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Integrative Approaches to Resveratrol in Diabetic Neuropathy: Mechanisms, In Silico Studies, and Future Directions

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ABSTRACT

Diabetic peripheral neuropathy, known as (DPN) is a frequent microcirculatory aggravation caused by diabetes and is largely due to oxidative stress, mitochondrial dysfunction, inflammation and metabolic imbalances. Resveratrol is a natural polyphenol found in many plants, such as grapes and peanuts. Due to its several properties including antioxidant, anti-inflammatory and neuroprotective effects, resveratrol has been highlighted as a potential treatment for DPN. The benefits of resveratrol arise from the activation of the SIRT1, AMPK and Nrf2 pathways, which improve mitochondrial function, inhibit NF-κB mediated inflammation and modulate TRPV4 mediated calcium toxicity. Preclinical studies show that resveratrol can restore nerve structure, decrease symptomatic pain caused by neuropathy, decrease oxidative stress and improve sensory function in models of diabetes. Studies using in silico methods, such as molecular docking, molecular dynamics, and predictions of ADMET also provide evidence for the multitarget effects of resveratrol at the molecular level on proteins associated with neuropathic disease. Early clinical trials found that resveratrol improved glycaemic control and responded favourably to neuropathy symptoms and overall quality of life, most effectively when combined with medical care. Despite its promising potential, poor bioavailability, rapid elimination via metabolism and lack of a standardised dose limit successful application of resveratrol as a systemic treatment for DPN. Continued research on resveratrol will focus on advancing unique drug delivery systems, creating more refined structural analogues, and increasing clinical evidence demonstrating efficacy on systemic neuropathy.

Keywords: Resveratrol, Diabetic Neuropathy, In Silico Studies, Future Directions

1. INTRODUCTION

A range of pathophysiological mechanisms is responsible for the development of diabetes, which is a chronic metabolic disorder characterized by hyperglycaemia. From immune-mediated destruction of B-cells, which leads to a deficiency of insulin, to non-responsivity or tolerance to insulin [1]. It is associated with derangement and compromise in tissues and organs, which include the heart, blood vessels, kidneys, nerves, and retina, accompanied by terminal organ damage [2]. Depending on these pathophysiological mechanisms, there are 3 categories of diabetes. Type 1 diabetes occurs because of insufficient insulin secretion as a result of destroyed β-cells. Hyperglycaemia becomes evident only after the loss of approximately 90% of pancreatic β-cells. Type 2 diabetes is triggered by inadequate sensitivity of B-cells to insulin. About 90-95% of cases consist of type 2 diabetes mellitus. Gestational diabetes is the third type, which occurs during pregnancy because of obesity and carbohydrate intolerance [3]. Marked hyperglycaemia is characterized by various symptoms such as polyuria, polydipsia, weight loss, impairment of growth, and susceptibility to certain infections. Diabetes induced chronic manifestations include nephropathy, retinopathy, and peripheral neuropathy [1].

Diabetic peripheral neuropathy (DPN) is the principal microvascular sequela of type 1 and type 2 diabetes mellitus that elevates morbidity and mortality potential because of extremity loss and wound development. DPN has been linked to various forms of peripheral nerve dysfunction, including nerve damage involving axons, painful and uneven weakness of proximal muscles, dysfunction of individual nerves, and impairment of autonomic functions, provided that alternative aetiologies are ruled out [4,5]. Symmetrical pain is observed in the terminal parts of the limbs. Gloves and socks sensation is the most typical manifestation of peripheral neuropathy [6]. Painful diabetic peripheral neuropathy is associated with a range of adverse outcomes, including impaired sleep quality, decreased occupational performance, diminished quality of life, heightened psychological distress (e.g., anxiety and depression), and a significant increase in healthcare utilization and costs [7]. Accurately determining the prevalence of DPN is crucial for raising awareness and strengthening efforts toward its prevention and management in diabetic populations. The

prevalence of DPN varies significantly across countries, with estimates reported at 8.4% in China, 48.1% in Sri Lanka, 29.2% in India, 56.2% in Yemen, 39.5% in Jordan, 71.1% in Nigeria, 16.6% in Ghana, and 29.5% in Ethiopia [8–15]. Variation in the reported prevalence of DPN can be attributed to discrepancies in diagnostic criteria, the forms of diabetes assessed, patient selection approaches, and the size of the study populations [5]. This review aims to provide a comprehensive overview of resveratrol as a potential therapeutic agent for diabetic peripheral neuropathy, focusing on its mechanism of action, preclinical evidence, computational studies, and translational challenges.

2. Pathophysiology of Diabetic Peripheral Neuropathy (DPN)

Diabetic peripheral neuropathy is a type of nerve damage that develops over time in people with diabetes. It mainly affects the sensory nerves, which are responsible for feeling, but can also involve the nerves that control automatic body functions and, to a lesser extent, those that control movement. In advanced diabetic neuropathy, the peripheral portions of sensory nerve fibres gradually cease and undergo a "dying-back" type of degeneration, meaning the damage starts at the most distant terminals in the skin or peripheral tissues and then moves towards the centre. This pattern reflects a length-dependent loss of axonal integrity, while the neuronal cell bodies (perikarya) in the dorsal root ganglia remain comparatively intact. In other words, although the outer branches of the sensory nerves deteriorate first, the main nerve cells themselves are initially spared, which explains why symptoms typically begin at the extremities, such as the toes and feet, before progressing upward. Considerable experimental data have demonstrated that the entire neuron from the soma to its distal terminals can be compromised by diabetes. Nevertheless, ongoing discussion concerns whether the primary injury occurs within peripheral axons and their associated Schwann cells or within the neuronal somata located in the dorsal root ganglia (DRG), which sustain axonal integrity [16]. Diabetic neuropathy is mainly axonal rather than demyelinating, but persistent high blood glucose can damage Schwann cells, and severe cases often show signs of myelin loss [17–19].

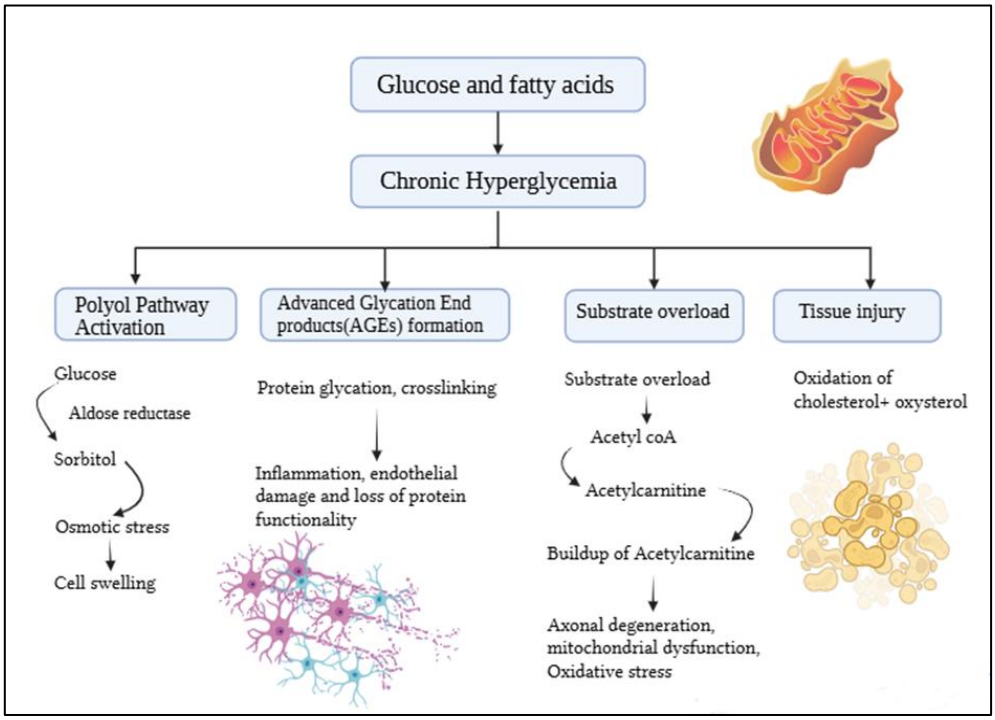

Figure 1: Pathophysiology of Diabetic Peripheral Neuropathy

2.1. Hyperglycemia and hyperlipidemia

In the peripheral nervous system, Schwann cells, DRG neurons, and axons have high energy demands and primarily utilize glucose and fatty acids as metabolic substrates. These are metabolized to generate NADH and $FADH_2$, which drive ATP production in mitochondria. Long-chain fatty acids undergo β-oxidation to form acetyl-CoA, which enters the citric acid cycle. In diabetes, however, substrate overload disrupts this process, leading to the conversion of excess acetyl-CoA into acylcarnitine. The accumulation of acylcarnitine in Schwann cells and DRG neurons is toxic and contributes to axonal degeneration, likely through mechanisms involving mitochondrial dysfunction and oxidative stress [20]. In mitochondria, NADH and FADH2 are mediated by complexes I-IV, and ATP is synthesized via oxidative phosphorylation. This process results in trace amounts of reactive oxygen

species (ROS), which are detoxified by intrinsic cellular antioxidants. Elevated substrate levels in diabetes result in failure of phosphorylation, leading to loss of ATP production and increased ROS levels, triggering mitochondrial dysfunction, metabolic and oxidative damage of Schwann cells and DRG neurons [21–23]. High glucose levels stimulate the polyol and hexosamine pathways, which culminate in the production of more ROS and inflammation [24]. Alteration or loss of protein functionality is induced by advanced glycation end products (AGEs), which also engage AGE-specific receptors (RAGE) to influence gene transcription and intracellular signal transduction [25]. Through these interactions, the secretion of pro-inflammatory mediators and the generation of reactive oxygen species are promoted. Tissue injury is mediated by oxidation of cholesterol to oxysterols [26].

2.2. Microvascular factors

In diabetes, small blood vessels don't work properly (Microcirculatory dysfunction), inducing additional neuronal impairment. Diabetes leads to a reduction of important substances comprising nerve growth factor (NGF), insulin growth factor, vascular endothelial growth factor (VEGF), and angiopoietin, which helps blood vessels to grow. Collectively, these observations indicate that the management of microvascular impairments in diabetes ought to be regarded as an adjunctive therapeutic strategy [27].

2.3. Sensitivity factor

Neuropathic pain arises due to damage or dysfunction in the somatosensory nervous system. It affects about 30–50% of individuals with diabetic neuropathy and is most experienced as a spontaneous burning sensation in the feet. [28]. The reason why only a subset of individuals with diabetic neuropathy develops neuropathic pain remains incompletely understood, although it is presumed to reflect a multifactorial interaction of predispositions, including genetic determinants, alterations in somatosensory pathways, and psychological influences in the context of stressors such as metabolic dysregulation in diabetes and the severity of neuropathic involvement [29]. For longer-term effects, the NGF-TrkA complex is internalized and retrogradely transported along the axon to the neuron's cell body in the dorsal root ganglion (DRG). Here, it induces lasting transcriptional changes that upregulate the expression of pain-related genes, ion channels, and neuropeptides like Substance P and calcitonin gene-related peptide (CGRP). This process increases neuronal excitability within the spinal cord, amplifying and perpetuating the pain signal centrally.

3. Resveratrol in DPN

Resveratrol found in natural plants and fruits such as *veratrum*, *polygonum cuspidatum*, grapes, and peanuts is a polyphenol which possesses a variety of beneficial effects, such as preventing oxidative stress injury, regulating blood sugar levels, inhibiting inflammation, and improving insulin resistance, in the treatment of many chronic diseases, such as Alzheimer's disease, Diabetes mellitus, coronary heart disease, and obesity [30]. Resveratrol activates NAD+-dependent deacetylase and Sirtl ,This activation improves mitochondrial function, activates endogenous antioxidant stress nuclear factor 2-related factor 2 (NF-E2-related factor2. Nrf2), and further increases the expression of detoxification enzymes in phase II, carry out free radicals scavenging, and alleviates tissue oxidative damage [31,32].

Diabetic peripheral neuropathy (DPN) is a debilitating and commonly occurring complication of diabetes mellitus, and its hallmark is progressive injury to peripheral nerves. Resveratrol has been studied extensively for its anti-inflammatory, anti-aging, antioxidant, and anticancer effects, as well as for its potential effect in neurodegenerative, degenerative musculoskeletal, and cardiovascular diseases (CVDs), all of which hold the promise for mitigating the pathophysiological processes involved in DPN [33].

3.1. Oxidative stress and antioxidant pathways

Over the past decade, Resveratrol as a nutraceutical compound has gained attention because of its therapeutic effects. This naturally occurring polyphenol has numerous pharmacological impacts, such as hepatoprotective, anti-diabetic, anti-cancer, antioxidant, anti-inflammatory, cardioprotective, and the ability to ameliorate dyslipidemia. These exceptional therapeutic effects may come mostly from its antioxidant activity [34].

3.1.1. Nrf2/ARE pathway Activation

The main antioxidant mechanisms of resveratrol is its effect on the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. Under physiological conditions, Nrf2 is retained in the cytoplasm by its inhibitor Keap1 (Kelch-like ECH-associated protein 1) which facilitates its degradation. Resveratrol interrupts the Keap1-Nrf2 connection, which stabilizes Nrf2. This allows Nrf2 to move into the nucleus, bind to the antioxidant response element (ARE), and increase the production of antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), heme oxygenase-1 (HO-1), and glutathione (GSH)-related enzymes.

In aging leukocytes, resveratrol continues to activate Nrf2 even when the AMPK pathway becomes less responsive. This shows that Nrf2 plays a strong role in resveratrol's antioxidant effect [34].

3.1.2 Direct radical scavenging and phenolic effect

In addition to signalling, the chemical structure of resveratrol, which has multiple phenolic hydroxyl groups, allows it to directly scavenge free radicals from reactive oxygen and nitrogen species (ROS/RNS). This provides a quick, non-enzymatic form of antioxidant defense.

3.2. Mitochondrial protection and energy metabolism.

Resveratrol also boosts energy-sensing and mitochondrial protective signalling through AMP-activated Protein Kinase (AMPK) and Sirtuin 1 (SIRT1). When resveratrol activates AMPK, it leads to the phosphorylation of PGC-1α (peroxisome proliferator-activated receptor gamma co-activator 1-alpha). PGC-1α then moves to the nucleus, and after SIRT1 deacetylates it, PGC-1α encourages mitochondrial biogenesis and antioxidant gene expression. Through this pathway, resveratrol helps maintain mitochondrial integrity, lowers reactive oxygen species (ROS) production, and improves cell resilience [35].

3.2.1. Autophagy, mitophagy, and mitochondrial quality control

Resveratrol encourages autophagy and mitophagy via the AMPK/mTOR/TFEB axis. This process helps remove damaged organelles, particularly mitochondria, which can produce ROS. Better mitochondrial quality control, therefore indirectly reduces oxidative stress [36].

3.3. Inflammatory pathways

Inflammasomes are key regulators of inflammation. The NLRP3 Inflammasomes is the most studied and is closely linked to inflammatory and neurodegenerative diseases. NLRP3 acts as an intracellular sensor that detects pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). This leads to its assembly and activation. The NLRP3 Inflammasomes complex includes the sensor protein NLRP3, the adaptor protein apoptosis-associated speck-like protein (ASC), and the enzyme procaspase-1. Procaspase-1 is crucial for activating caspase-1 and starting downstream inflammatory responses.

Modifying the NLRP3 Inflammasomes can help reduce conditions caused by NLRP3. Pro-inflammatory cytokines like IL-1β and IL-18 cause severe tissue damage and multi-organ dysfunction. Furthermore, the interactions between reactive oxygen species (ROS) and the NLRP3 Inflammasomes significantly influence immune and inflammatory responses. The NF-κB signalling pathway is strongly connected to inflammation; when it is inhibited, there is less production of pro-inflammatory mediators such as TNF-α and IL-1β. At the same time, protective proteins like Keap1, Nrf2, and HO-1 are produced more. Notably, disrupting the interaction between Keap1 and Nrf2 plays a role in these protective effects.

Resveratrol decreased the expression of inflammation related factors, including MCP-1, TNF-α, and IL-1 β, in the peripheral nerves, and NF-KB was also found to be inhibited in the diabetic peripheral nerves. The Nrf2 gene was knocked out, which altered the inflammatory microenvironment in the peripheral nerves. These changes have influenced the protective effect of resveratrol on the peripheral nerves [39].

4. In silico Approaches

4.1 Computer-Aided Drug Design

The process for drug discovery and development is challenging, time-consuming, and expensive. Computer-aided drug discovery (CADD) tools can act as a virtual shortcut, assisting in the expedition of this long process and potentially reducing the cost of research and development [40].

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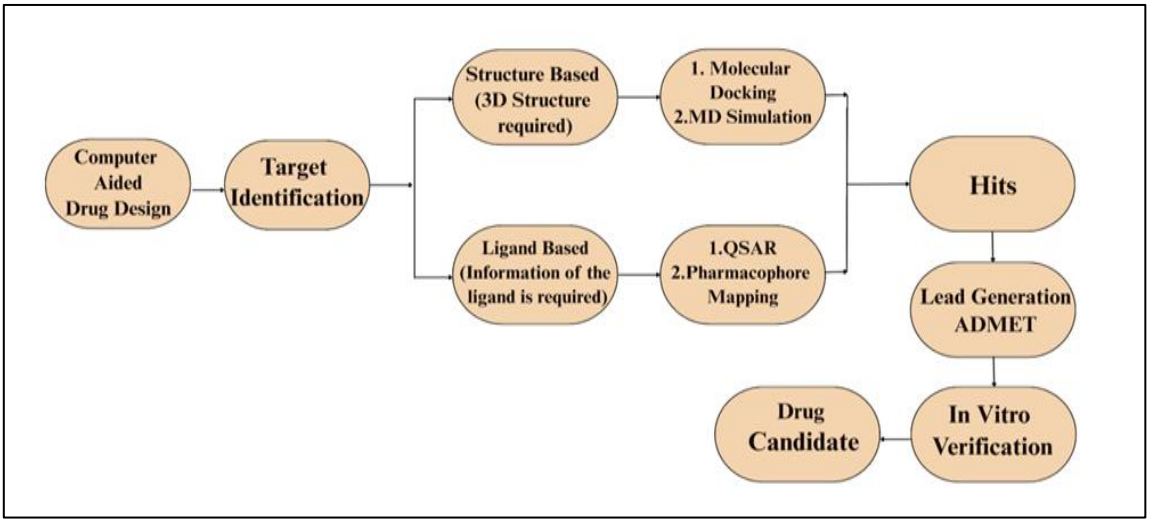

***Figure 2**: Schematic representation of a computer-aided drug discovery (CADD) pipeline. CADD methods are broadly classified into structure-based and ligand-based methods. Structure-based methods require the 3D information of the target to be known. Ligand-based methods are used when the 3D structure of the target is not known. They use information about the molecules that bind to the target of interest. Hits are identified, filtered and optimised potential drug candidates that will be experimentally tested in vitro*

4.2 Molecular Docking

Molecular docking has been widely employed to investigate the interaction of resveratrol with protein targets implicated in diabetes and its complications. In a recent systems pharmacology and docking study, resveratrol was evaluated against multiple diabetes-related proteins, including PPARA, ESR1, SLC2A1, SHBG, AR, AKR1B1, PPARG, IGF1R, RELA, PIK3CA, MMP9, AKT1, INSR, MMP2, TTR, and CYP2C[41]. Docking analyses revealed that resveratrol exhibited strong binding affinities to several of these proteins, with interaction energies in the physiologically relevant range (-6.0 to -9.0 kcal/mol). Key binding modes included hydrogen bonding via phenolic hydroxyl groups, π-π stacking interactions with aromatic residues, and stabilization within hydrophobic pockets of kinases and signalling proteins.

Of particular interest to diabetic peripheral neuropathy (DPN), resveratrol demonstrated favourable docking to proteins involved in neuroinflammation (RELA/NF-κB, MMP9, MMP2, CYP2C9), oxidative stress regulation (AKR1B1, AKT1, IGF1R), and insulin signalling (INSR, PIK3CA, PPARG). These targets overlap significantly with the molecular pathology of DPN, where oxidative stress, impaired insulin signalling, and extracellular matrix remodelling contribute to nerve damage and pain hypersensitivity. By binding stably to these proteins, resveratrol may exert a multi-target therapeutic effect, modulating inflammatory and metabolic pathways relevant to neuropathic progression.

Collectively, these docking results support the view that resveratrol acts as a pleiotropic modulator, interacting with diverse targets that converge on mechanisms central to DPN pathogenesis. Integrating docking with molecular dynamics and free-energy simulations in future studies could further validate these interactions and guide the rational optimization of resveratrol analogs for neuropathy therapy.

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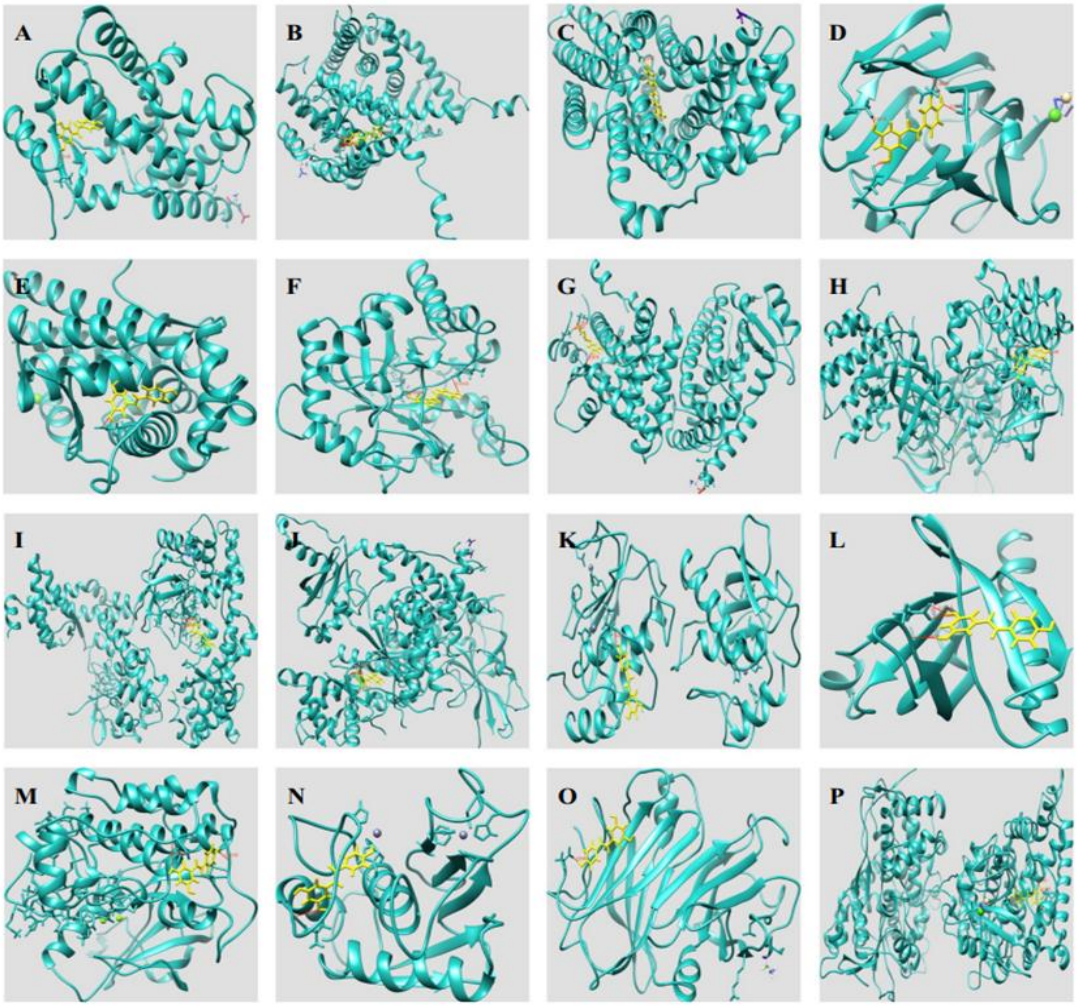

Drug	Targets	PDB ID	Energy (kcal/mol)	FullFitness (kcal/mol)	Estimated Delta G (kcal/mol)	Delta GvdW
RES	PPARA	117G	-6.74225	-1608.3	-7.98322	-47.0982
RES	ESR1	1A52	-4.39569	-2430.87	-7.97234	-46.6933
RES	SLC2A1	6THA	-8.32298	-1303.2	-7.72539	-45.941
RES	SHBG	6PYB	-4.02258	-1018.55	-7.72529	-44.1182
RES	AR	5CJ6	-7.58022	-1321.28	-7.50935	-41.8967
RES	AKR1B1	4PRT	-9.30686	-1535.5	-7.50572	-44.0213
RES	PPARG	6C1I	-5.15499	-3211.41	-7.43626	-38.423
RES	IGF1R	1JQH	-2.36975	-5357.27	-7.18328	-40.8937
RES	RELA	3RC0	-2.15755	-4707.42	-7.14368	-35.1925
RES	PIK3CA	6GVH	-4.2462	-4944.28	-7.06001	-35.1123
RES	MMP9	1GKC	-2.01194	-1975.08	-6.97222	-36.4449
RES	AKT1	1H10	2.16551	-1057.25	-6.89505	-2151.35
RES	INSR	1IR3	-0.910791	-2075.83	-6.87624	-32.0733
RES	MMP2	1HOV	-1.63272	-1190.34	-6.7931	-32.056
RES	TTR	1BZ8	5.40908	-1487.5	-6.58621	-31.7126
RES	CYP2C9	1OG2	-1.04103	-4625.68	-6.30214	-37.527

Figure 3: *The 3-dimensional map of the binding sites between RES and target proteins* ***A*** *PPARA,* ***B*** *ESR1,* ***C*** *SLC2A1,* ***D*** *SHBG,* ***E*** *AR,* ***F*** *AKR1B1,* ***G*** *PPARG,* ***H*** *IGFIR,* ***I*** *RELA* ***J*** *PIK3CA,* ***K*** *MMP9,* ***L*** *AKTL,* ***M*** *INSR,* ***N*** *MMP2,* ***O*** *TTR* ***P*** *CYP2C9.* ***RES*** *is shown in yellow. Target proteins are displayed as cyan. The places where RES and the target proteins are connected represent specific docking sites between RES and target proteins.* ***RES: resveratrol***

4.3 Molecular Dynamics Simulations

In a recent study, resveratrol and its structural analogs were simulated in complex with SIRT1, a protein implicated in oxidative stress regulation, mitochondrial function, and neuroprotection [42]. Over a 20 ns simulation window, resveratrol–protein complexes demonstrated rapid equilibration and sustained stability, as reflected by consistent RMSD values. Binding-site residues exhibited reduced flexibility (RMSF) when resveratrol analogs with stronger binding potential were present, indicating local stabilization of functionally important domains. Hydrogen bonds mediated by phenolic hydroxyl groups and aromatic stacking interactions persisted throughout the simulation, underscoring the chemical features essential for durable binding.

Free-energy calculations using the MM-GBSA method further supported these findings: resveratrol analogs with more favourable binding free energies formed stable complexes, while weaker binders showed higher fluctuations and a tendency toward dissociation. Importantly, these outcomes highlight a broader principle—structural modifications of resveratrol can significantly enhance or weaken stability within protein targets, offering direction for rational analog design.

Although the study centered on SIRT1, the methodological insights are generalizable to other targets implicated in diabetic peripheral neuropathy (DPN), including NF-κB (RELA), AKR1B1, MMP9, INSR, and PIK3CA[31]. These proteins mediate oxidative stress, inflammatory signalling, extracellular matrix remodelling, and impaired insulin signalling—hallmarks of neuropathic damage. MD simulations of resveratrol bound to such targets would be highly informative, as stability of interaction under dynamic conditions is essential to support therapeutic relevance.

4.4. ADMET and Pharmacokinetic Evaluation with BBB (Blood brain barrier) Prediction

When scientists work on developing a new therapy, one of the first things they look at is how the compound behaves inside the body. This is usually assessed through its ADMET properties—absorption, distribution, metabolism, excretion, and toxicity. Various computational tools, such as SwissADME, pkCSM, Chemsketch with ACD/Lab modules, and ADMET/SAR platforms, help researchers quickly judge whether a molecule has the basic characteristics of a potential drug [43]. These tools can predict how well resveratrol is absorbed from the gut, whether it can pass through biological membranes, and how it interacts with liver enzymes like the CYP450 family that play a key role in metabolism.[16]

A major concern in treating diabetic peripheral neuropathy (DPN) is whether resveratrol can cross the blood–brain barrier (BBB), since its protective actions are needed in both the central and peripheral nervous systems. Models like the BOILED-Egg in SwissADME or prediction tools in ADMETlab are used to estimate BBB penetration. Although resveratrol is lipophilic in nature it suggests that it can cross the barrier, its fast metabolism in the body reduces the amount that actually reaches nervous tissue.[44]

To get more understanding of how resveratrol moves and changes inside the body, researchers often rely on more advanced approaches such as physiologically based pharmacokinetic (PBPK) modelling. Software like PK-Sim and GastroPlus can imitate drug levels across different organs over time. These models help to estimate plasma concentrations, tissue distribution, and how quickly the compound is cleared. These are useful for improving dosage forms or designing modified versions of resveratrol that might maintain therapeutic levels for longer.

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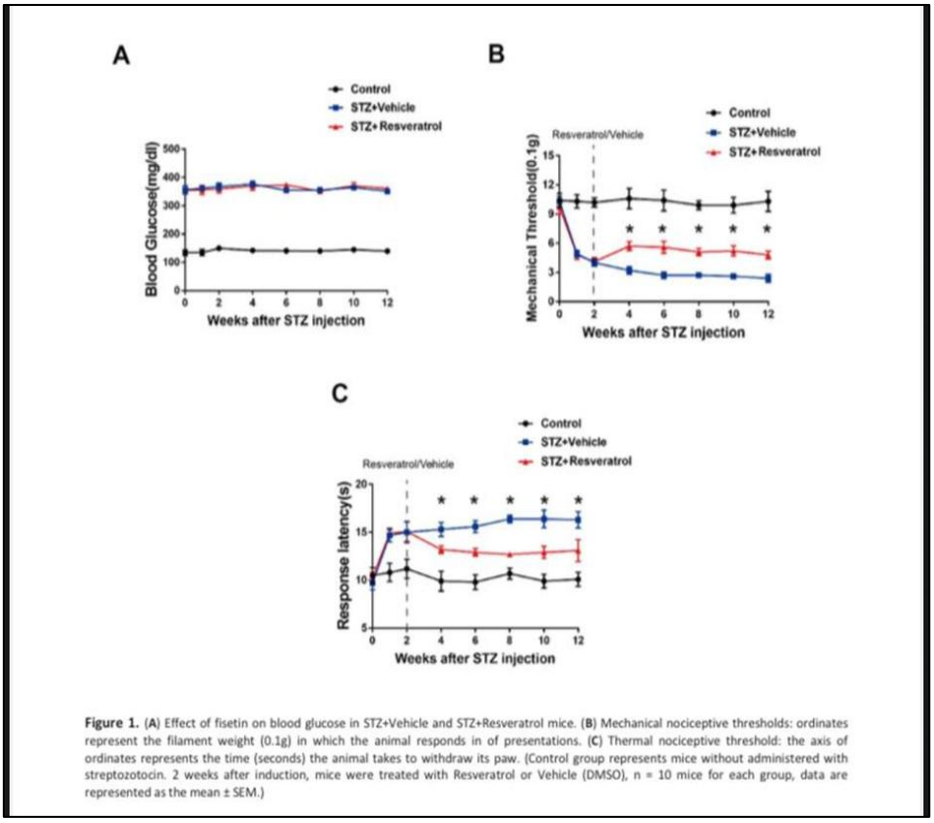

Figure 1. (A) Effect of fisetin on blood glucose in STZ+Vehicle and STZ+Resveratrol mice. (B) Mechanical nociceptive thresholds: ordinates represent the filament weight (0.1g) in which the animal responds in of presentations. (C) Thermal nociceptive threshold: the axis of ordinates represents the time (seconds) the animal takes to withdraw its paw. (Control group represents mice without administered with streptozotocin. 2 weeks after induction, mice were treated with Resveratrol or Vehicle (DMSO), n = 10 mice for each group, data are represented as the mean ± SEM.)

Figure 4: Effect of Resveratrol on Blood Glucose and Nociceptive Responses in STZ-Induced Diabetic Neuropathy [39]

Figure 1 shows how resveratrol affects blood sugar levels and pain sensitivity in mice with streptozotocin-induced diabetes. In Panel A, both groups that received STZ—whether treated with resveratrol or not—developed high blood glucose levels, confirming successful induction of diabetes. Resveratrol did not lower these elevated glucose levels, indicating that any benefits seen later are not due to changes in blood sugar control.

Panel B focuses on mechanical pain sensitivity measured using the von Frey test. Diabetic mice given only the vehicle showed a clear drop in their mechanical threshold, reflecting increased sensitivity to touch. Mice treated with resveratrol, however, regained much of this lost threshold, suggesting that the compound helps reduce mechanical allodynia and supports healthier nerve function.

Panel C shows the response to thermal stimuli through paw withdrawal latency. As expected, diabetic mice without treatment reacted more quickly, showing signs of thermal hyperalgesia. Resveratrol-treated mice displayed longer withdrawal times, similar to the control group, indicating a noticeable improvement in heat-related sensory responses.

Overall, these findings show that resveratrol effectively reduces both mechanical and thermal pain sensitivity in diabetic mice, even though it does not affect their blood glucose levels. This suggests that its protective effects on nerves likely stem from its antioxidant, anti-inflammatory, and mitochondrial-supporting properties rather than any influence on glycemic status [45].

4.5 Systems Biology and Omics Integration

DPN is not a simple condition that can be traced back for its cause or pathway. Because of all this, understanding how resveratrol fits into the picture requires looking at the body as a whole, not just one mechanism. That's where systems biology becomes useful.

There are many omics data available like gene expression profiles including (transcriptomics), patterns in protein changes (proteomics), and shifts in metabolites (metabolomics). When these datasets are analyzed together, they give a broader view of how resveratrol affects different processes. Tools like STRING, Cytoscape, NetworkAnalyst, MetaboAnalyst, DAVID, and KEGG make it possible to connect all this information and see which pathways might be involved.

These studies show that resveratrol can switch on the SIRT1/PGC-1α pathway, which helps mitochondria function better. It also seems to activate Nrf2, which supports the body's antioxidant response. On the other hand, it reduces the activity of NF-κB, a major factor behind inflammation. Protein-level studies back this up, showing changes in proteins linked to energy use and cell protection. Metabolomic results also point toward resveratrol helping to correct imbalances related to oxidative stress.

When all this information is pulled together through network pharmacology, it becomes clear that resveratrol isn't acting on one single point. Instead, it influences several areas at once — which makes sense, because DPN itself is caused by multiple overlapping factors.[46]

4.6. QSAR and Design of Improved Resveratrol Derivatives

Even though resveratrol has many beneficial effects, its limitations in stability and bioavailability have encouraged researchers to think about modifying its structure. This is where quantitative structure–activity relationship (QSAR) approaches come in. QSAR methods use mathematical models to relate the chemical structure of a compound to its biological activity. In simple terms, they look for patterns between features such as molecular weight, polarity, lipophilicity (LogP), and hydrogen-bonding ability with experimental results. With these patterns, new analogs can be predicted and designed. More advanced approaches like 3D-QSAR (e.g., CoMFA, CoMSIA) or pharmacophore modelling take into account the three-dimensional arrangement of atoms in resveratrol and compare it with other active compounds. These models highlight which parts of the molecule are most important for antioxidant or neuroprotective activity. In recent years, machine learning-based QSAR models have further improved accuracy. By using large datasets and algorithms, they can capture more complex patterns and make better predictions for new analogs. For resveratrol, this could mean designing derivatives with stronger neuroprotective effects, better BBB penetration, and slower metabolism [47].

5. Case studies

5.1 Anti-inflammatory effect of resveratrol attenuates the severity of diabetic neuropathy by activating the Nrf2 pathway

A 2021 experimental study conducted by Zhang et al. investigated the therapeutic potential of resveratrol in streptozotocin (STZ)-induced DPN, one of the most common and debilitating complications of diabetes mellitus. The researchers established a DPN mouse model by administering STZ and then divided the animals into two groups: one treated daily with resveratrol and the other receiving only the vehicle (DMSO). Over the course of 12 weeks, multiple behavioural, histological, and molecular assessments were carried out. Functionally, resveratrol-treated diabetic mice showed significant improvements in both pain and thermal sensitivity compared to vehicle-treated mice, indicating that the compound alleviated sensory abnormalities associated with neuropathy. Histopathological analysis revealed that the sciatic nerves of resveratrol-treated animals exhibited reduced myelin disintegration and axonal degeneration, suggesting that resveratrol conferred structural neuroprotection. On the molecular level, resveratrol enhanced the expression of nuclear factor erythroid 2-related factor 2 (Nrf2), a master regulator of antioxidant defenses, along with its downstream enzymes heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), and glutamate–cysteine ligase catalytic subunit (GCLC). At the same time, resveratrol suppressed the activation of the NF-κB pathway, a central mediator of inflammation, and reduced the levels of pro-inflammatory cytokines, including MCP-1, TNF-α, and IL-1β. Importantly, TUNEL staining showed a reduction in neuronal apoptosis in the resveratrol group, further confirming its neuroprotective role. To validate the mechanistic involvement of Nrf2, the investigators employed Nrf2 knockout mice, in which the beneficial effects of resveratrol were largely abolished, establishing that the observed neuroprotection was dependent on Nrf2 activation. These findings collectively highlight that resveratrol attenuates the severity of diabetic neuropathy through a dual mechanism of enhancing antioxidant defenses and suppressing neuroinflammation, primarily via modulation of the Nrf2 and NF-κB signalling pathways. The study thus underscores resveratrol's promise as a therapeutic agent for managing DPN, providing strong preclinical evidence to support its further exploration in the clinical setting [39].

5.2 Resveratrol modulates diabetes-induced neuropathic pain, apoptosis, and oxidative neurotoxicity in mice through TRPV4 channel inhibition

In a comprehensive preclinical investigation, Osmanlıoğlu and Nazıroğlu (2024) explored the potential neuroprotective role of resveratrol in diabetic peripheral neuropathy (DPN) using a streptozotocin (STZ)-induced diabetic mouse model. Thirty-two C57BL/6J mice were divided into four groups: control, resveratrol alone, STZ-diabetic, and STZ-diabetic treated with resveratrol. The intervention consisted of intraperitoneal administration of resveratrol at a dose of 25 mg/kg once daily. To assess the functional and molecular effects, the study employed a wide range of methods, including behavioural assays for pain (von Frey filament test and hot plate test), histopathological evaluation of dorsal root ganglion (DRG) neurons, calcium imaging and patch-clamp recordings to assess TRPV4 channel activity, mitochondrial oxidative stress assays, measurement of antioxidant enzyme and vitamin levels, and evaluation of apoptotic markers such as caspase-3, -8, and -9.

The findings revealed that STZ-induced diabetic mice developed sustained hyperglycemia and displayed significant mechanical allodynia and thermal hyperalgesia, which were accompanied by structural damage in DRG neurons. Electrophysiological and biochemical assessments showed marked upregulation of TRPV4 channel activity, excessive intracellular Ca^{2+} influx, overproduction of mitochondrial reactive oxygen species (ROS), depletion of antioxidant defenses, and increased activation of apoptotic pathways, particularly through caspase-dependent mechanisms. Treatment with resveratrol substantially mitigated these pathological changes. Specifically, it lowered blood glucose levels, improved pain thresholds, suppressed TRPV4-mediated Ca^{2+} entry into DRG neurons, decreased mitochondrial ROS production, and restored endogenous antioxidant enzyme activities and vitamin levels. Furthermore, resveratrol reduced caspase activation and apoptosis, thereby preserving neuronal integrity and function.

Overall, the study provided compelling evidence that resveratrol exerts its neuroprotective effects in diabetic neuropathy primarily by inhibiting TRPV4 channel activity, reducing oxidative stress, and preventing apoptosis. The authors concluded that "resveratrol alleviates STZ-induced neuropathic pain, oxidative neurotoxicity, and apoptosis through TRPV4 channel inhibition," highlighting TRPV4 modulation as a critical mechanism and suggesting resveratrol as a promising therapeutic candidate for the management of diabetic peripheral neuropathy [47].

5.3 The combined effect of mesenchymal stem cells and resveratrol on type 1 diabetic neuropathy

Wang et al. (2019) investigated the combined therapeutic potential of mesenchymal stem cells (MSCs) and resveratrol (RSV) in type 1 diabetic neuropathy using a non-obese diabetic mouse model. Individually, both MSCs and RSV demonstrated beneficial effects in improving hyperglycemia and reducing inflammation, but their combination produced the most significant improvement. Mice treated with MSCs + RSV showed near-normal blood glucose levels, higher C-peptide concentrations, and required the least insulin supplementation compared with diabetic controls. Histological analysis of the sciatic nerve revealed restored myelin structure, increased axonal diameter, and a higher number of myelinated fibres, suggesting marked neurodegeneration.

The combination therapy also modulated key molecular markers involved in inflammation and nerve repair. Levels of NF-κB were significantly reduced, while the expression of nerve growth factor (NGF) and myelin basic protein (MBP) was enhanced, indicating decreased inflammatory signalling and improved myelin integrity. These results suggest that RSV may potentiate the paracrine and neuroprotective effects of MSCs, possibly through SIRT1-related pathways that promote neuronal survival and repair. Overall, the study highlights a promising combinational approach targeting both metabolic dysfunction and neural damage in diabetic neuropathy, though further mechanistic and translational studies are warranted [48].

5.4 The Effects of Resveratrol Supplementation on the Quality of Life of Diabetic Patients with Neuropathy: Small Randomized Clinical Trial

In this randomized, double-blind, placebo-controlled clinical trial, researchers investigated the therapeutic effects of resveratrol supplementation on neuropathic symptoms and quality of life in patients with type 2 diabetes mellitus suffering from peripheral neuropathy. Sixty-one patients with clinically confirmed diabetic neuropathy were randomly divided into two groups: one group received 500 mg of resveratrol orally once daily in addition to standard antidiabetic therapy, while the control group received a placebo for a duration of three months. Clinical evaluation was performed using the RAND-36 Health-Related Quality of Life questionnaire, which assesses physical functioning, bodily pain, energy/fatigue, emotional well-being, and social and role functioning. Metabolic parameters such as fasting blood glucose and HbA1c were also measured before and after the intervention to monitor glycemic control.

The study results demonstrated that resveratrol significantly reduced fasting blood glucose levels compared to placebo, indicating improved glycemic regulation. Furthermore, patients treated with resveratrol showed notable improvement in bodily pain, physical functioning, vitality, and emotional well-being scores on the RAND-36 scale, reflecting both symptomatic relief and enhanced overall quality of life. These beneficial effects are attributed to resveratrol's pleiotropic mechanisms of action, including activation of the SIRT1 signalling pathway, attenuation of oxidative stress, inhibition of NF-κB-mediated inflammation, and enhancement of mitochondrial bioenergetics, all of which contribute to neuronal protection and improved peripheral nerve function.

Overall, the findings suggest that resveratrol supplementation exerts both metabolic and neuroprotective benefits in diabetic patients with peripheral neuropathy. By improving glycemic control and reducing neuropathic pain, resveratrol demonstrates potential as an effective adjunct therapy for managing diabetic neuropathy through its antioxidant, anti-inflammatory, and mitochondrial protective effects [49].

5.5 Impact of resveratrol and pharmaceutical care on type 2 diabetes mellitus and its neuropathic complications: A randomized placebo-controlled clinical trial

In a recent randomized, placebo-controlled clinical trial conducted by Amin et al. (2024), the impact of resveratrol supplementation with or without pharmaceutical care was evaluated in patients with type 2 diabetes mellitus complicated by peripheral neuropathy (*Journal of Clinical Pharmacy and Therapeutics*, 2024). The study enrolled 120 patients, who were randomly assigned into four groups: resveratrol 500 mg/day, placebo, resveratrol plus pharmaceutical care, and placebo plus pharmaceutical care, for a treatment duration of 90 days. The pharmaceutical care intervention consisted of comprehensive patient education, counselling, and active resolution of drug therapy problems. Clinical endpoints included glycemic control (fasting blood glucose [FBG] and HbA1c), neuropathy assessments (Michigan Neuropathy Screening Instrument [MNSI], Douleur Neuropathique 4 [DN4] questionnaire, and Visual Analog Scale [VAS] for pain), as well as electrophysiological measurements through nerve conduction studies. The authors report that "resveratrol supplementation significantly improved FBG and HbA1c levels, with the most pronounced reductions observed in patients receiving both resveratrol and pharmaceutical care" (Amin et al., 2024). Symptomatically, patients in the resveratrol groups demonstrated significant improvement in neuropathy indices, with the study noting that "resveratrol alone or in combination with pharmaceutical care markedly improved MNSI and DN4 scores and reduced VAS pain ratings compared with baseline and placebo groups" (Amin et al., 2024). Importantly, objective neurophysiological outcomes supported these findings, as "nerve conduction parameters including latency, amplitude, and conduction velocity in motor nerves (peroneal and tibial) were significantly improved in the resveratrol plus pharmaceutical care group" (Amin et al., 2024). Beyond direct pharmacological effects, the pharmaceutical care intervention was shown to further enhance clinical outcomes by reducing drug therapy problems and improving medication adherence. Taken together, the study concluded that "the combination of resveratrol and pharmaceutical care was superior to either intervention alone in ameliorating hyperglycemia, neuropathic pain, and impaired nerve function" (Amin et al., 2024). This trial provides one of the first robust pieces of clinical evidence supporting the role of resveratrol, particularly in synergy with structured pharmaceutical care, as a promising adjunctive strategy for managing diabetic peripheral neuropathy[49].

6. Potential challenges and considerations

6.1 Pharmacokinetic Challenges

A typical example of such a compound is resveratrol (RSV), which does not remain in the system. It is not very soluble in water and has a high first-pass metabolism in the gut and liver, so that when you swallow it, the majority of it is converted to glucuronide or sulfate before you get it in your bloodstream [46]. Although it is lipophilic and can be absorbed, only a small amount actually remains active, so it has a short plasma half-life and is difficult to keep at the therapeutic levels. The absorption of RSV is also a widely different variable, about the formulation of the product and the physiology of an individual, hence the blood levels of the viral substance are unpredictable. As stated in the Aging (2021) study, the mice were forced to receive a huge dose of RSV[39]. Concise, the instability and high metabolism of RSV make it not easily translatable to the clinic.

6.2 Dose and Safety Concerns

All in all, RSV is rather harmless and well-tolerated, yet no one knows the optimal dose or its long-term efficacy in humans. Labs usually dose animals with high concentrations, which do not apply to humans, so the figures are difficult to extrapolate. Excessive or excessive exposure may lead to stomach upsets, liver hormone changes, or blood-sugar-controlling medications. The mice studied in the Aging (2021) paper did not exhibit apparent toxicity after 12 weeks of oral RSV at 10 mL/kg of 10 per cent solution, which is also promising, but again, only in a preclinical context. Due to the absence of standardized human dose/scheduling regimes and possible interactions of the drugs, clinicians should move cautiously, titrate, and monitor patients closely to refine a definitive therapeutic range.

6.3 Mechanistic Considerations

Diabetic neuropathy is an ugly combination of oxidative stress, disorganized mitochondria, inflammation, and damage to small vessels. RSV intervenes on several fronts; Nrf2, SIRT1, AMPK, and NF-κB signalling are activated and deactivated to prevent that damage[46]. According to the Aging (2021) study, RSV increased antioxidant enzymes, such as HO-1, NQO1, and GCLC, reduced oxidative stress, and decreased proinflammatory cytokines (MCP-1, TNF-α, IL-1). It also assisted in the maintenance and preservation of the Schwann cells and the myelin sheath. These findings are consistent with those of other studies, which demonstrate that RSV has many targets of protection, but these effects can be adjusted to suitability by our genetics and metabolism.

6.4 Interactions of Drugs and Nutrients

Drug-Drug interactions represent interactions between drugs that are not associated with food intake.<|human|>Drug-Drug and Nutrient Interactions Drug-Drug interactions are interactions that occur between drugs that do not involve food consumption. RSV is potentially interactive with a wide range of other medications and particularly antidiabetic drugs such as metformin, sulfonylureas, and insulin, and it may alter their effect on glycemic regulation. It also interacts with blood-thinners and antiplatelet agents such as aspirin and warfarin, raising the risk of bleeding. Since RSV interferes with the Nrf2 and NF -kB pathways, incanto interacts with other antioxidants, anti-inflammatory medications, and metabolic controllers as well. The effects of the natural supplements or herbs are additive or neutral when combined with other natural supplements or herbs, depending on the amount and timing of usage. The Aging (2021) article did not delve into these interactions, but it did remind me of the widespread systemic activity of RSV, indicating that there may be significant overlap with most categories of therapies [46].

6.5 Formulation & Delivery

Classic RSV formulations continue to encounter enormous challenges: they disintegrate with exposure to light, heat, and pH shift, resulting in degradation during storage. The nanoencapsulation, liposomes, polymeric nanoparticles, micelles, and self-nanoemulsifying drug delivery systems (SNEDDS) tricks are newer delivery tricks that attempt to make it more soluble, stable, and able to penetrate tissues. In the experiment conducted by Aging (2021), the mice were inoculated with RSV intragastrically in a 10^{-} percent solution of DMSO, and it was demonstrated that even the comparatively developed delivery method requires further refinement to be used in humans consistently. The addition of sustained-release or glucose-sensitive carriers can increase its therapeutic index, but how to do so at a large scale and at a reasonable cost is an uphill challenge.

6.6 Clinical Evidence Gaps

Even though animal research supports the neuroprotective and antioxidant effects of RSV, the evidence has yet to be found in humans. The majority of human trials are concerned with metabolic or heart outcomes and have not narrowed down to neuropathic outcomes. The entire Resveratrol Paradox highlights the difference between the amazing laboratory findings and shaky human effectiveness, largely due to bad bioavailability and lack of a standard dosage. The Aging (2021) study, which was associated with diabetic mice subjected to STZ, once again supports the fact that we require actual translational studies to establish the safety and efficacy of STZ in humans over a prolonged period of time. Additionally, human trials are unpredictable in terms of formulation, time, and results, and it is difficult to compare them or come to a common opinion regarding benefits.

6.7 Regulatory and Commercialization Issues.

The legal status of RSV switches to nutraceutical, dietary supplement, and investigational drug in different regions, which confounds clinical approval, standardization, and uptake in the market. This is because the absence of a single classification implies that researchers cannot easily establish standards or replicate results. We also have no harmonized formulations and solid human pharmacokinetic data, which puts a spanner in the works of reproducibility. The study by Aging (2021) is preclinical, meaning that the gap between laboratory data and regulatory-level evidence to approve drugs is enormous. To succeed in the commercial market, RSV will require standardized formulations, established human PK, and the same clinical results that are consistent with the internationally accepted guidelines.

7. Future research directions

Numerous aspects of research concerning diabetic peripheral neuropathy (DPN) remain unexplored; however, several promising avenues of inquiry have been identified that may contribute to more effective disease management [50]. Although multiple therapeutic strategies have been introduced into clinical practice, the pharmacological management of DPN continues to pose a concern for healthcare providers. It is anticipated that future development of innovative therapeutic agents targeting mitochondrial metabolic regulation will enhance the management of DPN. Natural products for DPN treatment are also recommended for investigation, as they may offer safer and more cost-effective options for patients. Because alterations in metabolic pathways are directly implicated in the pathogenesis of DPN, identifying drugs that act on these pathways and undertaking large-scale clinical trials may facilitate the emergence of curative interventions rather than merely providing symptomatic relief as seen with conventional therapies [32]. Despite the considerable knowledge gained, largely due to an earlier nerve-centric emphasis on glucose alone, the outlook remains optimistic. Progress in understanding the clinical manifestations and optimal therapeutic strategies for diabetic neuropathy now provides a strong foundation for the ongoing paradigm shift in preclinical research [16].

Although resveratrol has shown great potential as a therapeutic candidate for diabetic peripheral neuropathy (DPN), its poor stability, rapid metabolism, and low oral bioavailability remain major challenges [46]. Future studies should therefore focus on structural optimization and rational drug design to create derivatives with improved pharmacological properties.

Another scope is to enhance blood–brain barrier (BBB) penetration, which is critical for resveratrol's neuroprotective effects. Increasing lipophilicity while maintaining sufficient water solubility can help derivatives cross the BBB more efficiently. Combining structural optimization with drug-delivery strategies, such as nanoparticle-based carriers or prodrug design, may further protect resveratrol analogs from early metabolism and ensure that higher concentrations reach peripheral nerves and the central nervous system [46].

Overall, future research should adopt a combined strategy: (i) design and synthesis of methoxylated and other substituted resveratrol analogs with better stability and bioavailability, (ii) computational screening using QSAR, pharmacophore modelling, and docking against DPN-related targets (e.g., SIRT1, PGC-1α, NF-κB), and (iii) integration of optimized derivatives with advanced drug-delivery systems. Such a stepwise approach could accelerate the development of next-generation resveratrol-based therapies for diabetic peripheral neuropathy.

8. Conclusion

We conclude that RSV is a highly promising, multitargeted natural compound for the treatment of DPN, considering its pleiotropic action in activating Nrf2/ARE and SIRT1/AMPK pathways, promoting antioxidant defense and mitochondrial function, while inhibiting NF-κB-mediated neuroinflammation. It is supported by preclinical and in silico data showing its effectiveness in blunting pain hypersensitivity, axonal damage, and apoptosis, while molecular docking has also established its favourable binding to crucial DPN targets like RELA/NF-κB and AKR1B1. However, successful clinical translation of RSV faces formidable challenges due to poor stability and low oral bioavailability caused by rapid first-pass metabolism, thus limiting its therapeutic potential. Therefore, future study on RSV should focus on structural optimization to develop its derivatives such as methoxylated analogs, of which pterostilbene is an example, and advanced drug delivery systems to surmount these pharmacokinetic limitations and facilitate large-scale clinical trials with an emphasis on neuropathic outcomes.

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