and anti-aging properties. RSV also facilitates self-renewal and multipotency of MSCs and plays a regulatory role in the survival of MSC therapy. However, factors such as concentration, time of administration, and duration of RSV administration are also important. The low water solubility of RSV and extensive first-pass metabolism in the gut and liver pose significant challenges for its bioavailability. After oral administration, it is quickly absorbed and mostly converted into glucuronide and sulfate metabolites, resulting in a systemic bioavailability, often reported to be less than 1%. Therefore, the low circulating level of the parent compound means that the concentrations needed to elicit effects in in vitro models are rarely achieved in vivo at safe oral doses. To improve the bioavailability of RSV, several methods, including the use of liposomes, polymeric NPs, lipid NPs, and cyclodextrins, can enhance its solubility, protect it from metabolism, and promote targeted delivery. According to the dose-response in RSV, low concentrations of this compound can enhance cellular proliferation, while higher concentrations may have inhibitory effects. In animal models of CVD, AD, and osteoporosis, low doses are often protective, but higher doses can exacerbate disease processes. Future studies should focus on the therapeutic effects of RSV and MSC transplantation on the diseases affecting organs beyond the liver, brain, heart, and kidney. Investigating the protective effects of RSV derivatives is also required. In this light, new biomaterials that can greatly ameliorate the release or bioactivity of RSV will certainly contribute to regenerative medicine. Additionally, to avoid the non-specific cytotoxic effect of RSV, optimization strategies should focus on the potential use of RSV-based NPs. Significant progress has been made in developing the next generation of RSV-based nanocarriers, which could play a crucial role in treating various human diseases. However, the main limitations of these nanocarriers include difficulties in increasing bioavailability and enhancing targeting capabilities. Therefore, when designing and developing novel nanovectors, it is essential to address biological barriers that hinder the delivery of cargo and maintain intact and active quantities of RSV during transfer to the target site. The translational gap between preclinical promise and clinical applications shows that there is still no conclusive clinical evidence to recommend RSV in any healthcare setting. This gap arises from several interconnected factors, such as high concentrations, controlled and homogeneous animal models, short-term interventions, and direct measurement of molecular/mechanistic endpoints. Combining RSV with conventional therapeutics (e.g., chemotherapy and radiotherapy) is a promising strategy to enhance efficacy, reduce side effects, or overcome drug resistance. RSV can inhibit or induce CYP enzymes and drug transporters, potentially altering the pharmacokinetics of co-administered drugs, which leads to toxicity or reduced efficacy. One of the challenges in cancer treatment is the limited number of clinical trials, particularly randomized controlled trials that investigate the use of RSV in combination with standard therapies. Most existing clinical data come from monotherapy trials. Further research is needed to explore the uptake, metabolism, cellular destination, and stability of both the original molecule and its metabolites. This research will help to clarify the biological activity of RSV and

[DOI: 10.61882/ibj.5210]

maximize its efficiency in cancer treatment, potentially extending to regenerative medicine.

DECLARATION

Acknowledgments
Not applicable.

Generative AI and AI-assisted technologies
No artificial intelligence tools were used in the preparation of this manuscript.

Ethical approval
Not applicable.

Consent to participate
Not applicable.

Consent for publication
All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions
EN, RR, SV, MR, PM, FS, ESH, ZJ, DR, FH, and FSH wrote the manuscript. EN and FSH revised the manuscript.

Data availability
All relevant data can be found within the manuscript.

Competing interests
The authors declare that they have no competing interests.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Supplementary information
The online version contains supplementary material.

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[DOI: 10.61882/ibj.5210]