



Resveratrol as a bioactive compound in Functional Food Science: Sources, quantification, and health implications

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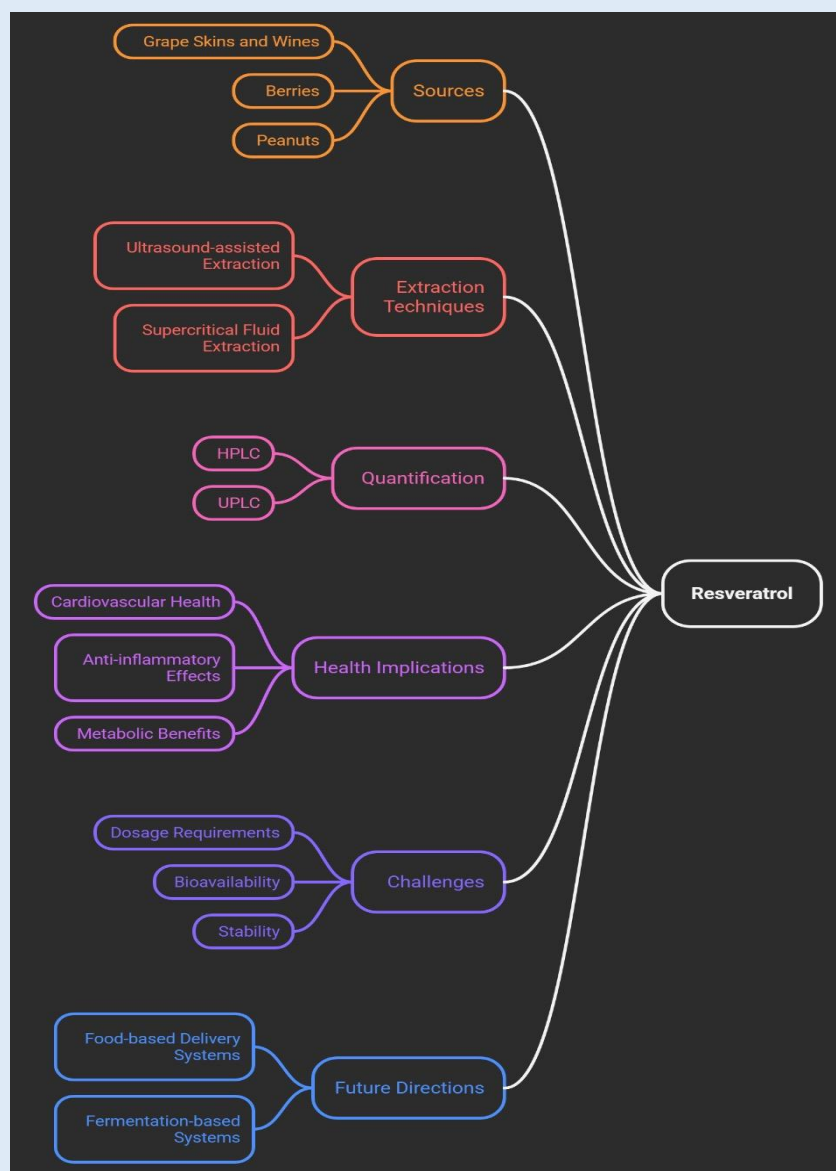
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ABSTRACT

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) has gained significant attention in the scientific community due to its broad biological activity at nutritionally relevant doses. This review summarizes the potential of resveratrol as a key bioactive compound in functional food science, with a focus on its dietary sources, extraction principles, quantification techniques, health benefits, and dosage requirements. Natural sources of resveratrol include grape skins and wines, grape leaves and vine tissues, berries, peanuts, and *Polygonum cuspidatum*, with concentrations highly dependent on cultivar, environmental conditions, and processing practices. Recent advances in extraction techniques have improved yield and enabled the recovery of resveratrol from sources with low native concentrations. Many methods have been developed to detect resveratrol at extremely low concentrations; however, these techniques are often affected by matrix effects and trans-to-cis isomerization. Biologically, resveratrol has shown promising results through signaling pathways such as SIRT1, NF- κ B, and PI3K/Akt/mTOR. Despite these findings, results from human clinical trials remain inconclusive, highlighting the need for additional in vivo investigations. Emerging studies aim to enhance resveratrol stability and deliver it through food matrices and fermentation-based systems. Overall, the development of standardized analytical methods and optimized formulations is essential to translate resveratrol's biological potential into practical and effective functional food applications.

Novelty: This review provides a critical evaluation of resveratrol’s transition from a botanical extract to a standardized functional food ingredient. Unlike previous summaries, this work integrates modern green extraction efficiencies (UAE, SCFE) with specific matrix-effect challenges in quantification. Furthermore, it aligns resveratrol research with the 17-step Functional Food Development framework, identifying current gaps in human clinical evidence and the necessity for stabilized food-based delivery systems to overcome bioavailability limitations.

Keywords: Resveratrol, Functional foods, SIRT1, NF-κB, Ultrasound-assisted extraction, Supercritical fluid extraction, HPLC, UPLC, Matrix effects, Trans-to-cis isomerization, Cardiovascular health, Apoptosis, Bioavailability, Dose-dependence.



Graphical Abstract: Resveratrol as a bioactive compound in Functional Food Science: Sources, quantification, and health Implications.

INTRODUCTION

Resveratrol, a naturally occurring polyphenolic compound, has garnered significant attention in functional food science due to its diverse health benefits and potential applications in disease prevention and treatment. Found predominantly in grapes, berries, and red wine, resveratrol is recognized for its antioxidant, anti-inflammatory, and cardioprotective properties. Its role in functional foods is particularly noteworthy as it offers health benefits beyond basic nutrition, making it a valuable component in nutraceuticals and pharmaceuticals. This introduction explores the sources, quantification methods, and health implications of resveratrol, highlighting its significance in functional food science.

Sources of Resveratrol: Resveratrol is primarily found in grapes, berries, peanuts, and red wine, with grapes being the most significant source due to their high concentration of this compound [1, 2]. The compound exists in two isomeric forms, *cis*- and *trans*-resveratrol, with the latter being more stable and biologically active [3]. Environmental factors such as light, air exposure, and temperature can affect the stability and solubility of *trans*-resveratrol, influencing its availability in food sources [3].

Quantification of Resveratrol: Various analytical techniques are employed to quantify resveratrol, including chromatographic methods like RP-HPLC and LC-MS/MS, which are noted for their sensitivity and specificity [4]. These methods are essential for ensuring accurate measurement of resveratrol content in different matrices, such as wine and serum, and for developing effective nutraceutical formulations [4]. Challenges in quantification include isomerization and photodegradation, necessitating stringent sample-handling protocols to maintain accuracy [4].

Health Implications: Resveratrol exhibits a wide range of biological activities, including antioxidant, anti-inflammatory, anticancer, and neuroprotective effects, making it a promising candidate for preventing and treating chronic diseases such as cardiovascular diseases, cancer, and neurodegenerative disorders [5, 6]. Its cardioprotective effects are particularly well-documented, with studies showing its ability to decrease LDL cholesterol, increase HDL cholesterol, and prevent arterial blockage [1]. Despite its health benefits, resveratrol's bioavailability is limited due to rapid metabolism, which poses a challenge for its therapeutic use [7].

While resveratrol holds significant promise in functional food science, its low bioavailability and stability present challenges that need to be addressed to fully harness its health benefits. Future research may focus on developing novel delivery systems and derivatives to enhance its pharmacokinetic profile and therapeutic efficacy. Resveratrol's alignment with functional food standards makes it particularly attractive for natural preventative purposes. This article walks through the extraction techniques, quantification methods, and overall health benefits of nutritional resveratrol.

Literature Selection: A comprehensive search was conducted using PubMed, Google Scholar, and the FFHDJ ecosystem databases (2023–2025). Keywords included "Resveratrol," "Functional Food," and "Extraction Techniques." Inclusion criteria focused on peer-reviewed studies providing quantitative data on extraction yields or clinical biomarkers. Exclusion criteria involved studies lacking standardized quantification methods or non-English publications.

Resveratrol from the Perspective of Functional Food Science: Resveratrol is produced in response to stress and other environmental factors [8, 9]. Post-harvest processing steps, particularly fermentation and storage

conditions, significantly influence resveratrol levels in wines and grape-derived products [10]. Resveratrol has been shown to modulate specific chemical pathways in humans and animals at nutritional doses. Pathways such as Nrf2 and NF-κB are responsible for antioxidant and anti-inflammatory responses. Resveratrol has also demonstrated anti-aging and longevity effects by modulating pathways such as SIRT1 [11, 12, 16]. Additionally, clinical data indicates that resveratrol supports cardiovascular health, particularly endothelial function and vascular markers. It has also proven to enhance glycemic control and insulin sensitivity in individuals with type 2 diabetes and insulin resistance. Overall, resveratrol's ability to regulate these pathways and manage chronic disease risk highlights its potential

as a preventive nutritional agent [13, 16].

Dietary and Botanical Sources of Resveratrol:

Resveratrol is found in a variety of dietary and botanical sources, with levels varying depending on the plant species, plant part, and processing methods. Recognizing this variability is important when developing functional foods to ensure that they provide nutritionally meaningful doses. While grapes and grape-derived products are the most well-known sources, several non-grape plants and commercial ingredients also serve as natural and fortified options [22]. The table below outlines the main food categories and ingredients, their typical roles, key features, and example studies that report their resveratrol levels.

Table 1: Sources of resveratrol and their benefits.

Source/Product Type	Key Resveratrol Details	DOI
Red vs. white grape skins and wines	Red grape skins and red wines contain higher resveratrol than white grapes and white wines because of greater skin contact during fermentation and typically show ranges of about 0.1–14 mg/L in reds vs. roughly 0.1–2 mg/L in whites.	[15, 17, 23]
Influence of variety, climate, and fermentation	Cultivar, climate (temperature, sunlight), fungal pressure and winemaking practice (maceration time, skin contact) all modulate resveratrol content in grapes and wines	[15]
Grape leaves and vine tissues	Grape leaves and vine prunings are resveratrol-rich but underused botanical sources that can be processed into valuable extracts	[19, 27]
Leaf extracts and vine-based supplements	Ultrasound-assisted and other intensified extraction methods from grape leaves are being explored to produce resveratrol-rich ingredients suitable for nutraceutical use	[19]
Berries (blueberries, cranberries, mulberries)	Several berries, especially Vaccinium species (blueberries, cranberries), contain detectable resveratrol and related stilbenes, though typically at lower levels than grapes . A study highlights the high concentration of polyphenols in blueberry-based supplements, where one capsule (0.305 g) can correspond to 200 mg of blueberry extract.	[20, 22]
Peanuts and peanut skins	Resveratrol is present in peanuts, peanut butter, and especially peanut sprouts/skins, making peanuts one of the more important non-grape dietary sources. The highest extraction yield of resveratrol using ultrasonic-assisted extraction could be up to 1.1%	[24-26]
Polygonum cuspidatum (Japanese knotweed)	Roots of Polygonum (Fallopia) cuspidatum are widely used as a high-yield commercial source of resveratrol for supplements and fortified foods. Study participants received "200 mg of PCE standardized to contain 20% trans-resveratrol equivalent to 40 mg trans-resveratrol.	[27-29]
Resveratrol-enriched beverages	Functional beverages, including enriched juices and wines, are being developed to deliver standardized resveratrol doses within food matrices	[31,32]
Capsules/tablets and other supplements	Capsules and tablets containing purified resveratrol or plant extracts are the predominant commercial forms, allowing controlled dosing in clinical and preventive settings	[33]

Source/Product Type	Key Resveratrol Details	DOI
Fermented and conceptual functional products	Conceptual and experimental products include fermented foods and beverages designed to enhance resveratrol stability, transformation, or interaction with gut microbiota within a functional food framework .	[31, 50]

Different sources of resveratrol offer distinct advantages and limitations, influenced by availability, cost, and legal regulations. For health purposes, combining high-concentration natural ingredients with supplements helps maintain precise dosing. Together, these factors guide the selection of delivery methods for resveratrol in preventive healthcare products.

Extraction Techniques: There are numerous methods for extracting resveratrol, but four have become increasingly popular. Extraction efficiency of resveratrol is strongly influenced by solvent polarity, extraction time, and temperature, necessitating careful optimization to maximize yield while minimizing degradation [21]. Traditional mechanical extraction, ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), and supercritical and pressurized fluid extraction (SCFE) have become standard practice in extracting phenols from various sources.

Traditional mechanical extraction involves the use of an alcohol-water solution, heated shaking to break the cell wall, and acid reflux. Specifically, grape/pomace is mixed in a 50-70% ethanol-water solution at a 10-30mL/g ratio. This amalgamation is then subjected to 30-60 min of shaking/reflux at 40-60°C, yielding up to 45.7 mg/g of total phenolics including trans-resveratrol. Although this procedure is environmentally friendly, results in a high yield of phenolics, and is scalable for industrial use, it is time consuming and energy intensive [18].

Ultrasound-assisted extraction (UAE) achieves higher extraction rates than traditional maceration-based techniques. In a study, the Box–Behnken Experimental Design (BBD) was used to optimize polyphenol content and antioxidant capacity by varying water content, solid/liquid ratio, temperature, and

extraction time. The study concluded that 1.05-2.90 mg/g trans-resveratrol was obtained from vine shoots/peanut skins, using 50-70% less solvent than maceration. UAE is beneficial because it uses fewer harmful solvents and is generally considered as a green solution for stilbene extraction [19, 31].

In another study, microwave-assisted extraction (MAE) was performed on macerated grapes at 600W microwave power for 2 minutes per cycle, with three cycles total. After the microwave cycles, they followed with sonication at 53kHz at 100% amplitude for 20 minutes. This procedure resulted in a trans-resveratrol concentration of 0.23 mg/100 g dry weight in the juice. Compared to the enzymatic method, the combined MAE and sonication techniques allowed for the detection of more antioxidant polyphenols, like tR, indicating that MAE was more effective in assessing antioxidant capacity. However, the results from sonication, whether cold or thermosonication, were lower than those from enzymatic treatment [18, 36].

Since phenolic compounds include water-soluble components, they are highly suitable for supercritical and pressurized fluid extraction (SFE). A study on grape seeds involving SCFE extractions (temperature 80 °C; CO2 flow rate 69 g/min; pressure 250 bar; duration 60 min) found that the total polyphenols remained mostly unchanged. Overall, the main advantage of using supercritical and pressurized fluids for resveratrol extraction is the preservation of compound quality and purity, as the process is conducted under controlled light and air conditions, minimizing degradation reactions [18, 33].

After resveratrol is extracted from its sources, the residue must be purified. In one study, silica gel column chromatography was used for purification, and the purified product was analyzed using HPLC-PDA. The

procedure involved dissolving the residue in ethanol. The optimal solvent system for column chromatography was determined via TLC. The mobile phase, a mixture of chloroform, ethyl acetate, and formic acid in a 25:10:1 ratio, was applied to a pre-conditioned silica gel column. The column was eluted with this mixture, collecting 25 fractions of 15 mL. Positive TLC results led to combining and evaporating the fractions. UV fluorescence at 254 nm confirmed the presence of the standard and extract. The combined fractions were dissolved in ethanol for HPLC-PDA analysis [31].

Analytical Quantification: High-Performance Liquid Chromatography (HPLC) is well known for its high precision in detecting small amounts of a compound [34]. Its ability to detect analytes at the nanogram level makes it particularly suitable for resveratrol analysis. HPLC is also compatible with polar and nonpolar, large and small, and heat-sensitive molecules making it highly versatile for food, pharmaceutical, and biomedical analysis. One study compared different types of chromatography-based spectroscopy, demonstrating the high accuracy of HPLC and related methods [39].

LC-MS, also known as liquid chromatography-tandem mass spectrometry, combines HPLC with a mass spectrometer instead of a UV detector. This method offers far superior selectivity and sensitivity compared to UV-only HPLC [35, 39].

Ultra Performance Liquid Chromatography (UPLC), in contrast to LC-MS and HPLC, is a rapid technique that prioritizes speed over accuracy. A novel study on the detection of resveratrol in rat plasma used UPLC to guide their assessment. Each test lasted 6 minutes and yielded intra-day precision of 101.4%, within 10%, which was acceptable for bioanalytical ranges. The advantages of UPLC for resveratrol include high sensitivity, the ability to detect multiple compounds per test, and extreme speed. It is, however, very costly to operate and own a machine capable of withstanding high pressure compared to traditional HPLC [40].

Factors Influencing Measurement Sample preparation for resveratrol typically involves dissolving a measured amount in an alcohol or organic solvent. Similarly, a study prepared a primary resveratrol stock solution (1 mg/mL) by dissolving 0.01 g of resveratrol in 10 mL of acetonitrile [38]. This stock was stored at -80°C until use [38].

Trans-resveratrol is unstable under light, basic pH, and elevated temperature, which can cause isomerization to *cis*-resveratrol. Factors contributing to isomerization include sunlight, UV light at 254 nm or 365 nm, alkaline conditions, and heat [38].

To assess the effects of *trans*-resveratrol on matrix components, the study analyzed tissue-dependent shifts in chromatographic retention times and observed significant variations in matrix factors. For example, Resv-3-G, which eluted at 1.47 min in standard solution, shifted to 0.78 min in brain homogenate, indicating that co-extracted matrix components influenced analyte retention. Across six biological matrices, matrix factor (MF) values showed consistent patterns of suppression or enhancement. Resveratrol caused ion enhancement (MF > 1) in all tissues except urine, whereas its conjugated metabolites exhibited substantial ion suppression, with Resv-4'-G showing the most suppression, with MF values as low as ~ 0.04 in kidney homogenate. The variability in retention times and MF indicated that matrix composition greatly impacted ionization efficiency and chromatography. To address this, the study employed stable isotope-labeled internal standards, which underwent the same matrix effects, enabling accurate correction of analyte responses across all tissue types [39].

Functional Food Development Framework: According to the Functional Food Development framework proposed by Martirosyan and Stratton (2023), the creation of a legitimate functional food product requires a rigorous 17-step approval process. This review directly facilitates the first five stages of this paradigm: identifying the bioactive compound (Step 2), establishing dosage benchmarks

through standardized quantification (Step 3), and characterizing the mechanisms of action and biomarkers (Steps 4 and 5). While current research has successfully navigated these early preliminary stages, the transition to Step 12 (Clinical Trials) remains the primary bottleneck for resveratrol due to conflicting human data and bioavailability challenges [40].

Health Benefits and Bioactivity Overview: As highlighted in this article, resveratrol is a bioactive phytoalexin with anti-inflammatory, antioxidant, metabolic regulatory, stress resistance, aging, immune regulation, and circadian rhythm effects that impact numerous diseases [30]. Its ability to control SIRT1 activation offers benefits similar to those of caloric restriction [45, 46]. In clinical studies, resveratrol has been shown to modulate pathways such as NF- κ B, Wnt, and PI3K/Akt/mTOR, which promote cell survival and tissue remodeling and reduce inflammation. It has also been demonstrated to activate PGC-1 α and PPAR signaling while inhibiting mTOR in hepatocellular carcinoma models [42, 44].

In cardiovascular health, resveratrol improved endothelial function, lowered LDL cholesterol, inhibits platelet aggregation, and decreases the expression of adhesion molecules associated with atherosclerosis. In diabetes, resveratrol improved glycemic and cardiometabolic markers. Its anticancer effects include inducing apoptosis, inhibiting tumor growth, and disrupting oncogenic signaling pathways across various cancer types [19, 43–45].

However, because resveratrol is rapidly metabolized, these health benefits are difficult to achieve given the current lack of high-concentration resveratrol in the consumer market [11]. In models of estrogen (E2) deficiency, such as ovariectomized (OVX) rats, a late introduction of low-dose resveratrol (5mg/kg) after the establishment of glucose intolerance was not effective in rescuing impaired glucose tolerance [46]. Recent work on childhood obesity further emphasizes that effective

resveratrol use requires well-defined doses, timing, and delivery formats tailored to pediatric populations [47].

Safety, Dosage, and Functional Food Application:

Clinical trials show that resveratrol typically causes adverse effects only at high doses. In one study, SRT501 caused severe renal toxicity in a patient with multiple myeloma. Currently, there aren't many bioavailable forms of resveratrol, with most circulating as glucuronide and sulfate conjugates. As a result, peak plasma levels of resveratrol remain extremely low. Human trials have also confirmed dose-dependent, nonlinear effects: low doses activate antioxidant pathways, whereas very high doses may increase oxidative stress [48].

Overall, results across clinical trials are inconsistent [45, 49]. In studies on diabetes and cardiovascular studies, resveratrol has been shown to improve health outcomes, but in cancer patients, it rarely has an effect. Variability in study design, dosing strategies, and outcome measures across human trials has contributed to inconsistent findings regarding the clinical efficacy of resveratrol [49]. This is because disease-specific metabolism likely plays a role: patients with chronic inflammation or hepatic dysfunction metabolize resveratrol differently, leading to heterogeneous clinical outcomes. With further research and development of extraction techniques, resveratrol has the potential to make a significant contribution to functional food science and its applications [49].

Natural vs. Synthetic Resveratrol Sources: Natural sources of resveratrol, such as grapes and *Polygonum cuspidatum*, are preferred for functional food applications due to consumer demand for "clean label" ingredients. However, natural extracts often face challenges regarding seasonal variability, environmental conditions, and the presence of complex matrix components that can interfere with quantification. Conversely, synthetic resveratrol offers high purity and consistent dosing, yet it may lack the synergistic effects

of co-extracted polyphenols found in whole-food sources. Integrating high-concentration natural ingredients with standardized supplements is currently the most effective strategy for maintaining precise dosing in preventive healthcare products.

Novelty and Current Research Trends: Clinical studies indicate that resveratrol provides anti-inflammatory, heart-protective, brain-supportive, and metabolic benefits. However, challenges related to its effective dosage, absorption, and long-term safety limit its widespread use. To improve the stability and delivery of resveratrol, food-based approaches have gained popularity. Recent research shows that grape pomace enriched with *Lactobacillus casei* can be converted into stable, nutrient-rich powders using convective and infrared drying techniques.

In one study, infrared drying at 50°C reduced processing time by 14.3% while preserving high levels of anthocyanins, with 28 types identified, mainly cyanidin-3-O-glucoside. The powders maintained probiotic quality for 2 weeks at 4°C, and the extracts demonstrated potential to combat diabetes by inhibiting α -amylase, with infrared-dried samples showing stronger effects than conventionally dried ones [50]. Overall, these findings underscore the potential of polyphenols like resveratrol for use in health-supporting and functional foods, especially when embedded in stable, active delivery systems.

CONCLUSION

Resveratrol is a food-derived bioactive that links plant defense chemistry with human health, providing antioxidant, anti-inflammatory, cardiometabolic, and gut-related benefits. However, practical application requires standardized analytical methods for the extraction, quantification, and stability testing of raw materials and finished products to ensure that labeled doses correspond to those used in clinical trials. Human studies using standardized formulations and well-defined

endpoints are still necessary to determine resveratrol's effectiveness, dose, response, relationships, and safety across different populations [49]. Resveratrol remains a promising but evolving candidate for disease prevention, integrating diet, lifestyle, and targeted functional foods.

Abbreviations: Akt, protein kinase B; BBD, Box–Behnken Design; BCH, botanical crude homogenate; CO₂, carbon dioxide; HPLC, high-performance liquid chromatography; HPLC-PDA, high-performance liquid chromatography with photodiode array detection; IR, infrared; LC-MS, liquid chromatography–mass spectrometry; MAE, microwave-assisted extraction; MF, matrix factor; mTOR, mechanistic target of rapamycin; NF- κ B, nuclear factor kappa-B; Nrf2, nuclear factor erythroid 2–related factor 2; PI3K, phosphoinositide 3-kinase; SCFE, supercritical and pressurized fluid extraction; SIRT1, sirtuin 1; TLC, thin-layer chromatography; UAE, ultrasound-assisted extraction; UPLC, ultra-performance liquid chromatography; UV, ultraviolet; Wnt, Wingless-related integration site.

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