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Resveratrol as a bioactive compound in diabetes management

Resveratrol como um composto bioativo no manejo do diabetes

Resveratrol como compuesto bioactivo en el manejo de la diabetes

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ABSTRACT

Objective: To analyze the potential of resveratrol as a bioactive compound in the management of diabetes mellitus and its complications, addressing its mechanisms of action, bioavailability limitations, and technological challenges regarding its application in functional foods and therapeutic products. **Literature review:** Resveratrol is a stilbene polyphenol with well-established antioxidant and anti-inflammatory properties. In diabetes, it contributes to glucose homeostasis by improving insulin sensitivity, enhancing cellular glucose uptake through GLUT4 transporters, protecting pancreatic β-cells against oxidative stress, and inhibiting carbohydrate-digesting enzymes such as α-glucosidase. Beyond glycemic control, resveratrol may attenuate damage in target organs, helping to prevent chronic microvascular and macrovascular complications, including nephropathy, retinopathy, neuropathy, and cardiomyopathy, particularly through modulation of the SIRT1/AMPK signaling axis. However, its practical application faces significant challenges due to its low oral bioavailability, rapid metabolism, and the high instability of the trans-isomer when exposed to light and heat. **Final considerations:** Resveratrol exhibits considerable potential in the field of metabolic health. However, to make its practical application viable, the development of advanced delivery systems, such as micro and nanoencapsulation, is essential, guaranteeing its stability in functional foods and therapeutic efficacy.

Keywords: Resveratrol, Diabetes mellitus, Functional food.

RESUMO

Objetivo: Analisar o potencial do resveratrol como composto bioativo no manejo do diabetes mellitus e suas complicações considerando seus mecanismos de ação, limitações de biodisponibilidade e desafios tecnológicos para aplicação em alimentos funcionais e produtos terapêuticos. **Revisão bibliográfica:** O resveratrol é um polifenol da família dos estilbenos com reconhecidas propriedades antioxidantes e anti-inflamatórias. No diabetes, atua na homeostase da glicose ao melhorar a sensibilidade à insulina, aumentar a captação celular via transportadores GLUT4, proteger as células β pancreáticas contra o estresse oxidativo e inibir enzimas digestivas de carboidratos, como a α-glicosidase. Além do controle glicêmico, o resveratrol atenua danos em órgãos-alvo, prevenindo complicações crônicas micro e macrovasculares, como nefropatia, retinopatia, neuropatia e cardiomiopatia, especialmente pela modulação do eixo

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SIRT1/AMPK. Contudo, sua aplicação enfrenta sérios desafios devido à baixa biodisponibilidade oral, rápida metabolização e alta instabilidade do isômero trans à luz e ao calor. **Considerações finais:** O resveratrol apresenta um amplo potencial no campo da saúde metabólica. Contudo, para viabilizar sua aplicação prática, é imprescindível o desenvolvimento de sistemas avançados de entrega, como o micro e nanoencapsulamento, garantindo sua estabilidade em alimentos funcionais e eficácia terapêutica.

Palavras-chave: Resveratrol, Diabetes mellitus, Alimentos funcionais.

RESUMEN

Objetivo: Analizar el potencial del resveratrol como compuesto bioactivo en el tratamiento de la diabetes mellitus y sus complicaciones, considerando sus mecanismos de acción, limitaciones de biodisponibilidad y desafíos tecnológicos para su aplicación en alimentos funcionales y productos terapéuticos. **Revisión bibliográfica:** El resveratrol es un polifenol de la familia de los estilbenos con propiedades antioxidantes y antiinflamatorias. En la diabetes, contribuye a la homeostasis de la glucosa al mejorar la sensibilidad a la insulina, aumentar la captación de glucosa mediante transportadores GLUT4, proteger las células β pancreáticas frente al estrés oxidativo e inhibir enzimas digestivas de carbohidratos, como la α-glucosidasa. Además del control glucémico, puede atenuar el daño en órganos, ayudando a prevenir complicaciones microvasculares y macrovasculares, como nefropatía, retinopatía, neuropatía y cardiomiopatía, especialmente mediante la modulación del eje SIRT1/AMPK. Su aplicación práctica enfrenta importantes desafíos debido a su baja biodisponibilidad oral, rápido metabolismo y alta inestabilidad del isómero trans frente a la luz y al calor. **Consideraciones finales:** El resveratrol presenta amplio potencial en la salud metabólica. Sin embargo, para viabilizar su aplicación práctica, es esencial desarrollar sistemas avanzados de liberación, como la micro y la nanoencapsulación, que garanticen su estabilidad en alimentos funcionales y su eficacia terapéutica.

Palabras clave: Resveratrol, Diabetes mellitus, Alimentos funcionales.

INTRODUCTION

The global rise in chronic non-communicable diseases, particularly diabetes mellitus (DM), obesity, and cardiovascular disorders, has intensified the search for dietary components capable of promoting health and preventing disease (KOUSHKI M, et al., 2024). In this context, bioactive compounds derived from plants have gained attention due to their potential physiological benefits beyond basic nutrition. Among these compounds, polyphenols represent one of the most abundant and widely studied groups, owing to their diverse chemical structures and biological activities.

Resveratrol (3,5,4′-trihydroxystilbene) is a naturally occurring polyphenol belonging to the stilbene family. It is synthesized by several plant species as a defense mechanism against environmental stressors such as pathogen attacks, ultraviolet radiation, and physical injury (AHMAD I e HODA M, 2020; VESTERGAARD M e INGMER H, 2019; ZHANG LX, et al., 2021). Over the past decades, resveratrol has emerged as a compound of considerable scientific interest due to its broad spectrum of biological activities, including antioxidant, anti-inflammatory, cardioprotective, neuroprotective, anticancer, and antidiabetic effects (KAURAV M, et al., 2026).

The initial interest surrounding resveratrol was largely driven by the so-called “French Paradox,” which has been attributed to regular consumption of red wine, a dietary source of resveratrol (KAURAV M, et al., 2026). More recently, increasing attention has been directed toward the potential role of resveratrol in the prevention and management of diabetes mellitus. Given the growing global burden of diabetes and its associated complications (KOUSHKI M, et al., 2024), identifying compounds capable of modulating glucose metabolism and improving insulin sensitivity is important. However, despite the large body of experimental evidence supporting its antidiabetic effects, clinical findings remain inconsistent, highlighting the need for further investigation into its efficacy in humans.

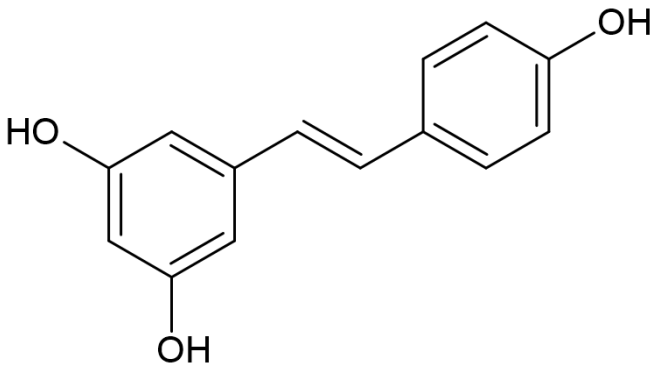
This narrative review aims to summarize and critically discuss the current scientific knowledge regarding resveratrol, focusing on its physicochemical properties, metabolism, dietary sources, and antidiabetic mechanisms.

LITERATURE REVIEW

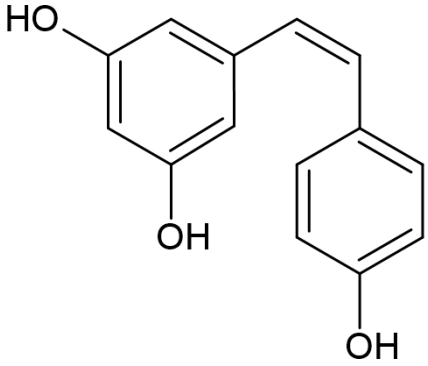
Chemical Structure and Physicochemical Properties

Resveratrol, chemically known as trans-3,5,4′-trihydroxystilbene, is a stilbene compound characterized by a C6–C2–C6 carbon skeleton consisting of two aromatic rings linked by an ethylene bridge (**Figure 1**). It exists in two isomeric forms: cis and trans, with the trans isomer being the most stable, abundant in nature, and biologically active form (AHMAD I e HODA M, 2020; VESTERGAARD M e INGMER H, 2019; ZHANG LX, et al., 2021). In its pure solid state, trans-resveratrol exhibits a highly crystalline structure (MARWA A, et al., 2025). However, trans-resveratrol is highly chemically unstable. It is sensitive to environmental factors such as light, heat, and ultraviolet radiation, which can induce photolysis, oxidative degradation, and isomerization to the cis form (KAURAV M, et al., 2026). Thermal exposure is particularly detrimental to its antioxidant potential due to this isomerization process (MARWA A, et al., 2025).

Figure 1 - Chemical structures of the two isomeric forms of resveratrol: trans-resveratrol and cis-resveratrol. Created using ACD/ChemSketch® software. License available at: https://www.acdlabs.com/resources/free-chemistry-software-apps/chemsketch-freeware/#freeware-license/. Accessed on June 5, 2026.



trans-resveratrol



cis-resveratrol

Source: Santa Rosa LN e Pires ACS, 2026.

From a physicochemical perspective, resveratrol is a lipophilic compound with extremely low solubility in water – approximately 0.548 mg/mL - but high solubility in organic solvents such as ethanol - 50 mg/mL - and dimethyl sulfoxide (DMSO) - 16 mg/mL - (MARWA A, et al., 2025; *PubChem Compound Summary for CID 445154, Resveratrol.*, n.d.). Its limited aqueous solubility, combined with extensive first-pass metabolism in the liver and colon, leads to a remarkably low oral bioavailability of approximately 1% (KAURAV M, et al., 2026). These factors pose significant challenges for its therapeutic efficacy and practical applications in food and pharmaceutical systems (KAURAV M, et al., 2026; MARWA A, et al., 2025).

To overcome these limitations, various delivery strategies have been developed to enhance its stability, solubility, and bioavailability. Formulations based on nanotechnology, such as encapsulation in liposomes, nanoemulsions, and solid lipid nanoparticles, protect the compound from degradation.

Furthermore, the formation of complexes with cyclodextrins and proteins has emerged as a highly effective approach (JEANDET P, et al., 2021; MARWA A, et al., 2025; SILVA PM, et al., 2023). Manufacturing techniques like spray drying can also be utilized during encapsulation to convert crystalline resveratrol into a higher-energy amorphous state, which is thermodynamically more soluble and facilitates faster drug release (MARWA A, et al., 2025).

Metabolism, Bioavailability, and Toxicity

Resveratrol exhibits relatively high absorption rates when administered orally, with studies indicating that approximately 70% to 75% of the ingested compound is absorbed in the gastrointestinal tract via passive diffusion (HUANG DD, et al., 2020; POÓR M, et al., 2022).

Despite this high absorption, its oral bioavailability is extremely low - typically less than 1%. This limitation is primarily due to a rapid and extensive first-pass metabolism occurring in the intestinal enterocytes and hepatic cells, which significantly reduces the levels of unchanged resveratrol in the systemic circulation, leading to a short plasma half-life of approximately 8 to 14 minutes (KOUSHKI M, et al., 2024; POÓR M, et al., 2022; SILVA PM, et al., 2023).

Once absorbed, resveratrol is rapidly metabolized in intestine and liver through glucuronidation and sulfation, resulting in the formation of more water-soluble metabolites such as resveratrol-3-glucuronide, resveratrol-3-sulfate, and dihydroresveratrol (KAURAV M, et al., 2026; KOUSHKI M, et al., 2024; POÓR M, et al., 2022; SILVA PM, et al., 2023). Although these conjugated metabolites retain antioxidant activity, sulfation may reduce the bioavailability of the original compound. These metabolites are then distributed throughout the body and eventually excreted in urine (HUANG DD, et al., 2020).

Regarding safety, resveratrol is generally considered well tolerated and non-toxic at moderate doses (KOUSHKI M, et al., 2024). Clinical studies suggest that doses up to 5 g/day for short periods are safe in humans (KAURAV M, et al., 2026; ZHANG LX, et al., 2021). However, high doses may lead to adverse effects such as gastrointestinal discomfort, interactions with medications, and inhibition of cytochrome P450 enzymes, which can interfere with drug metabolism (KAURAV M, et al., 2026; POÓR M, et al., 2022; SHAITO A, et al., 2020; SILVA PM, et al., 2023). Therefore, while resveratrol shows promise as a therapeutic agent, careful consideration of dosage and long-term safety is necessary.

Dietary Sources of Resveratrol

Initially discovered in the root of the white hellebore (*Veratrum grandiflorum*) in 1940, resveratrol is widely distributed in the plant kingdom and has been identified in over 100 plant species across 34 botanical families (KAURAV M, et al., 2026; TROMBINO S, et al., 2025).

Its presence is particularly notable in grapes (*Vitis vinifera*), where concentrations can reach 36.60 µg/g in the fruit and 50 to 100 mg/kg in fresh skins (TIAN B e LIU J, 2020; TROMBINO S, et al., 2025).

Other significant edible sources include peanuts (*Arachis hypogaea*, 15.00 µg/g), berries (such as blueberries, ranging from 0.007 to 5.88 µg/g, and cranberries), pineapples (9.12 µg/g), mulberries, pomegranates, pistachios, and cocoa. Interestingly, extremely high concentrations have been reported in the seeds of *Paeonia suffruticosa* (up to 870.00 µg/g) and the dried roots of *Polygonum cuspidatum*, which serve as a major commercial source for extraction (TIAN B e LIU J, 2020).

The concentration of resveratrol in foods varies depending on factors such as plant species, terroir, ripeness, environmental conditions, and processing methods. Among processed foods, red wine is one of the most significant dietary sources (ranging from 0.1 to 14.3 µg/mL and sometimes up to 20 mg/L) due to the fermentation and maceration processes involving prolonged contact with grape skins and seeds, where resveratrol is concentrated (TROMBINO S, et al., 2025). Beyond wine, other processed foods also contribute to dietary intake, including cocoa products, dark chocolate, peanut butter, jams, dried fruits, and cranberry-based products (BOUCHARD J, et al., 2026).

Despite its presence in various foods, the amount of resveratrol obtained through a typical diet is relatively low - often ranging from a few micrograms to about 4 mg per day. This intake is substantially lower (approximately 1,250 times) than the doses commonly investigated in clinical studies, which may reach up to 5 g/day in humans, highlighting the difficulty of achieving pharmacologically relevant concentrations through diet alone and explaining the growing interest in supplementation and functional food development (SILVA PM, et al., 2023).

Biological Effects of Resveratrol

Resveratrol has been associated with numerous health-promoting effects, primarily attributed to its antioxidant and anti-inflammatory properties. It acts as a scavenger of reactive oxygen species (ROS), thereby reducing oxidative stress, and actively stimulates endogenous antioxidant defenses by promoting the activities of enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. Furthermore, it activates the Nrf2 signaling pathway, thereby reducing oxidative stress and lipid peroxidation (e.g., reducing malondialdehyde levels), which are key factors in the development of chronic diseases (KE J, et al., 2023; KOUSHKI M, et al., 2024).

Additionally, resveratrol modulates signaling pathways involved in inflammation by suppressing pro-inflammatory cytokines including TNF-α, IL-1β, IL-6, and IL-8. These actions contribute to its protective effects in several disorders. In neurodegenerative disorders, including Alzheimer's disease, resveratrol reduces oxidative damage, promotes the intracellular proteasome-mediated degradation of beta-amyloid plaques, and acts as a copper-chelating agent (KAURAV M, et al., 2026). In oncology, resveratrol demonstrates chemopreventive properties by interfering with carcinogenesis, inducing cell cycle arrest, and promoting autophagy and apoptosis in cancer cells through the modulation of SIRT1, Akt/mTOR and p38-MAPK pathways (KAURAV M, et al., 2026; XIAO X, et al., 2025). However, most evidence supporting these effects derives from experimental studies, and further clinical trials are required to confirm their therapeutic relevance in humans.

The compound also exhibits lipid-lowering properties and can improve endothelial function, further supporting its cardioprotective role. Resveratrol significantly decreases the production of apolipoproteins such as ApoB-100 and ApoB-48, reducing adipocyte size, and improving insulin sensitivity. It can improve endothelial function by enhancing flow-mediated vasodilation and stimulating nitric oxide release through the activation of endothelial nitric oxide synthase (KAURAV M, et al., 2026). These multifaceted biological activities highlight resveratrol as a promising candidate for disease prevention and health promotion.

Antidiabetic Effects of Resveratrol

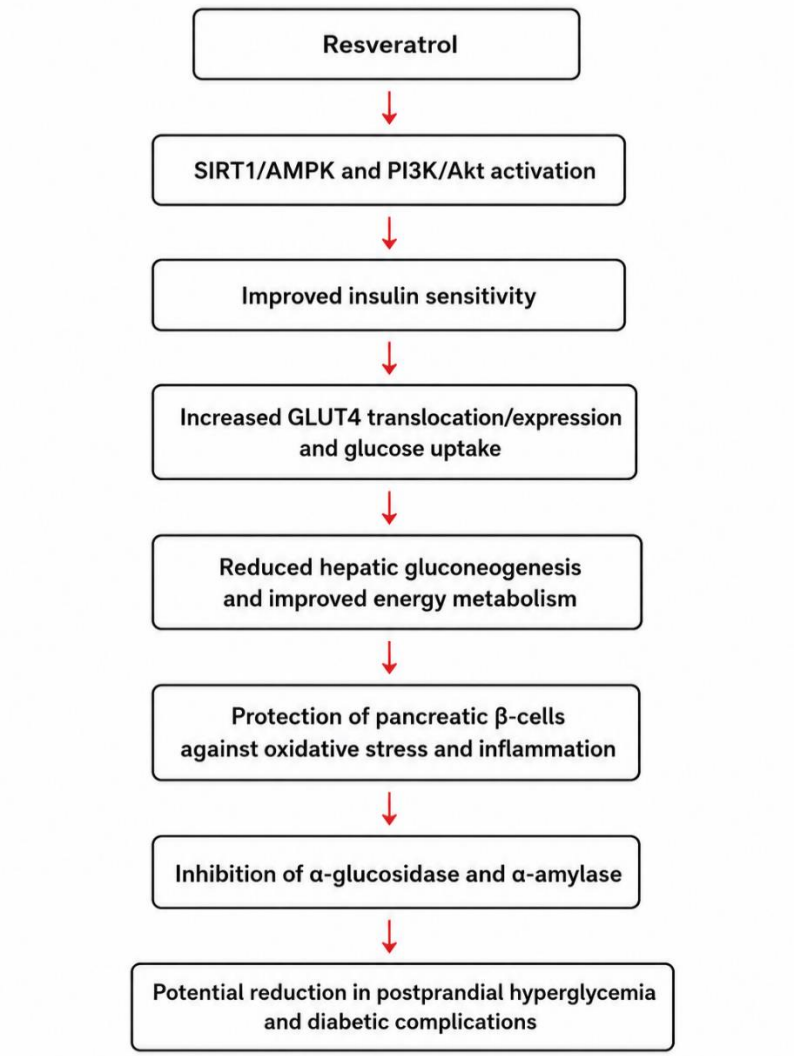
DM is a metabolic disorder with Type 2 Diabetes Mellitus (T2DM) currently considered a global epidemic responsible for approximately 90% of all diabetes cases. It is characterized by chronic hyperglycemia resulting from a progressive deficiency in insulin secretion by pancreatic β-cells and the ineffective utilization of glucose by peripheral tissues.

The core pathophysiology involves a critical disarrangement between insulin release and cellular glucose uptake, predominantly affecting glucose transporter receptors, which is heavily influenced by the interaction of genetic predisposition, environmental factors, and obesity. The increasing prevalence of diabetes worldwide - affecting an estimated 8.5% of the worldwide population - underscores the need for effective preventive and therapeutic strategies.

Because DM is often a silent disease that can precipitously lead to acute emergencies, such as ketoacidosis, and devastating chronic microvascular and macrovascular complications, including diabetic nephropathy, severe cardiovascular events, retinopathy, and neuropathy, early and multifactorial interventions are essential (ALENCAR F, et al., 2025).

While lifestyle modifications and standard pharmacological agents like metformin remain the conventional therapies, the search for novel bioactive molecules to counter these complex metabolic and systemic damage is continuously expanding. Resveratrol has demonstrated significant potential in modulating various aspects of glucose metabolism and insulin function. Its antidiabetic effects can be attributed to multiple mechanisms which are summarized in **Figure 2** and discussed below.

Figure 2 - Main proposed mechanisms underlying the effects of resveratrol on glucose metabolism and the prevention of diabetes mellitus-associated complications.



Source: Santa Rosa LN e Pires ACS, 2026.

Improvement of Insulin Sensitivity

Insulin resistance is a hallmark of type 2 diabetes and is characterized by a reduced response of peripheral tissues to insulin. Resveratrol has been shown to improve insulin sensitivity in both animal and human studies. Experimental studies in diabetic rodents have demonstrated that resveratrol administration improves insulin signaling and glycemic control while attenuating hepatic lipid accumulation, which is considered a primary driver of insulin resistance (SZKUDELSKA K, et al., 2021).

Clinical trials in patients with type 2 diabetes have also reported improvements in insulin sensitivity following resveratrol supplementation. For instance, clinical interventions ranging from low doses (5 mg twice daily for 4 weeks) to higher doses (1 g/day for 45 days) have resulted in significant reductions in fasting blood glucose, glycated hemoglobin (HbA1c), and overall insulin resistance (BRASNYÓ P, et al., 2011; KAURAV M, et al., 2026).

The underlying mechanisms involve the activation of key signaling pathways such as the SIRT1/AMPK axis and the PI3K/Akt pathway. Furthermore, the reduction of oxidative stress and the increase in the pAkt:Akt ratio collectively led to more efficient intracellular insulin signaling and enhanced insulin action (BRASNYÓ P, et al., 2011; KAURAV M, et al., 2026; KOUSHKI M, et al., 2024).

Enhancement of Glucose Uptake and Metabolism

Glucose uptake in muscle and adipose tissues is primarily mediated by the glucose transporter GLUT4. In diabetic conditions, the expression and translocation of GLUT4 are often impaired. Resveratrol has been shown to increase GLUT4 expression in rats and promote glucose uptake in specific skeletal muscles, such as the soleus muscle, even after short-term administration (e.g., 3 mg/kg/day), while also upregulating GLUT2 expression in the liver. This effect is mediated through the activation and phosphorylation of signaling pathways such as PI3K/Akt and AMP-activated protein kinase (AMPK), both of which play crucial roles in cellular energy homeostasis (CHI TC, et al., 2007; KOUSHKI M, et al., 2024).

Beyond glucose transporters, resveratrol induces beneficial alterations in metabolic enzyme levels, which subsequently increase glycolysis and glycogen synthesis in skeletal muscles. Simultaneously, it decreases gluconeogenesis and increases hepatic glycogenesis, thereby reducing hepatic glucose output (KOUSHKI M, et al., 2024).By enhancing glucose uptake and utilization, resveratrol contributes to improved postprandial glycemic control without requiring a compensatory increase in insulin production and maintains overall metabolic balance.

Protection of Pancreatic β-Cells

Pancreatic β-cells are responsible for insulin production and secretion. In both type 1 and type 2 diabetes, these cells are often damaged due to chronic hyperglycemia, lipotoxicity, glucotoxicity, and the consequent oxidative stress and systemic inflammation (KOUSHKI M, et al., 2024; MEDEN A e MIČETIĆ-TURK D, 2026). Animal, human, and *in vitro* studies show that resveratrol exhibits protective effects on β-cells by reducing oxidative stress and inhibiting the production of reactive oxygen species. Specifically, it enhances the antioxidant capacity of pancreatic cells by elevating the levels of endogenous enzymes such as superoxide dismutase, catalase, and glutathione S-transferase, while promoting the phosphorylation of the nuclear factor erythroid 2-related factor-2 (Nrf2).

Furthermore, resveratrol mitigates β-cell degeneration by inhibiting the poly (ADP-ribose) polymerase (PARP) enzyme and suppressing inflammatory cascades via the inhibition of the NF-κB and NLRP3 pathways. The activation of key molecular targets, particularly SIRT1 and AMPK, plays a central role in these protective effects, not only preserving β-cell mass and function but also enhancing glucose-stimulated insulin secretion through SIRT1-dependent mechanisms (KOUSHKI M, et al., 2024; MEDEN A e MIČETIĆ-TURK D, 2026).

Experimental animal studies corroborate these mechanisms; for instance, oral administration of 5 mg/kg/day over 30 days significantly reduced oxidative peroxide markers in the pancreatic cells of diabetic rats, while subcutaneous injections of 1 and 10 mg/kg in ovariectomized models led to an actual increase in β-cell numbers (HUANG DD, et al., 2020; LI Y, et al., 2018; PALSAMY P e SUBRAMANIAN S, 2010). Overall, resveratrol can preserve β-cell function, increase cell survival, and even promote β-cell regeneration in experimental models. These effects are particularly important in preventing the progression of diabetes and maintaining insulin production.

Inhibition of Carbohydrate-Digesting Enzymes

Another mechanism by which resveratrol may contribute to glycemic control is through the inhibition of carbohydrate-digesting enzymes. Recent studies have demonstrated that resveratrol can directly inhibit α-glucosidase, an intestinal enzyme responsible for the hydrolysis of complex carbohydrates into absorbable monosaccharides. Mechanistic analyses revealed that resveratrol interacts with the enzyme through hydrogen bonding and hydrophobic interactions, resulting in a mixed-type inhibitory effect that may delay carbohydrate digestion and reduce postprandial glycemia (WANG R, et al., 2023).

Furthermore, recent chemical modification studies have developed resveratrol derivatives, such as prenylated stilbenoids, that exhibit even more potent α-glucosidase inhibitory activities (TROMBINO S, et al., 2025). In addition, derivatives and oligomeric forms of resveratrol have shown inhibitory activity against α-amylase, another key enzyme involved in starch digestion, suggesting that stilbene-based compounds may

modulate multiple stages of carbohydrate breakdown (VISVANATHAN R, et al., 2024). Although further in vivo and clinical studies are required, these findings highlight the potential of resveratrol as a natural complementary approach for postprandial glycemic management.

Prevention of Secondary Diabetic Complications

While tight glycemic control is essential, the high mortality and morbidity associated with diabetes mellitus are largely attributed to its chronic complications, including nephropathy, retinopathy, neuropathy, and cardiomyopathy. Resveratrol has emerged as a promising candidate for mitigating these conditions due to its antioxidant and anti-inflammatory properties. However, much of the available evidence derives from in vitro and animal studies, and further clinical investigations are required to establish its therapeutic efficacy in humans.

Diabetic Nephropathy: Experimental studies suggest that resveratrol may exert renoprotective effects by reducing albuminuria and attenuating structural alterations, such as tubular atrophy, mesangial expansion, and fibrosis. These effects have been associated with activation of the SIRT1/AMPK signaling pathway, which may reduce apoptosis and oxidative stress in renal tissues (KOUSHKI M, et al., 2024).

Diabetic Retinopathy: Chronic hyperglycemia compromises the blood-retinal barrier, increasing vascular permeability, oxidative stress, inflammation, and retinal cell death. Experimental studies have suggested that resveratrol may exert protective effects on retinal tissues by reducing oxidative stress, preserving blood-retinal barrier integrity, attenuating inflammatory signaling, and inhibiting apoptosis through pathways involving SIRT1 activation and mitochondrial protection. However, most available evidence derives from in vitro and animal models, and further clinical studies are required to confirm its therapeutic efficacy in diabetic retinopathy (HARLEY O, et al., 2026).

Diabetic Neuropathy and Foot Ulcers: Peripheral neuropathy, combined with vascular occlusion and localized hyperinflammation, characterized by the overproduction of pro-inflammatory cytokines, are associated with the development of diabetic foot ulcers (OLIVEIRA MN, et al., 2026). Improvements in pain perception, thermal sensitivity, and nerve fiber preservation are reported following resveratrol administration. These effects appear to be mediated by the inhibition of the NF-κB inflammatory pathway and the activation of Nrf2, which bolsters endogenous antioxidant defenses in the peripheral nerves (KOUSHKI M, et al., 2024).

Diabetic Cardiomyopathy: Hyperglycemia-induced oxidative stress eventually leads to unfavorable ventricular remodeling, cardiac hypertrophy, and heart failure (KOUSHKI M, et al., 2024). Resveratrol appears to improve left ventricular diastolic relaxation and preserves the functional abilities of mature cardiac cells (JOJIMA K, et al., 2023). By activating SIRT1 and the PGC-1α pathway, resveratrol may enhance mitochondrial function and attenuate cardiomyocyte apoptosis and oxidative stress injury (KOUSHKI M, et al., 2024; RAHMANI S, et al., 2024).

Limitations and Technological Challenges of Resveratrol Application

Despite the promising biological activities attributed to resveratrol, several limitations hinder its translation into effective clinical and nutritional applications. One of the major challenges is its low oral bioavailability. Although approximately 70-75% of orally administered resveratrol is absorbed, less than 1% reaches the systemic circulation in its free form due to rapid metabolism in the intestine and liver. Rapid glucuronidation and sulfation significantly reduce the concentration of unmetabolized resveratrol available to target tissues, raising concerns about whether the concentrations used in many in vitro studies can be achieved in vivo. Another important limitation is the physicochemical instability of resveratrol. The biologically active trans isomer is highly susceptible to degradation and isomerization when exposed to light, oxygen, and elevated temperatures, leading to the formation of the less active cis isomer. This instability may compromise the preservation of its biological properties during food processing, storage, and gastrointestinal transit.

Consequently, the beneficial effects reported in cell culture and experimental animal models do not always translate directly into human clinical outcomes. Variability in absorption, metabolism, and tissue distribution may also contribute to the different results from those observed across clinical trials. These

factors underscore the importance of developing delivery systems capable of enhancing stability and systemic availability.

FINAL CONSIDERATIONS

Resveratrol can be considered a promising bioactive compound to support the management of diabetes mellitus, particularly due to its antioxidant and anti-inflammatory effects and its potential role in improving insulin sensitivity, glucose uptake, pancreatic β-cell protection, and the modulation of microvascular and macrovascular complications. However, its low oral bioavailability, rapid metabolism, physicochemical instability, and heterogeneous clinical outcomes still limit its practical application. Therefore, well-designed clinical studies are needed to establish appropriate doses, long-term safety, and therapeutic efficacy, as well as to develop delivery systems, such as microencapsulation, nanoencapsulation, liposomes, and nanoemulsions, capable of improving its stability and biological availability.

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