# A Systematic Review of Application of Resveratrol and the Recent Progress of the Drug Delivery System

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**Abstract:** Background: Resveratrol is a natural compound in plants like grapes and peanuts, it's an antioxidant used in supplements and medicine. It's a colorless crystal soluble in organic solvents, with poor water solubility but high cell membrane permeability. It exists in cis and trans forms. Objective: To explore the background of resveratrol, this review comprehensively summarizes the recent advances in resveratrol including its application in cancer, type-2 diabetes mellitus, vascular disease, and the delivery system. Data sources: We performed a narrative review, based on relevant articles written in English from a PubMed search, using the following search terms: "resveratrol", and "bioavailability" and "bone health" or "cancer", or "cardiovascular", or "diabetes" or "estrogen" or "weight management" or "metabolism". Results: Cancer's aggressive nature requires multiple therapies, but they often cause side effects. Resveratrol (RSV) is a promising cancer treatment due to its fewer adverse effects. It inhibits cancer cell growth and promotes cell death by targeting specific pathways. Recent studies also examine the relationship between polyphenol intake and diabetes markers in overweight/obese individuals with metabolic syndrome. Increased polyphenol intake may reduce these markers, particularly in those with pre-diabetes. However, findings vary due to study heterogeneity. Vascular endothelial dysfunction is a critical factor in cardiovascular diseases. Phytochemical compounds, like resveratrol have antioxidative and anti-inflammatory properties that protect the cardiovascular system. Resveratrol prevents inflammation, reduces oxidative stress, and improves endothelial function, making it a promising therapy for cardiovascular diseases. To face the limitation like its low solubility and rapid metabolism, the drug delivery system has also been studied in this review. Various nanodelivery systems, including liposomes, polymeric nanoparticles, and inorganic nanoparticles, have shown promise in overcoming these challenges by improving solubility, biocompatibility, and therapeutic efficacy. Conclusions: While recent advancements in resveratrol's application show promise, further research is needed to optimize nanoformulations, validate efficacy in vivo, and tackle challenges like scalability and toxicity. Overall, these developments offer a promising path to maximize resveratrol's therapeutic potential in clinical settings.

## 1 Introduction

Resveratrol ($C_{14}H_{12}O_3$), as a natural plant toxin, is produced by plants to protect them from environmental stress and pathogenic invasion. [1] It is also a natural polyphenol with antioxidant properties, found in grapes, red wine, peanuts, and some medicinal plants, and can be used as a dietary supplement or in natural medicine. [2] Resveratrol is a colorless needle-shaped crystal, easily soluble in organic solvents such as ethanol, ethyl acetate, and acetone. It has poor water solubility but high cell membrane permeability, making it a BCS II compound.[3] There are mainly two forms of resveratrol in nature: cis and trans-resveratrol, as shown in figure 1. [4]

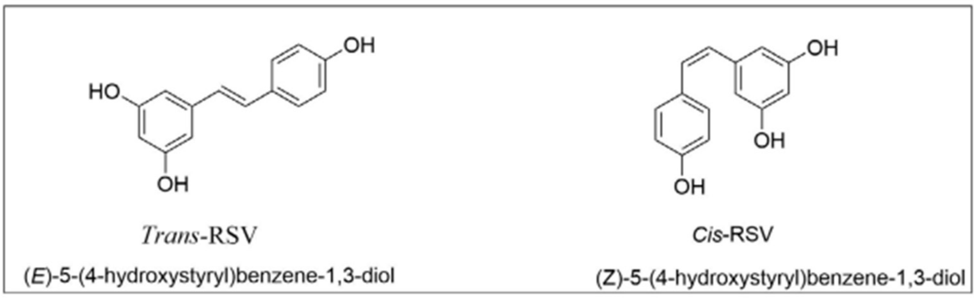


**Fig. 1.** The trans and cis form of RSV

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Under ultraviolet irradiation, the trans-isomer of resveratrol glycoside can be converted into the cis-isomer, where the physiological activity of the trans-isomer is greater than that of the cis-isomer, and the monomer activity is greater than that of the glycoside. [5] Resveratrol is usually present in plants in a stable trans-glycoside form. Resveratrol is unstable under light, and trans-resveratrol can be stably present in ethanol for several months under complete darkness, but its stability is slightly lower at high pH (≥10); while cis-resveratrol is more stable under light avoidance conditions only at neutral pH. [6] Human intestinal glucosidase can hydrolyze resveratrol glycosides into cis and trans-resveratrol, among which the cis structure has various biological functions, especially prominent antioxidant, cardiovascular disease prevention, immunity enhancement, and anticancer effects. The major effects of RSV are shown in Figure 2. [7]

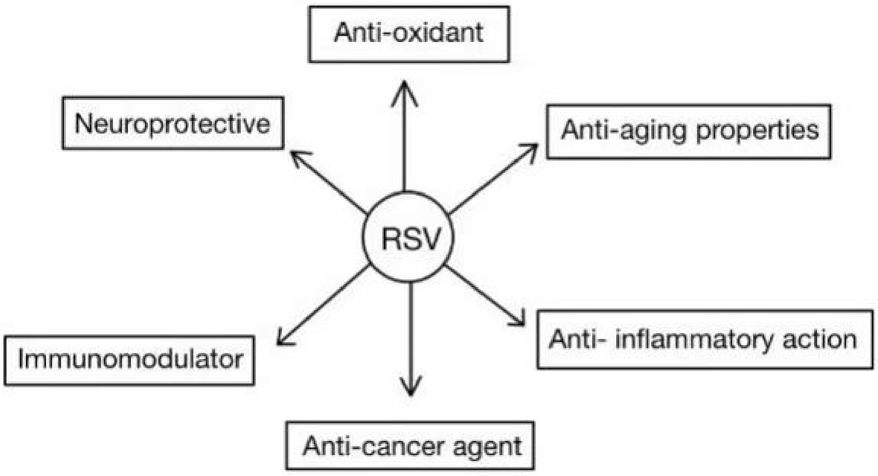


**Fig. 2.** Biological activities of RSV

Resveratrol has been extensively researched globally, holds promise as a natural medicine for preventing and treating diseases. Studies demonstrate its efficacy in mitigating oxidative reactions, inflammation, and offering vascular protection. [7]It also shows benefits in skin health, bone recovery, blood glucose control, and symptom relief for various conditions. However, its instability and low bioavailability present challenges, requiring effective delivery methods, especially for targeting the colon. [8]

Various studies have explored different methods of encapsulating resveratrol to improve its stability, release time, and therapeutic effects. [9] Encapsulation in corn protein nanoparticles with subsequent pectin encapsulation showed controlled release in both stomach and small intestine environments. [10] Chitosan nanoparticles and microcapsules were also used, exhibiting prolonged release and enhanced antioxidant activity. [11]A water-based gel carrier composed of specific alginates and low methoxy pectin was developed to protect resveratrol in the intestine. Despite these advancements, the optimal encapsulation approach remains unclear. [12]

## 2 Applications of Resveratrol

The theoretical significance of conducting resveratrol research and experiments includes exploring its potential applications in medicine and health. Scientists study its impact on cellular processes, its ability to combat oxidative stress, and its potential role in preventing or treating diseases such as heart disease, cancer, diabetes, and neurodegenerative diseases. [13]

Resveratrol is associated with the activation of sirtuins, which are a class of proteins related to longevity. Through these studies, we have also found metabolic benefits of resveratrol: people are interested in understanding how resveratrol affects metabolism, including its effects on insulin sensitivity, lipid metabolism, and obesity-related diseases. [14] Laboratory studies involving resveratrol typically include cell culture experiments, animal model experiments, and sometimes human trials to explore its potential health benefits and mechanisms of action. [15]

The practical significance includes conducting experiments in controlled environments to understand the mechanisms of action of resveratrol, its absorption and metabolism in the body, its safety, and its effectiveness in preventing or treating specific health conditions. [16] These studies typically involve cell culture, animal models, and occasional human trials to assess its potential therapeutic applications.

Although there have been promising findings in preclinical studies, clinical evidence supporting the beneficial effects of resveratrol on human health is still evolving. [17] Research is currently underway to determine the optimal dosage, potential side effects, and whether the effects observed in laboratory settings can translate into tangible health benefits for people. [18]

## 3. Method

Relevant articles regarding Resveratrol and its bioavailability were retrieved from PubMed, using the following keywords: "Resveratrol" and "bioavailability" or "bone health" or "cancer", or "cardiovascular", or "diabetes" or "estrogen" or "weight management" or "metabolism".

Article type was only selected for clinical trials, randomized controlled trial, review and meta-analysis. These articles can provide comprehensive summaries of research on a particular topic of resveratrol with findings from multiple studies. Duplicate articles and studies in languages other than English or adults were excluded. Studies prior to 2021 were excluded. However, there were some additional research performed for resveratrol and bioavailability and "bone health" and "estrogen". Very limited studies were found between 2022 and 2024. Therefore, the timeline has been extended to 2019, for more information. This review comprehensively summarizes the recent advances in the application of resveratrol in cancer, type-2 diabetes mellitus, vascular diseases therapy and it bioavailability and function on metabolism. (Figure 3)

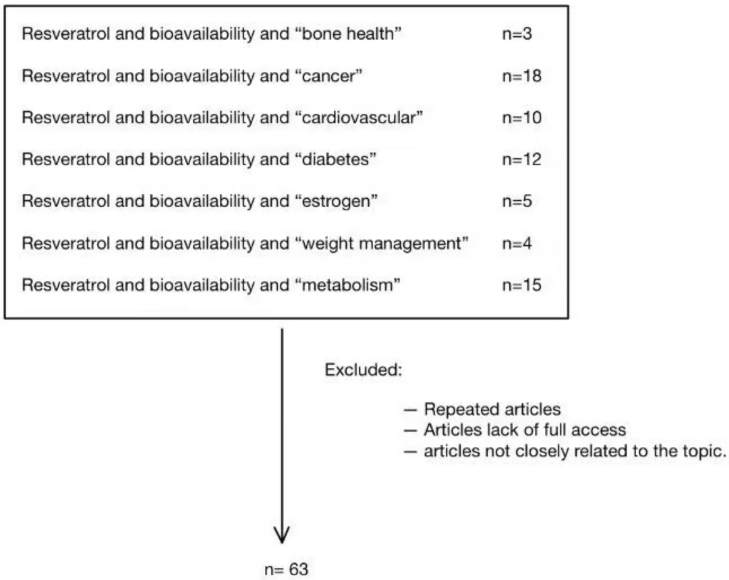


**Fig. 3.** The method chart of sorting and organizing research articles.

## 4. Cancer

The uncontrollable and metastatic nature of cancer exacerbates its severity and unpredictability, leading to the utilization of numerous therapies and medications for its management. [19] Cancer incidence is higher among individuals in developed countries, often attributed to their lifestyle. Among the plethora of phytoconstituent molecules, resveratrol (RSV) emerges as a promising candidate for cancer treatment due to its comparatively lower adverse effects on the body. [20] RSV impedes cell proliferation initiation and progression by modulating pathways such as the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway. It reduces the expression of cell cycle-regulated proteins like cyclin E, cyclin D1, and proliferating cell nuclear antigen (PCNA), while promoting apoptosis through the release of cytochrome c from mitochondria.

While RSV is known for its antioxidant and anti-cancer properties, its effects on various pathways, including inhibition, modulation, and activation, as well as induction, contribute to its beneficial effects. Consequently, the development of patented formulations reflects a growing interest in RSV's potential. Moreover, beyond its anti-cancer activity, RSV finds applications in nutraceuticals, herbal products, and pharmaceutical industries, further expanding its versatility and potential impact. Resveratrol (RSV) exhibits a wide range of molecular mechanisms in cancer treatment. RSV can exert anti proliferative and pro apoptotic effects by inhibiting multiple signaling pathways within tumor cells. For example, RSV can reduce tumor cell proliferation and survival by inhibiting the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mTOR signaling pathway. In terms of cell cycle regulation, RSV can reduce the expression of cyclin D1 and cyclin E, leading to cell cycle arrest in the G1 phase. RSV enhances the apoptosis of cancer cells by promoting the release of cytochrome c from mitochondria, activating the caspase cascade reaction. In addition, RSV inhibits tumor angiogenesis and cuts off the nutritional supply to the tumor by affecting angiogenic factors in the tumor microenvironment, such as vascular endothelial growth factor (VEGF).

## 5. Type-2 Diabetes Mellitus

Polyphenols demonstrate anti-diabetic effects by controlling essential biomarkers linked to type 2 diabetes mellitus (T2DM), such as fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), and insulin resistance (IR), while also modulating other metabolic, inflammatory, and oxidative stress pathways. Numerous pre-clinical and vivo studies support these effects of resveratrol. Sarfraz et al. (2023) explored the development of resveratrol drug delivery systems and their application prospects in cancer treatment, emphasizing the potential of nanotechnology in improving the bioavailability and anticancer effects of resveratrol.

There are plenty of research discuss the recent prospective analysis that explored the relationship between resveratrol intake and levels of HbA1c and blood glucose in overweight/obese individuals with metabolic syndrome (MetS). These articles indicate that higher consumption of specific classes of (poly)phenols is linked to decreased levels of these biomarkers, especially advantageous for individuals with pre-diabetic conditions. However, the findings vary depending on statistical models applied, with significant associations sometimes conflicting. Despite data collected from a large sample population, the complexity of dietary changes and confounding factors in the trial complicates interpretation. In clinical trials addressing participant homogeneity, test products, placebo, and bioavailability are necessary.

There are a lot of challenges in establishing definitive effects of (poly)phenols against type 2 diabetes mellitus (T2DM) due to the high heterogeneity of studies and variable results. Identifying individuals who respond best to these compounds, particularly those with pre-diabetes or T2DM, is crucial. However, issues such as diverse test products and insufficient characterization of placebos hinder accurate assessment of (poly)phenols' effects. Understanding the metabolic fate of (poly)phenols and their association with antidiabetic effects is essential, requiring more bioavailability studies. Overall, there is some evidence backing the regulatory advantages of (poly)phenols in combating T2DM, further research addressing these challenges is needed for consistent and sufficient evidence to recommend their use in specific populations. In the field of diabetes, resveratrol (RSV) plays a role through a variety of molecular mechanisms to improve insulin sensitivity and regulate glucose and lipid metabolism. RSV activates the AMP activated protein kinase (AMPK) pathway, which is a key regulator of cellular energy balance and can increase glucose uptake and inhibit liver glucose production. In addition, RSV affects the synthesis and oxidation of fatty acids by regulating transcription factors such as peroxisome proliferator activated receptor gamma (PPAR gamma) and sterol regulatory element binding protein 1c (SREBP-1c), thereby reducing blood lipid levels. RSV also has anti-inflammatory effect and can reduce the expression of proinflammatory cytokines such as tumor necrosis factor alpha (TNF - α) and interleukin-6 (IL-6), which play a central role in chronic low-grade inflammation related to diabetes.

## 6. Vascular Disease

Epidemiological research has shown that consistent intake of medicinal plants, fruits, and vegetables enhances vascular well-being and lowers the likelihood of cardiovascular diseases, largely because of the phytochemical compounds present in these natural sources. Comprehensive literature reviews were carried out to uncover studies demonstrating the vascular protective properties of phytochemical compounds. Resveratrol shielded circulating endothelial cells from apoptotic harm induced by oxLDL by diminishing Lox-1-mediated activation of the Bax-mitochondria-cytochrome c-caspase protease pathway, as evidenced in Evidence-Based Complementary and Alternative Medicine. Moreover, it enhanced the expression of endothelial nitric oxide synthase (eNOS), leading to heightened nitric oxide production from endothelial cells. The escalated production of endothelial nitric oxide has the potential to ameliorate endothelial function and promptly lower systolic blood pressure, which holds significance in averting cardiovascular disease.

Animal studies support the vascular protective effects of resveratrol, showing its ability to prevent vascular dysfunction induced by metabolic disorders like high-fructose diet and obesity. Epidemiological studies have linked red wine consumption to reduced cardiovascular disease mortality, which has been attributed to resveratrol. It possesses antioxidative, anti-inflammatory, and antitumor properties, providing multidimensional protection to the cardiovascular system, particularly the vasculature. Research has demonstrated that resveratrol effectively suppresses reactive oxygen species (ROS) production and inflammatory markers in endothelial cells, protecting against vascular inflammation induced by various agents like TNF-α and cigarette smoke extract. Furthermore, resveratrol targets enzymes involved in prostaglandin activity, reducing vascular inflammation. It also exhibits antioxidant effects by inhibiting ROS generation and activating endogenous antioxidant systems in endothelial cells. Additionally, resveratrol has antiapoptotic effects, preventing endothelial cell apoptosis and promoting endothelial nitric oxide production, which improves endothelial function and reduces blood pressure. Overall, resveratrol demonstrates promising potential in protecting and improving vascular health through various mechanisms, making it a valuable therapeutic agent for cardiovascular diseases.

Repurposing existing medications for alternative applications is a valuable strategy for discovering new therapies with established safety profiles. Cardiovascular diseases, characterized by oxidative stress and inflammation, are targeted by many phytocompounds and medications. While extensive research has investigated the vascular protective effects of active phytocompounds, ongoing developments focus on improving the bioavailability of resveratrol.

## 7. Resveratrol Delivery

Researchers have developed various nano delivery systems to enhance their clinical potential. The following are some major nano delivery systems, each with unique advantages and limitations, as shown in Table 1.

**Table 1.** Advantages and limitations of various nano delivery systems

| Nanodelivery system | Advantage | Limitations |
|---|---|---|
| Liposomes | • High biocompatibility | • Poor stability |

| | | |
|---|---|---|
| | ● Protect the drug from degradation<br>● Easy to prepare | ● There may be a lower cellular uptake |
| Polymeric nanoparticles | ● Highly customizable<br>● Controlled release<br>● Improve drug solubility | ● Possible non-biodegradability issues<br>● Potential long-term toxicity issues |
| Solid lipid nanoparticles | ● Improves stability<br>● Sustained release effect<br>● The biocompatibility is good | ● Possible lipid oxidation problem<br>● The preparation process is complex |
| Inorganic Nanoparticles | ● High drug loading<br>● Unique physical and chemical properties | ● Potential biocompatibility and toxicity issues<br>● Possible long-term safety issue |
| Nanoemulsions | ● High stability<br>● Improve drug solubility and absorption | ● Possible interface stability issues<br>● Long-term storage may present challenges |
| Protein-Based Nanoparticles | ● High biocompatibility and biodegradability<br>● And that target property of the medicine is improved | ● Possible immunogenicity issues<br>● The preparation cost is high. |
| Exo somes | ● Excellent biocompatibility and targeting<br>● Can be used for natural information exchange between living cell | ● Low production efficiency<br>● Surface modification and drug loading may present technical challenges |

Resveratrol is known for its diverse pharmacological activities, faces limitations in clinical efficacy due to factors such as low permeability, light-induced isomerization, auto-oxidation, and rapid metabolism. Various nanodelivery systems, including liposomes, polymeric nanoparticles, lipid nanocarriers, micelles, nanocrystals, inorganic nanoparticles, nanoemulsions, protein-based nanoparticles, exosomes, macrophages, and red blood cells (RBCs), have demonstrated significant potential in addressing these limitations by improving solubility, biocompatibility, and therapeutic efficacy. The research encompasses recent progress in nanoencapsulation of resveratrol and suggests methods for enhancing the pharmacokinetics of current nanoformulations, refining targeting, mitigating toxicity, and optimizing drug release and encapsulation efficiency.

In order to address the solubility and metabolism issues of resveratrol, researchers have been exploring innovative delivery systems. Li et al. (2023) discussed in detail the latest progress in improving the stability and bioavailability of resveratrol using nanotechnology based drug carriers, providing new ideas for the clinical application of resveratrol. RSV encounters challenges such as poor water solubility and bioavailability due to extensive metabolism by the liver and intestine, including its own metabolites inducing further metabolism. Consequently, only a minimal amount of unchanged RSV is excreted in urine. Polymer nanoparticles are versatile tools used in drug delivery and diagnostics. They can encapsulate therapeutic agents for targeted delivery, minimizing side effects while enhancing efficacy. Additionally, they are employed in diagnostics to detect biomarkers, aiding in disease diagnosis and treatment monitoring. To overcome those limitations, researchers have explored nanocarriers as delivery systems, enhancing topical penetration and significantly improving bioavailability and permeability.

Encapsulation of RES into specific nanocarriers, including liposomes, polymeric nanoparticles, solid lipid nanoparticles (SLNs), protein-based nanoparticles, and inorganic nanoparticles, addresses these challenges by modulating drug release to achieve therapeutic plasma concentrations and improve bioavailability. Polymer nanoparticles are extensively utilized due to their high encapsulation efficiency, reducing the required amount of nanocarriers, and minimizing potential toxic effects. These nanoparticles can be tailored by adjusting their composition and structure and functionalizing their surface for targeted RES delivery to specific cell receptors. While synthetic nanoparticles like inorganic nanoparticles and nano-emulsions have limitations such as low encapsulation capacity and safety concerns, biologically derived carriers offer improved biological distribution, cellular uptake, and controlled drug release with higher biocompatibility and lower toxicity. However, obtaining bionic nanocarriers like proteins and exosomes on a large scale remains a challenge. Additionally, studies are required to expand our understanding of the pharmacokinetics, biodistribution, toxicity, and biocompatibility of RES-loaded nanoformulations and validate their efficacy in vivo.

## 8. Conclusion

In conclusion, resveratrol holds significant promise with diverse pharmacological activities and potential therapeutic applications in various health conditions, including cancer, type-2 diabetes mellitus, and vascular diseases. Despite its extensive benefits, challenges such as poor water solubility, low bioavailability, and rapid metabolism have hindered its clinical efficacy. However, recent advancements in resveratrol delivery systems, particularly through nanotechnology, offer promising solutions to address these limitations. Various nanocarriers, including liposomes, polymeric nanoparticles, and protein-based nanoparticles, have shown significant potential in improving the solubility, biocompatibility, and therapeutic efficacy of resveratrol. These nanoencapsulation strategies not only enhance drug delivery but also allow for targeted delivery to specific cell receptors, minimizing potential toxic effects and optimizing drug release kinetics. Furthermore, biologically derived carriers offer improved biological distribution and controlled drug release with higher biocompatibility. Despite these advancements, further research is needed to optimize resveratrol nanoformulations, validate their efficacy in vivo, and address challenges related to scalability, toxicity, and long-term bioactivity. Overall, the recent progress in resveratrol delivery systems represents a promising avenue for overcoming its limitations and unlocking its full therapeutic potential in clinical applications.

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