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Neurotherapeutic Potential of Resveratrol: A Comprehensive Review of Its Neuroprotective Mechanisms in Mitigating Cognitive Decline

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Abstract

Cognitive decline is a term used to refer to the decline in neurocognitive development of a person hence the loss of language skills, memory, or executive functions. The new directions in the prevention of cognitive impairment involve the consumption of phytonutrient-dense diets. To some extent this review aims to understand the impact of resveratrol in inhibition of neuro inflammation involved in cognitive impairment. To conduct a population, intervention, comparison, outcome and time tissue search was performed with an emphasis on gathering preclinical studies and clinical research on the molecular effects that resveratrol has on neuro inflammatory pathways including insight into neuronal apoptosis and synaptic plasticity. It will be seen in the preclinical and clinical studies that due to its effect on sirtuin proteins of resveratrol reduces activity of NF-κB thus lowers inflammation response in the brain. By doing this, further worsening of neuro inflammatory markers, neuronal death as well as deterioration of the synaptic plasticity that is pivotal to the preservation of cognition is avoided. The studies done in this subject show that resveratrol has the ability to be developed for use in the management of illnesses that affect cognition. Therefore, this analysis defines the molecular mechanisms by which resveratrol perform therapeutic role to ameliorate cognitive impairment. In so doing, the development of resveratrol as a nutritional supplement or lead drug candidate can best be achieved if the drug's role in neuro degeneration is fully understood.

Keywords: Cognitive Function, Neurodegenerative Diseases, Neuroinflammation, NF-κB Pathway, Resveratrol, Sirtuins.

Introduction

Cognitive decline is a comprehensive term encompassing various conditions and diseases, with aging being a common factor (1). It is essential to report that cognitive decline cannot always be due to aging but can be attributed to other lifestyle factors (2). Cognitive decline refers to reduced cognitive abilities that include memory, attention, language, and problem-solving skills. The degree of decline can vary between mild and severe, adversely affecting daily life and independence. It is essential to consider other factors than aging to alleviate the illness, revealing the molecular mechanisms contributing to the development of this illness (3). It can also result from other factors like brain injury, environmental influences, health conditions such as mild cognitive impairment (MCI), different forms of dementia, or even lifestyle factors like inadequate diet, lack of exercise, and insufficient sleep (4). Globally, approximately 50 million individuals are affected by dementia. Furthermore, with a new case emerging every three seconds, the number of individuals diagnosed with dementia is expected to triple by 2050 (5). Countries must focus on reducing modifiable risk factors for dementia due to the rising number of dementia cases, the disease's significant social and economic burden, and the lack of a cure. Risk reduction is the focal point of the third action area of the Global Action Plan on the Public Health Response to Dementia, 2017–2025. The proper activation of numerous protective inflammatory mechanisms, including the production of pro-inflammatory mediators and the protection of neurons, is the most important stage in the neuro protective activity of resveratrol against cognitive decline (6). The regulatory mechanism includes anti-inflammatory,

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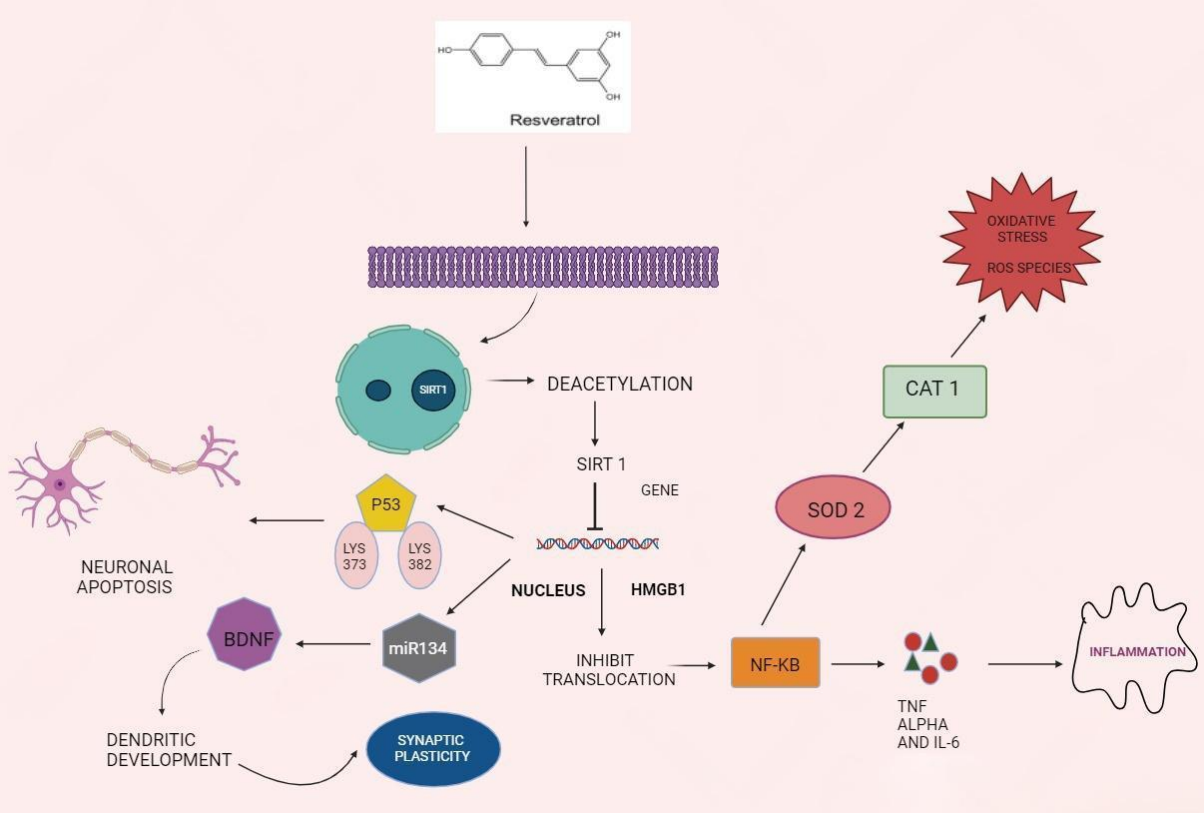

Figure 1: Resveratrol-Induced SIRT1 Signalling in Neuroprotection and Anti-Inflammatory Pathways

anti-oxidative, and anti-apoptotic processes, as well as regulation of autophagy, improvements in the plasticity of synaptic pathways, and increases in cerebral blood flow. Thus, suggesting Resveratrol is likely to offer promising therapeutic approaches for slowing down cognitive decline, promoting healthy aging and restoring brain functions. This review examines recent developments in understanding how resveratrol delays age-related cognitive decline mediated through different pathways. A thorough systematic literature review was conducted to evaluate the impact of resveratrol on neuroinflammation via its interaction with the sirtuin-dependent NF-κB pathway (Figure 1). The review involved searching various scientific databases, including Web of Science, Scopus, PubMed, and Google Scholar, using specific keywords such as "resveratrol," "neuroinflammation," "sirtuins," "NF-κB pathway," "cognitive function," "neurodegenerative diseases," and "inflammation modulation," among others. To further explore the basis for resveratrol's anti-inflammatory and neuroprotective properties, in vivo studies using animal models were conducted, which were crucial in verifying the biological significance of these molecular mechanisms and their effects on cognitive health and neuro-inflammatory states. Clinical trials were also pivotal in determining the practical applicability of these preclinical insights, focusing on the assessment of resveratrol's safety, effectiveness, and potential as a therapeutic option for individuals affected by or at risk for neurodegenerative disorders. Resveratrol offers a novel approach to treating neurodegenerative diseases due to its capacity to protect against neurological damage and improve cognitive function by modulating different neuronal pathways (7). To develop targeted treatments aimed at lowering neuroinflammation and improving brain health, it is imperative to comprehend the underlying mechanisms of resveratrol's beneficial effects.

Neuroinflammation

The neuroprotective properties of resveratrol are primarily attributed to its capacity to stimulate multiple pathways. Resveratrol binds directly to (silent information regulator sirtuin 1) SIRT1, boosting its enzymatic function by increasing its affinity for (nicotinamide adenine nucleotide) NAD+ (its essential coenzyme) and its acetylated

target molecules (8). This elevation is achieved either through the up regulation of genes related to NAD+ synthesis or the suppression of enzymes that break down NAD+, additionally, experiments conducted on various neural cells have shown that the SIRT1 activator, resveratrol, diminishes inflammatory cytokines by inhibiting the transcriptional activity of NF-κB (9). By obstructing NF-kB activation, resveratrol diminishes the production of inflammatory molecules like interleukin-1beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), which play pivotal roles in the development of neurodegenerative conditions (10). Pre-treatment with resveratrol increased the expression of SIRT1, inhibited the neuroinflammatory response in the hippocampus, and improved cognitive function in aged models (11). SIRT1 has been shown to counteract IL-1β-induced pro-inflammatory stress via the TLR2/SIRT1/NF-κB pathway, exhibiting anti-inflammatory properties A lack of SIRT1 was found to exacerbate microvascular inflammation in obese mice with sepsis. Conversely, treatment with resveratrol led to a reduction in leukocyte/platelet adhesion and the expression of E-selectin/ICAM-1 (intercellular adhesion molecule 1), alongside an increase in SIRT1 expression, which collectively contributed to enhanced survival rates (12). Research has shown that reducing STAT1, JAK2, p-JAK2, p-STAT3, and blocking the (janus kinase/signal transducers and activators of transcription) JAK/STAT1 signalling pathway can reduce inflammation, control (B-cell lymphoma 2) Bcl-2 and Bax levels, and aid in the restoration of brain function (13). On the other hand, enhancing p-JAK1, p-STAT3, or hyperactivating the JAK2/STAT3 pathway might decrease inflammation and encourage the SOCS (suppressor of cytokine signalling) to provide negative feedback (14). It has been discovered that in in vitro hypoxia/OGD (oxygen glucose deprivation) models, resveratrol inhibits the mitochondrial death pathway and controls the expression of the proteins Bcl-2, Bax, and caspase-3(15).

Free Radical Mechanism

Research has indicated that resveratrol provides anti-oxidant effects to skin cells and tissues by inhibiting the NF-kB pathway, which also counteracts the oxidative stress associated with diabetes (16). Furthermore, it protects skeletal muscle from oxidative injury and reduces nitric oxide (NO) synthesis and inducible nitric oxide synthase (iNOS) expression. Resveratrol has been shown to possess anti-inflammatory potential by its inhibition action on the production of pro-inflammatory cytokines such as TNF-α, interleukin (IL)-1β, and IL-6, and its phosphorylation potential of STAT1 and STAT3(17). In addition it is found to reduce the accumulation of reactive oxygen species (ROS) and it's up regulation in the expression of antioxidant enzymes, thereby reducing the development of oxidative stress (18). Resveratrol promotes the activation of SIRT1, a protein essential in the management of cellular stress responses (19). Further this leads to the upregulation of antioxidant enzymes such as catalase (CAT) and superoxide dismutase 2 (SOD2), which mitigate oxidative damage and offer neuroprotection. Resveratrol initiates the formation and stability of transcriptional complexes by up regulating the expression of antioxidant enzymes and ROS elimination (20). Animal studies revealed that resveratrol treatment can decrease the oxidative stress-induced damage in the hippocampus, promote apoptosis, and up regulate the SIRT1 expression (21). It also found to maintain the normal levels of glutathione (GSH), an essential antioxidant depleted by neurotoxic substances like amyloid beta (Aβ, 22).Resveratrol's action on SIRT1 leads to the reduced expression of pro-inflammatory mediators such as iNOS, ICAM-1, IL-6, and (vascular cell adhesion molecule 1) VCAM), thus conferring protection against the damage to endothelial cells caused by oxidative stress(23).This modulation of cellular pathways pertinent to oxidative stress and inflammation positions resveratrol as a potentially effective treatment for neurodegenerative illnesses.

Neuronal Apoptosis

Various studies elucidate that resveratrol orchestrates its neuroprotective effects through modulation of the SIRT1/RhoA(Ras homolog family member A) signaling cascade with amelioration of cognitive dysfunction in adult rats, attributable to the attenuation of neuronal apoptosis (24). Notably, prophylactic administration of RSV prior to anaesthesia induction emerged as superior to ameliorating postoperative cognitive dysfunction (POCD) compared to its administration post-anaesthesia

(25). Further mechanistic insights revealed that RSV augmented cellular viability, diminished intracellular Ca2+ concentrations, and mitigated Aβ25–35-induced apoptosis in neuronal cells (26). Detailed molecular analysis indicated that RSV effectively reinstated the expression of Aβ25–35-suppressed SIRT1, thereby facilitating neuroprotection against Aβ25–35 in PC12 cells (27). This protective mechanism was predominantly mediated by the upregulation of SIRT1 expression, which sequentially led to the inhibition of Rho-associated kinase 1 (ROCK1) activity These findings accentuate the capacity of RSV to traverse the blood-brain barrier and exhibit salient biological activities, including anti-inflammatory, antioxidative, and anti-apoptotic properties. Acting as a potent agonist of silent information regulator 2 homolog 1 (SIRT1), RSV triggers the activation of SIRT1-dependent neuroprotective pathways, offering a protective shield in the brain against a myriad of diseases, notably through the modulation of the cAMP/(adenosine monophosphate-activated protein kinase)AMPK/SIRT1 axis and suppression of p53-mediated apoptotic pathways (Figure 2) (28). This study not only corroborates the neuroprotective potential of RSV in mitigating cognitive impairment induced by sevoflurane (SEV) exposure in neonatal mice but also pioneers the exploration of its therapeutic implications in adult rat models, shedding light on the pivotal role and mechanistic pathways of RSV in pre- and post-operative cognitive impairment mitigation.

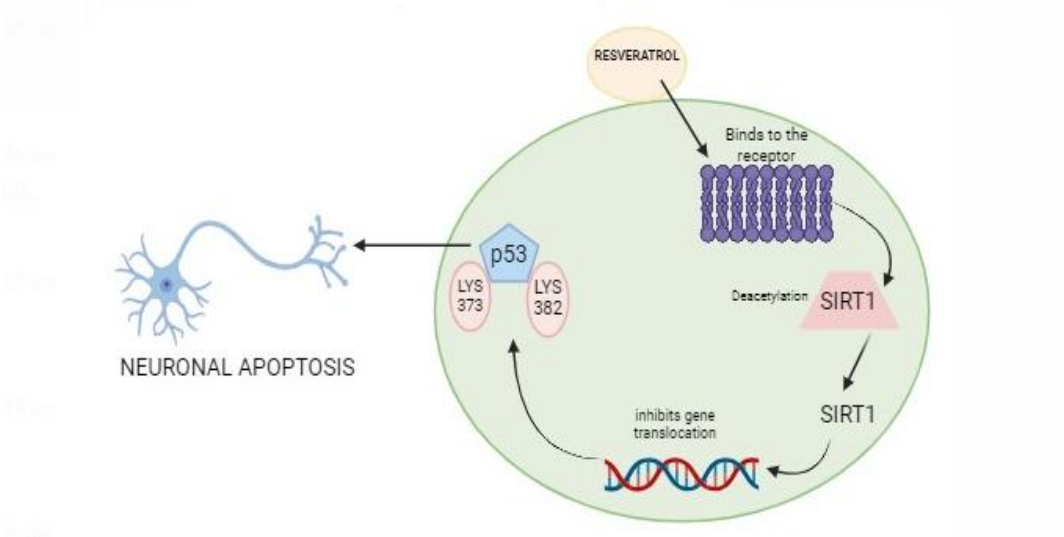

Figure 2: Resveratrol-Mediated SIRT1 Activation Pathway in p53-Dependent Regulation of Neuronal Apoptosis

Synaptic Plasticity

Resveratrol enhances cerebral blood flow and synaptic plasticity. Activation of SIRT1 and Brain-Derived Neurotrophic Factor (BDNF) mechanisms is crucial for cognitive processes and neural adaptability, leading to the occurrence of these effects (29). Resveratrol (RSV) can penetrate the blood-brain barrier, facilitating increased antioxidant enzyme activity and activating SIRT1-associated pathways (30). This promotes glial activation and hippocampal neurogenesis. These effects are brought about by activating SIRT1 and Brain-Derived Neurotrophic factor (BDNF) mechanisms essential for cognitive processes and neural adaptability. Activating SIRT1 and Brain-Derived Neurotrophic Factor (BDNF) mechanisms is essential for cognitive processes and neural adaptability, which brings about these effects. The inhibition of (microRNA-134) miR-134 and the activation of the (cAMP-response element binding protein - Brain-Derived Neurotrophic Factor) CREB-BDNF axis are stimulated by the SIRT1-YY1 (Yin-Yang 1) complex, which is significant in the transcription of BDNF (Figure 3) (31). BDNF transcription is essential for dendritic growth and enhances synaptic function. Its regulatory impact on amyloid precursor protein expression and spatial working memory enhancement has been documented (32). Furthermore, genomic analyses indicate RSV's normalisation of hippocampal gene expression related to neurogenesis and synaptic flexibility, highlighting its protective role against neurotoxic substances like lead (Pb), suggesting its

potential as an adjunctive therapeutic option (33). Ensuring the modulation of synaptic markers, namely (synapsin 1) Syn-1,(LIM domain kinase 1) LIMK1, and NL-1, by a (BDNF) brain-derived neurotrophic factor is crucial for the proper functioning and adaptability of neurons (34). The modulation of synaptic markers such as Syn-1, LIMK1, and NL-1 by (BDNF, brain- derived neurotrophic factor essential for neuronal functionality and plasticity has been confirmed (35). These results highlight the potential of resveratrol as a natural intervention that could improve cognitive performance, alleviate menopausal symptoms, and enhance overall human well-being.

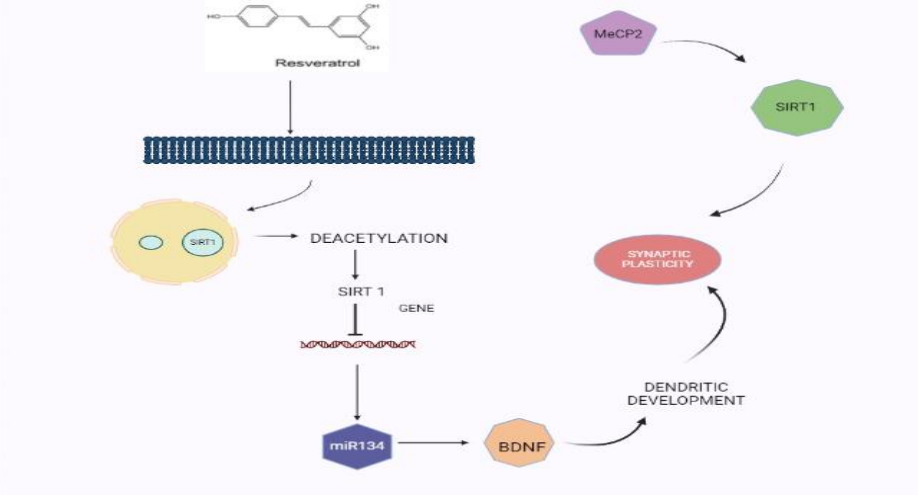

Figure 3: Resveratrol-Induced SIRT1-Mediated Modulation in Synaptic Plasticity and Dendritic Development

Cognitive decline is a rising global public health concern, especially in the elderly population. Research statistics indicate that there is a considerable rise in the percentage of aged population (60 years) experiencing mild cognitive impairment, with a higher probable increase in rate among those aged over 70 with neuropsychiatric symptoms (36).The influence of genetic, nutritional, and metabolic factors on cognitive impairment and dementia in older adults is essential, with vascular pathology and inflammation being involved in the pathogenesis of these conditions (37). Resveratrol is an important phytochemical with reported promising action in alleviating conditions related to the development of cognitive disorders. Long-term randomized clinical trials are required to substantiate the belief that it influences various cellular target pathways as shown in Table 1, which may provide a protective function in delaying the start of cognitive decline (38). Resveratrol is reported to improve several metabolic syndrome components, such as insulin resistance and blood pressure, with its reported low bioavailability parameters (39). The primary mechanism includes direct activation of SIRT1, inhibition of NF-κB, and modulation of the JAK/STAT pathway. These pathways are essential in controlling neuroinflammation and apoptosis by down regulating pro-inflammatory cytokines like IL-1β and TNF-α (40). Resveratrol's role in enhancing AMPK activity has been shown to impact the mitochondrial biogenesis and energy homeostasis with positive impact on neuronal health. Secondary mechanisms, evolving from primary with indirect downstream effects, such as increased antioxidant defense through upregulation of enzymes like SOD2 and catalase, and regulation of synaptic plasticity via BDNF- and CREB-mediated pathways. This differentiation between primary and secondary mechanisms will provide a clearer understanding of resveratrol's multifaceted therapeutic potential in neurodegenerative diseases, highlighting its holistic impact on neuroprotection and cognitive health. Thus, the development of formulations with improved bioavailability is essential in the near future to study the benefits of resveratrol. Furthermore, the safety profile and tolerability of resveratrol are supportive of its development as a nutraceutical to treat cognitive illness. There is no reported evidence of the interaction of resveratrol with conventional drugs available on the market to treat the illness. Thus, the inclusion of resveratrol as a nutritional and dietary supplement in addition

to conventional therapy can be advocated to delay the onset of cognitive illness in different age groups. Resveratrol has been shown to activate SIRT1, a protein crucial for neuronal health, and inhibit beta-amyloid aggregation—a key factor in AD pathology. A 52-week randomized trial reported that resveratrol treatment Aβ40 levels in cerebrospinal fluid and improve cognitive decline in Alzheimer patients (41). Resveratrol has demonstrated anti-inflammatory and antioxidant effects by reducing pro-inflammatory cytokines (e.g., TNF-α, IL-6) and decreasing oxidative stress markers in the brain (42). Although resveratrol consistently improves cerebral blood flow and markers of inflammation, more large-scale, high-quality trials are needed to confirm its therapeutic potential in clinical settings. Overall, these findings suggest resveratrol as a promising candidate for neuroprotection, though further research is warranted to optimize its use in clinical practice.

Resveratrol has low bioavailability due to rapid metabolism and poor absorption. When ingested, it undergoes extensive first-pass metabolism in the intestines and liver, resulting in low systemic availability (43). Most of the compound is converted into its glucuronide and sulfate conjugates, limiting its concentration in the bloodstream. Strategies to enhance bioavailability include formulation approaches like nanoparticle delivery systems, liposomal encapsulation, and the use of resveratrol analogs or prodrugs, which can help increase its stability and improve its therapeutic efficacy.

Table 1: Resveratrol Mechanisms in Mitigating Cognitive Decline and Their Descriptions

Mechanism	Description	Key Findings	Reference
Neuroinflammatory Mechanisms	Resveratrol combines with sirtuin proteins to downregulate the activity of NF-κB It reduces responses to inflammation in the brain.	Survival of neurons, supporting the critical synaptic plasticity for preserving cognitive functions, and avoiding neuroinflammatory markers.	(44,45)
Effect of Antioxidant	Resveratol prevents oxidative stress by increasing the activity of antioxidant enzymes and harvesting free radicals.	A reduction in the intensity of oxidative stress caused damage in the hippocampus, a return to normal levels of glutathione, and a protective role against neurotoxic substances.	(18,46)
Synaptic Plasticity	Resveratrol increases the blood flow to cerebral, synaptic plasticity and induces mechanisms of BDNF for crucial cognitive processes.	Alterations of synaptic markers, increases in the growth of dendrites, and enhancement of spatial working memory.	(47,48)
Mechanisms of Anti-Apoptotic	Resveratrol alters signaling of SIRT1/RhoA and prevents neuronal apoptosis.	Improvement of cognitive dysfunction, decreases the concentration of intracellular Ca2+, prevents neuronal cells apoptosis.	(24,49)
Molecular Pathways	Resveratrol affects multiple cellular pathways, including SIRT1/AMPK,and controls oxidative stress and neuroinflammation.	Activation of SIRT1 dependent pathways, inhibition of p53-mediated apoptotic pathways.	(50,51)

Conclusion

Resveratrol a polyphenolic phytonutrient which is widely used from ancient time in medicine for maintaining the neurological health of the brain and to provide protection against neurodegenerative diseases like Alzheimer's Parkinson, Huntington's diseases etc. The compound has multiple target pathways of action, including the modulation of sirtuin activity, which is a cellular target pathway that has been shown to contribute significantly to the inhibition of neuroinflammation, increase in cellular lifespan and improvement in genome stability. Through the regulation of sirtuin activity, resveratrol decreases neuroinflammation, maintains cognitive function, and promotes neuronal health and possibly extends the age of onset of neurodegenerative diseases. Resveratrol has strong antioxidant activity thus reducing oxidative stress, and free radical, prevented neurons from damage and apoptosis, and helped to preserve the blood-brain barrier. This in turn aids in maintaining the synaptic function, stimulate neurogenesis and neurogenesis, and the formation of new neurons. In addition, resveratrol has positive effects on the process of synaptic plasticity which is essential for learning and memory therefore, it may be useful in the treatment of the cognitive deficit and neurodegenerative disorders. Taken together, the present review underscores the therapeutic value of resveratrol in modulating cognitive dysfunction and neurodegeneration, which points to a promising direction for the creation of new therapeutic strategies for age-related cognitive decline and neurodegenerative disorders and confirms the effectiveness of resveratrol as an auxiliary remedy for maintaining and treating neurological disorders. The neuroprotective effects of Resveratrol are thus expected because it can easily pass through the blood brain barrier which makes it appropriate to be used in treating neurological conditions.

Abbreviations

RSV: Resveratrol, SIRT1: silent information regulator1, RhoA: Ras homolog family member A, AD: Alzheimer disease, BDNF: Brain-Derived Neurotrophic Factor, Aβ: amyloid beta, JAK/STAT: Janus activated kinase, NF-κB: nuclear factor κB, AMPK: adenosine monophosphate (AMP)-activated protein kinase.

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Author Contribution

JR-Formulating idea, obtaining material, reviewing producing first draft. VSK, RS and YS- Revising drafting and referencing the draft.

Conflict of Interest

The authors declare there is no conflict of interest.

Ethics Approval

This article has not performed any animal or human clinical studies.

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