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Review

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Trans-Resveratrol as a Health Beneficial Molecule: Activity, Sources, and Methods of Analysis

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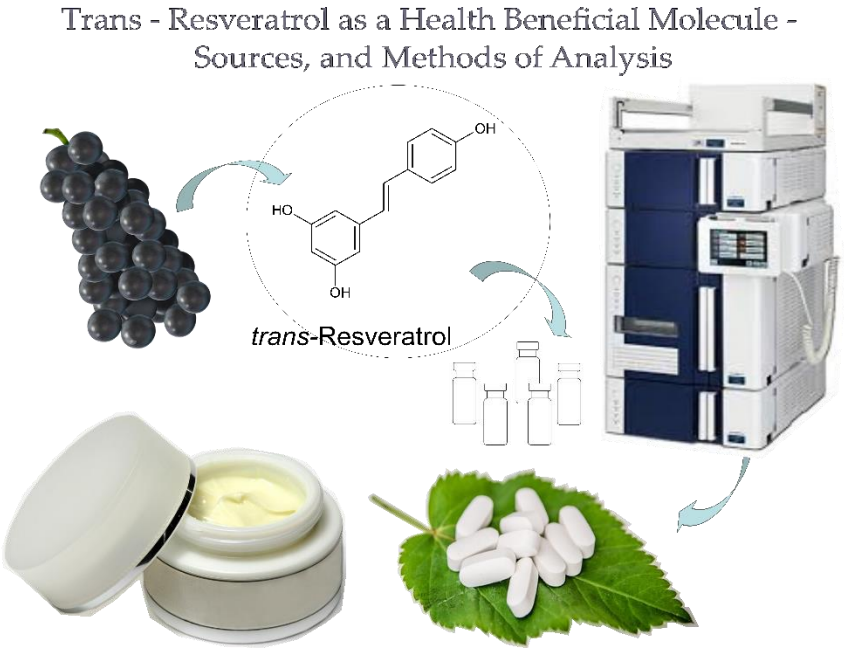

Abstract: *Trans*-Resveratrol, a natural polyphenol found in various plant species, has gained significant attention due to its potential health-promoting properties. This article reviews the biological activities attributed to *trans*-Resveratrol, its dietary sources, and the analytical methods employed for its quantification. The compound antioxidant, anti-inflammatory, anticancer, cardioprotective, and neuroprotective activities are discussed in detail. Furthermore, the sources of *trans*-Resveratrol, including grapes, berries, and certain nuts, are examined in terms of their content variability and factors influencing production. Various chromatographic, spectroscopic, and immunoassay methods for the analysis of *trans*-Resveratrol in different matrices are also explored. This comprehensive overview underscores the significance of *trans*-Resveratrol as a potential molecule for enhancing human health and longevity.

Keywords: *trans*-Resveratrol, health-beneficial activity, methods of analysis

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Introduction

Trans-Resveratrol (3,5,4'-trihydroxystilbene) is a naturally occurring polyphenol that has garnered attention in recent years due to its purported health benefits. It is present in a variety of plant species, where it serves as a protective agent against environmental stressors such as UV radiation, pathogens, and injury. Studies have suggested that *trans*-Resveratrol may contribute to the health-promoting effects associated with diets rich in fruits, vegetables, and red wine [1, 2]. The presence of *trans*-Resveratrol in wine has been proposed as a contributing factor to the observed phenomenon known as the "French Paradox." This paradox refers to the relatively low incidence of coronary heart disease among the French population despite a diet rich in saturated fats. Wine consumption, particularly red wine, has been associated with cardiovascular health benefits, and *trans*-Resveratrol is believed to play a role in this context. *Trans*-Resveratrol, found in grape skins and consequently present in red wine, possesses antioxidant and anti-inflammatory properties. These attributes are thought to contribute to the maintenance of endothelial function, reduction of oxidative stress, and improvement of lipid profiles, all of which are factors associated with cardiovascular well-being [3]. However, it is important to note that the French Paradox is a complex phenomenon influenced by a combination of dietary, lifestyle, and genetic factors. While *trans*-Resveratrol presence in wine is intriguing, it represents just one element within a larger matrix of variables that contribute to the cardiovascular health benefits observed in certain populations [4].

(Figure 1). The biosynthesis of trans-resveratrol begins with the conversion of 4-hydroxycinnamoyl-CoA to p-coumaroyl-CoA [5–7]. This reaction is catalysed by the enzyme 4-coumaroyl-CoA ligase. The next step involves the transformation of *p*-coumaroyl-CoA into trans-Resveratrol. This conversion occurs through a series of enzymatic reactions. Stilbene synthase (STS), a key enzyme in Resveratrol biosynthesis. It condenses three molecules of malonyl-CoA with one molecule of *p*-coumaroyl-CoA to form a trans-Resveratrol intermediate called linear tetraketide., which is then cyclised and modified to form the stilbene nucleus. Thereafter, the action of the STS or of the trans-Resveratrol-3-O-methyltransferase allows the formation of trans-Resveratrol derivatives, such as piceatannol or pterostilbene. Additionally, environmental factors and genetic variations can influence the production of trans-Resveratrol in plants, making it a subject of ongoing research in the field of plant biochemistry [8].

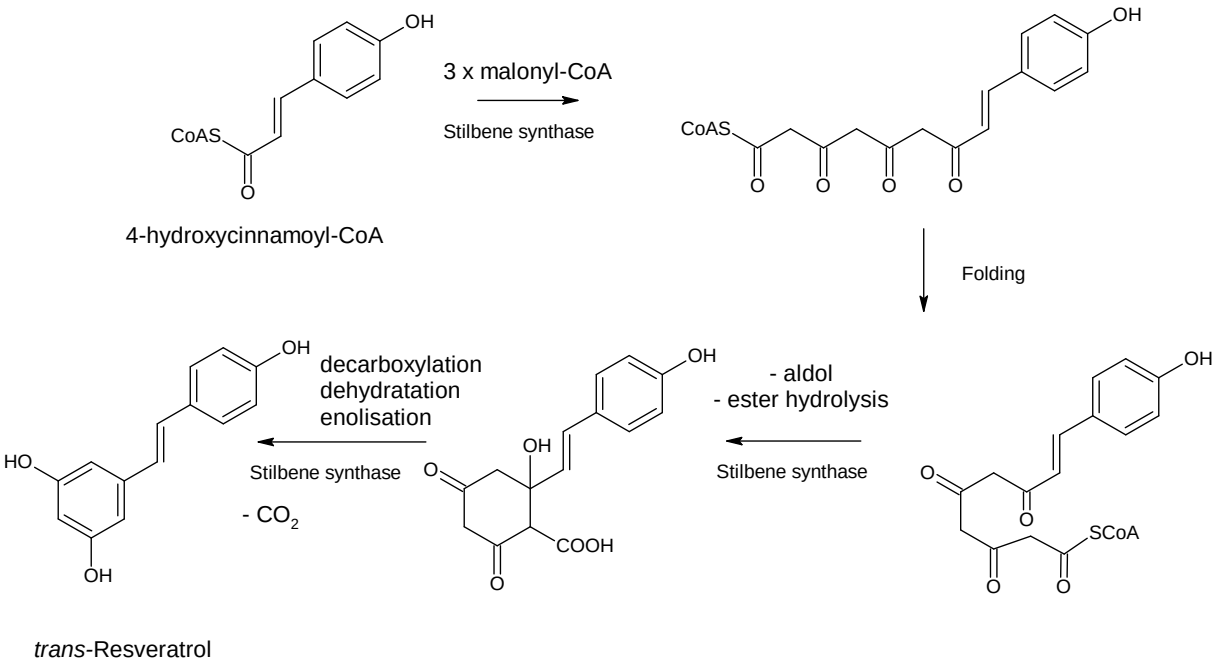

Fig. 1. *Trans*-Resveratrol biosynthesis pathway [5]

Although trans-Resveratrol has been a recognized phenomenon for years, recent studies have shed new insights on this compound, particularly regarding its mechanism of action. Consequently, many aspects of its therapeutic activity should be considered, including its capacity to influence human receptors, its ability to penetrate physiological barriers, and the potential metabolic byproducts that could exert effects on our body. Resveratrol [9, 10]. This article discusses the diverse biological activities of *trans*-Resveratrol, its dietary sources, and the methods used for its accurate quantification.

Biological activities of *trans*-Resveratrol

Antioxidant activity

Trans-Resveratrol is recognized for its potent antioxidant properties, attributed to its ability to scavenge free radicals and reactive oxygen species (ROS). It activates endogenous antioxidant enzymes and protects cellular components from oxidative damage, thereby contributing to the prevention of chronic diseases associated with oxidative stress [11].

Li et al. [12], conducted a comprehensive exploration into the antioxidative potential of *trans*-RResveratrol from mulberry (*Morus alba*). This investigation encompassed a battery of *in vitro* assays rooted in distinct mechanistic principles, which collectively provide a thorough assessment of the compound antioxidant capacities. In the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay, *trans*-Resveratrol demonstrated an IC_{50} (half maximal inhibitory concentration) value of 15.54 µg/ml, accompanied by scavenging rates ranging from 29.56% to 75.63%, contingent upon concentration. These outcomes underscored *trans*-Resveratrol ability to effectively neutralize free radicals, a fundamental attribute of antioxidant activity. Moreover, in the 2,2'-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assay, *trans*-Resveratrol exhibited superior antioxidant activity in comparison to the reference compound L-ascorbic acid, as indicated by IC_{50} values of 2.86 µg/ml and 5.18 µg/ml, respectively. This differential potency underscores the compound efficacy in quenching free radicals. Additionally, the oxygen radical scavenging capacity (ORAC) assay revealed that *trans*-Resveratrol exerted robust antioxidant activity, expressed in Trolox equivalent units at 23.12 µmol TE/g (Trolox equivalent per g). This further affirms its capacity to combat oxidative stress. Further investigation involving HepG2 cells (human liver cancer cell line) unveiled intriguing insights. *Trans*-Resveratrol pretreatment inhibited the production of ROS, indicating its ability to curtail oxidative stress within the cells. Most notably, *trans*-Resveratrol treatment within this cellular context also reversed the AAPH 2,2' azobis(2-amidinopropane) dihydrochloride) - induced depletion of catalase (CAT), superoxide dismutase (SOD), and glutathione (GSH) levels, augmenting their concentrations in a concentration-dependent manner. These findings collectively underscore the multifaceted antioxidant potential of *trans*-Resveratrol [12], positioning it as a promising candidate for combating oxidative stress-related challenges [12].

In their study, Hangun-Balkir and colleagues [13] evaluated the potent antioxidative capacity of *trans*-Resveratrol through DPPH assay. The outcomes, quantified using spectrophotometric techniques, unveiled a remarkable inhibitory concentration IC_{50} of 4.70 mg/ml for the tested *trans*-Resveratrol. This compelling result underscores the great antioxidant capabilities of *trans*-Resveratrol, positioning it as a powerful candidate among antioxidants in the realm of oxidative stress mitigation [13]. In their comprehensive study, Ferrier et al. [14] conducted an examination of polyphenolic compounds within grapevine cane

extracts to unravel the key contributors to their antioxidant capacity. This investigation encompassed the analysis of 42 metabolites across a diverse array of 44 grape varieties, each harboring unique chemical profile. The assessment of antioxidant potential relied on two widely recognized methods: the ABTS and DPPH assays. These tests are fundamental in antioxidant research as they evaluate a substance ability to neutralize free radicals and fight oxidative stress through a mixed mode of neutralization's mechanism, i.e. hydrogen atom transfer (HAT) and single electron transfer (SET). Among all the identified compounds, several emerged as principal drivers of antioxidant activity. Notably, *trans*-Resveratrol took center stage as a pivotal antioxidant agent. Alongside *trans*-Resveratrol, other compounds including *trans*-piceatannol, *trans*-ε-Viniferin, hopeaphenol, isohopeaphenol, and cis/*trans*-vitisin B, also showcased substantial antioxidant capabilities. *Trans*-Resveratrol and its fellow polyphenols, as determined by the ABTS and DPPH assays, play a crucial role in strengthening the antioxidant defenses within grapevine cane extracts. These findings underscore the significance of these compounds in combating oxidative stress and underpin their potential as valuable contributors to overall health and well-being [14].

In their investigation, Gülçin and colleagues [15] assessed the antioxidant potential of *trans*-Resveratrol through an array of diverse antioxidant assays, shedding light on its comparative efficacy with selected reference compounds. To comprehensively evaluate its antioxidant capabilities, *trans*-Resveratrol was subjected to multiple assays, including the DPPH, ABTS, and N,N-dimethyl-p-phenylenediamine (DMPD) tests. Additionally, assessments encompassed chelating activity on ferrous ions (Fe^{2+}), hydrogen peroxide scavenging, and superoxide anion radical scavenging. The findings revealed a noteworthy superiority of *trans*-Resveratrol in the DPPH assay, where it exhibited a markedly lower IC_{50} value of 17.8% in contrast to α-tocopherol (IC_{50} = 28.3%) and Trolox (IC_{50} = 25.5%), the latter two serving as reference compounds. This result underscores *trans*-Resveratrol heightened efficacy in neutralizing free radicals. Similarly, in the ABTS test, *trans*-Resveratrol demonstrated a potent radical cation scavenging activity, attaining an EC_{50} value of 6.96 µg/ml, further confirming its robust antioxidant potential. *Trans*-Resveratrol also exhibited substantial effectiveness in the DMPD assay, with an EC_{50} value of 9.5 µg/ml, reaffirming its ability to counter oxidative stress. Furthermore, the chelating effect of *trans*-Resveratrol on ferrous ions was particularly notable at a concentration of 20 µg/ml, reaching an impressive 86.3% of oxidation inhibition process. This underscores its role in sequestering metal ions that can contribute to oxidative damage. In the realm of superoxide anion radical scavenging, *trans*-Resveratrol demonstrated a substantial inhibitory effect, surpassing a level of 71.8%, which marked efficacy exceeded that of the reference compounds. Additionally, the hydrogen peroxide scavenging activity of *trans*-

Resveratrol, measured at a concentration of 30 µg/ml, reached 19.5%, further highlighting its multifaceted antioxidant capacities. Collectively, these findings elucidate the excellent antioxidant potential of *trans*-Resveratrol, positioning it as a promising candidate for combating oxidative stress and its associated health implications [15].

Anti-aging activity

Trans-Resveratrol advantageous effects on the human body are well-established, primarily through its activation of the protein, sirtuin-1 (SIRT1). According to Howitz et al. (2003) [16], *Trans*-Resveratrol reduces the Michaelis Menten constant of SIRT1, enhancing cell survival by promoting SIRT1-mediated deacetylation of p53. In yeast, *Trans*-Resveratrol emulates calorie restriction by triggering sir2 pathway, fostering DNA stability, and prolonging lifespan by 70% [16]. Interestingly, *Trans*-Resveratrol primarily functions to mitigate inflammation and curtail oxidative damage in tissues. Furthermore, its anti-aging attributes relying on SIRT1 activation are also able to improved oxidative metabolism in vital organs such as the heart, blood vessels, muscles, and kidneys [17]. Additional investigations have demonstrated that when a SIRT1 inhibitor like nicotinamide is present, *Trans*-Resveratrol is still able to induce SIRT1 activity [16, 18].

In their study, Subedi and others [18] investigated the effectiveness of *trans*-Resveratrol-enriched rice (RR) in mitigating skin aging induced by ultraviolet B (UVB) radiation. The research illuminated the profound impact of both *trans*-Resveratrol alone and *trans*-Resveratrol-enriched rice in modulating key molecular players. Specifically, these forms of *trans*-Resveratrol exhibited a significant reduction in the production of proapoptotic proteins, including caspase 3, p53, Bax, and cytochrome C. These proteins play pivotal roles in cellular senescence and programmed cell death (apoptosis), and their downregulation highlights the ability of *trans*-Resveratrol to counteract these aging-associated processes. Furthermore, both *trans*-Resveratrol forms exerted regulatory effects on proinflammatory cytokines, specifically tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6). Additionally, they downregulated the expression of inflammatory mediators such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). These mediators are key players in the inflammatory response, and their suppression indicates the anti-inflammatory properties of *trans*-Resveratrol and *trans*-Resveratrol-enriched rice. In summary, the study underscores the roles of these proteins and mediators in skin aging and demonstrates the potential of *trans*-Resveratrol and *trans*-Resveratrol-enriched rice in mitigating these aging-related processes and inflammatory responses [18].

Another investigation of Bastianetto and colleagues [19] described the protective effect of *trans*-Resveratrol, focusing on its impact on human keratinocyte (HaCaT) cells. These cells were subjected to the damaging effects of sodium nitroprusside (SNP), a known inducer of cellular damage, in order to scrutinize the compound protective potential. The results of this study unveiled the remarkable protective effect exhibited by *trans*-Resveratrol against SNP-induced toxicity, with an EC_{50} value of 14.7 µM. This highlights the compound capacity to shield skin cells from the detrimental effects of SNP exposure. Furthermore, *trans*-Resveratrol displayed a dose-dependent reduction in SNP-induced caspase-3 activity, with the most potent effect observed at a concentration of 10 µM. Caspase-3 is a key mediator of cellular apoptosis, and its modulation by *trans*-Resveratrol underscores the compound role in counteracting cell death processes. Notably, *trans*-Resveratrol exerted a complete blockade of caspase-9 activity. Caspase-9 is another pivotal player in apoptotic pathways, and its inhibition by *trans*-Resveratrol underscores the compound comprehensive protective effect on skin cells. In essence, this study underscores the significance of *trans*-Resveratrol as a potent protector of skin cells, emphasizing its ability to mitigate SNP-induced toxicity and modulate key mediators of cellular apoptosis, thus promoting skin cell health and resilience [19].

Anti-inflammatory effects

Trans-Resveratrol anti-inflammatory effects are attributed to its capacity to inhibit pro-inflammatory mediators, such as cytokines and chemokines. ResveratrolIt modulates various signaling pathways involved in inflammation, thus holding potential for the management of inflammatory diseases [20].

Trans-Resveratrol, a compound found in various plants, exhibits anti-inflammatory properties. It has the ability to regulate the expression of genes associated with a wide range of molecular targets. It functions as an inhibitor of cyclooxygenases and 5-lipoxygenase, enzymes involved in inflammatory processes. *Trans*-Resveratrol also influences the activity of nuclear factor-kappa beta (NF-kB), a key regulator of immune responses, along with numerous protein and lipid kinases. Furthermore, it affects sirtuins, a class of NAD+-dependent enzymes involved in deacetylation and mono-ADP-ribosylation reactions [21].

The Resveratrol-enriched rice (RR) was also studied by Kang et. al [22] in 2,4-dinitrochlorobenzene (DNCB)-induced NC/Ng mouse model of atopic dermatitis, an inflammatory skin disease. Based on the results, the severity of dermatitis was lowered by both treatments *trans*-Resveratrol alone and *trans*-Resveratrol-enriched rice. However, *trans*-Resveratrol-enriched rice was more effective in epidermis thickening reduction and significantly reducing transepidermal water loss (TEWL) improving skin hydration. In addition, *trans*-

Resveratrol-enriched rice treatment also decreases the levels of several markers of inflammation involved in this disease, namely the interleukin-31 (IL-31) and immunoglobulin E (IgE). In addition, *trans*-Resveratrol-enriched rice has also an inhibitory effect on the secretion of Il-6 and Il-1β in TNF-α/IFN-γ-induced human keratinocyte (HaCaT) cells [23].

Anticancer potential

Numerous studies have highlighted the potential of *trans*-Resveratrol in preventing and treating various types of cancer. It exerts its effects by inducing apoptosis, inhibiting angiogenesis, and interfering with cell cycle progression in cancer cells. However, the concentration required for these effects may limit its clinical application [23].

In their research, Chow et al. [24] investigated the potential cancer-preventive effects of Resveratrol on healthy volunteers. To assess this, they conducted oral co-administrations of CYP metabolic probe drugs, namely caffeine (for CYP1A2), dextromethorphan (for CYP2D6), losartan (for CYP2C9), and buspirone (for CYP3A4). These drugs are commonly used to gauge the activity of specific cytochrome P450 (CYP) enzymes in the body, which play essential roles in drug metabolism. The results of the study confirmed that the administration of 1 mg of Resveratrol for a period of 4 weeks effectively inhibited the phenotypic markers associated with the above-mentioned CYP enzymes [24]. This suggests that Resveratrol may have potential cancer-preventive properties, possibly through its influence on these key enzymes involved in drug metabolism.

In their comprehensive investigation, Nguyen et al. [25] embarked on a meticulous exploration of the intricate molecular mechanisms underlying the influence of *trans*-Resveratrol-containing freeze-dried grape powder (GP) on the Wingless-Related Integration Site (Wnt) signaling pathway within the colonic mucosa of individuals. Their study uncovered a mode of action whereby lower concentrations of *trans*-Resveratrol/GP exerted a discernible downregulation effect on critical Wnt target genes. These genes, namely *myc*, *jun*, *cyclinD1*, and *axinII*, hold pivotal roles within the Wnt signaling cascade. The gene *myc*, encoding the *Myc* protein, orchestrates fundamental processes in cell growth and proliferation, with its aberrant overexpression often linked to tumorigenesis. Jun, derived from the *jun* gene, encodes proteins in the Jun family, which are instrumental in transcriptional regulation and cell cycle control; their dysregulation can contribute to oncogenic events. CyclinD1, the product of the *CCND1* gene, governs the orderly progression of cells through the intricate cell cycle, with its overexpression being a hallmark of several cancer types. *AxinII*, also known as *Conductin*, represents a gene pivotal in the negative regulation of the Wnt signaling pathway, exerting substantial influence over cell fate determination and proliferation. Notably, this

investigation unveiled that lower concentrations of *trans*-Resveratrol/GP, particularly at an intake level of 80 mg/day, demonstrated a remarkable potential to modulate the Wnt signaling pathway. This intricate molecular interplay bears profound implications for the maintenance of colonic health and holds promise as a potential dietary intervention strategy to mitigate the risk of colorectal diseases [25]. In essence, this study illuminates the intricate molecular mechanisms through which *trans*-Resveratrol interfaces with cellular processes within the colonic mucosa, offering profound insights into its therapeutic potential against cancer [25].

Cardioprotective effect

Trans-Resveratrol has been associated with cardioprotective effects, including the improvement of lipid profiles, reduction of blood pressure, and enhancement of endothelial function. These effects contribute to its potential role in mitigating cardiovascular diseases [10, 26]. Li and colleagues [27] conducted a comprehensive investigation into the potential protective effects of Resveratrol against myocardial Ischemia-Reperfusion (I/R) injury. This condition involves damage to the heart upon the restoration of blood flow following a period of insufficient supply. They employed an experimental model known as oxygen-glucose deprivation/reoxygenation (OGD/R) using H9c2 cells to replicate the conditions of I/R injury. Their findings unveiled critical aspects of Resveratrol mechanisms of action. Malondialdehyde (MDA), a marker of oxidative stress and lipid peroxidation typically elevated during I/R injury, was notably reduced upon treatment with Resveratrol at a concentration of 10 μmol/L. This reduction signified Resveratrol potential to alleviate oxidative stress, a marker of I/R injury. Additionally, Resveratrol treatment led to an increase in Fe^{2+} content, a significant finding as iron contributes to the formation of harmful free radicals that exacerbate cellular damage during I/R injury. The rise in Fe^{2+} content suggested that Resveratrol may offer protection against iron-mediated oxidative stress. Ferroptosis, a distinctive form of regulated cell death characterized by iron-dependent lipid peroxidation, was notably suppressed by Resveratrol. This suppression was attributed to the upregulation of two vital protective proteins, peroxidase 4 (GPX4) and ferritin heavy chain 1 (FTH1), both of which play crucial roles in mitigating lipid peroxidation and iron-related damage. Furthermore, the study delved into the modulation of autophagy, a cellular process with dual roles in the context of I/R injury. Resveratrol significantly reduced the protein expression levels of key autophagy markers, including Beclin-1, NCOA4, and LC3. This suggests that Resveratrol may influence autophagy in a manner that is beneficial for mitigating the detrimental effects of I/R injury. The research conducted by Li et al. provides valuable insights into the multifaceted mechanisms through which Resveratrol

may confer protection against myocardial ischemia-reperfusion injury, offering potential avenues for therapeutic intervention in this context [27].

Sebai and others [28]. conducted a rigorous examination to elucidate the cardioprotective properties of Resveratrol in the face of lipopolysaccharide (LPS)-induced oxidative stress in rats. This study centered on several key biochemical markers, shedding light on the mechanisms through which *trans*-Resveratrol exerts its cardioprotective effects. Superoxide Dismutase (SOD), a critical enzyme in the defense against oxidative stress, showed a significant increase in activity, exceeding 20 U/mg, in the LPS/*trans*-Resveratrol group. This elevation in SOD activity underscores *trans*-Resveratrol role in fortifying cellular defenses, which is pivotal in mitigating oxidative damage within the heart. Furthermore, the heart Malondialdehyde (MDA) levels, indicative of lipid peroxidation and oxidative stress, registered a noteworthy decline, dropping to less than 0.6 nM/mg with *trans*-Resveratrol treatment. This reduction in MDA levels underscores the compound's capacity to curtail oxidative harm within cardiac tissue. Intriguingly, Nitric Oxide (NO), a multipart signaling molecule in cardiovascular physiology, exhibited a decrease in tissue levels, surpassing 3 µM/mg, in the LPS/*trans*-Resveratrol-treated group. This decline in NO levels may be interpreted as a means by which *trans*-Resveratrol fosters a more balanced and less detrimental oxidative environment within the heart. Lastly, the study identified a significant increase in heart iron levels, exceeding 100 µM/mg, in the LPS/*trans*-Resveratrol group. The precise implications of this elevated iron content in the context of cardioprotection warrant further exploration. In conclusion, Sebai et al. research underscores the multifaceted cardioprotective potential of *trans*-Resveratrol, as evidenced by its ability to enhance SOD activity, reduce MDA levels, modulate NO levels, and influence heart iron levels in response to LPS-induced oxidative stress in rats [28]. These findings contribute valuable insights into the intricate mechanisms underlying Resveratrol role in combatting oxidative damage within the cardiovascular system [28].

Anti-diabetic activity

Trans-Resveratrol holds significant promise in the prevention of diabetes, particularly type 2 diabetes, which is characterized by insulin resistance and impaired glucose metabolism. Its potential impact on diabetes prevention lies in its multifaceted mechanisms of action. *Trans*-Resveratrol has been shown to improve insulin sensitivity by enhancing the function of insulin receptors and promoting glucose uptake in insulin-resistant tissues, such as skeletal muscle and adipose tissue. Moreover, as mentioned previously, it can mitigate inflammation, a key contributor to insulin resistance, by suppressing the production of pro-inflammatory cytokines [29]. Additionally, *trans*-Resveratrol exhibits anti-oxidative properties, which help to reduce

oxidative stress in pancreatic beta cells. These cells are responsible for insulin production, and their protection from oxidative damage is essential for maintaining proper insulin secretion. Furthermore, *trans*-Resveratrol appears to activate the AMP-activated protein kinase (AMPK), a cellular energy regulator. AMPK activation enhances cellular energy expenditure, leading to improved glucose utilization and lipid metabolism [30]. Another crucial aspect of *trans*-Resveratrol potential in diabetes prevention is its ability to modulate lipid metabolism. It can lower triglyceride levels, improve cholesterol profiles, and reduce fat accumulation in liver and adipose tissues. These effects are beneficial in preventing the development of metabolic syndrome, a precursor to type 2 diabetes [31].

In their research, Szkudelska et al. [32] delved into the effects of *trans*-Resveratrol on the dysregulation associated with diabetes in Goto-Kakizaki (GK) rats, a well-established model for studying type 2 diabetes. Specifically, they explored how *trans*-Resveratrol, administered at a dose of 20 mg/kg of body weight, influenced key aspects of glucose metabolism and insulin signaling in these rats. One noteworthy finding of their study was that *trans*-Resveratrol effectively mitigated abnormalities in the expression and phosphorylation levels of the insulin receptor within the skeletal muscle of GK rats. This receptor is a crucial component of insulin signaling, and its proper functioning is essential for glucose uptake into cells. Furthermore, the research revealed that *trans*-Resveratrol played a role in restoring the expression of specific proteins related to intracellular glucose transport, namely glucose transporter 4 (GLUT4) and translocase of the outer mitochondrial membrane 20 (TUG), within the adipose tissue of GK rats. GLUT4 is responsible for facilitating glucose entry into cells, particularly muscle and fat cells, in response to insulin, while TUG is involved in the regulation of GLUT4 transport to the cell membrane, ensuring efficient glucose uptake. These findings underscore the potential of *trans*-Resveratrol to ameliorate diabetes-associated dysregulation in insulin signaling and glucose transport, offering insights into its therapeutic implications for managing diabetes and related metabolic disorders [32]. Tomé-Carneiro and colleagues [33] conducted a study to examine the impact of *trans*-Resveratrol-enriched grape extract on patients with type 2 diabetes mellitus, with a specific focus on peripheral blood mononuclear cells (PBMCs). PBMCs are a type of white blood cell found in the bloodstream that play a role in immune response and inflammation regulation. The study involved the administration of the grape extract at two different concentrations: 8 mg/day for the first 6 months and 16 mg/day for the subsequent 6 months. The results of their research revealed several significant changes in the patients' PBMCs, shedding light on how Resveratrol may function in the treatment or prevention of diabetes. Firstly, the Resveratrol-enriched extract led to a reduction in the levels of alkaline phosphatase (ALP) and interleukin 6 (IL-6). Alkaline phosphatase is an enzyme that plays a

role in various metabolic processes, and its decrease may reflect improved metabolic function. IL-6 is a pro-inflammatory cytokine, and its reduction suggests a potential anti-inflammatory effect of the grape extract. Furthermore, the extract significantly decreased the expression of pro-inflammatory cytokines such as C-C motif chemokine ligand 3 (CCL3), interleukin 1β (IL-1β), and tumor necrosis factor-α (TNF-α). These cytokines are known contributors to chronic inflammation, a key factor in the development and progression of type 2 diabetes. In summary, this study highlights the potential of *trans*-Resveratrol-enriched grape extract in modulating the immune response and inflammation in patients with type 2 diabetes mellitus, suggesting its therapeutic potential in managing this condition [33].

In conclusion, *trans*-Resveratrol significance in diabetes prevention is underpinned by its multifaceted mechanisms, including improved insulin sensitivity, anti-inflammatory properties, antioxidant effects, and modulation of lipid metabolism. While more research is needed to fully elucidate its clinical potential, these mechanisms make *trans*-Resveratrol a compelling natural compound for those seeking to reduce their risk of developing diabetes and improve overall metabolic health.

Anti-obesity activity

Obesity represents a pressing global health concern, characterized by an excessive accumulation of body fat that can lead to a range of detrimental health outcomes. It is associated with an increased risk of chronic diseases such as type 2 diabetes, cardiovascular diseases, certain cancers, and musculoskeletal disorders, along with a reduced quality of life. *Trans*-Resveratrol has already gained scientific attention for its potential health benefits, including its role in metabolic regulation [34]. Studies have suggested that *trans*-Resveratrol may influence metabolic pathways by activating enzymes like AMP-activated protein kinase (AMPK) and enhancing the expression of key regulators of cellular energy metabolism such as SIRT1 and PGC-1α. These effects may lead to improved energy utilization and the regulation of fat storage [11, 30].

In a study conducted by Timmers and colleagues [35], the impact of a 30-day oral supplementation regimen with pure *trans*-Resveratrol (at a daily dose of 150 mg) on metabolic alterations in obese individuals was investigated. The findings of this research shed light on the significant scientific implications of *trans*-Resveratrol supplementation.

First and foremost, *trans*-Resveratrol was found to activate a key enzyme known as AMP-activated protein kinase (AMPK) within muscle tissue. This activation, in turn, led to an increase in the levels of two important regulators of metabolic processes, namely SIRT1 and PGC-1α. SIRT1 plays a role in regulating cellular energy production, while PGC-1α is involved

in mitochondrial biogenesis and oxidative metabolism. These effects imply that *trans*-Resveratrol may have the potential to enhance the body metabolic activity and energy production, which can be crucial for individuals struggling with obesity [35].

Furthermore, the study also noted a decrease in adipose tissue lipolysis following the application of *trans*-Resveratrol. Adipose tissue lipolysis is the process by which fat stored in adipose tissue is broken down into fatty acids and released into the bloodstream. The reduction in lipolysis indicates that *trans*-Resveratrol may have a role in limiting the release of fatty acids from fat stores, potentially aiding in the prevention or management of obesity by reducing the availability of stored fat for energy utilization [35].

Alberdi et. al [36] investigated how the addition of *trans*-Resveratrol to the rats' diets for six weeks, at a daily dose of 30 mg, influenced the generation of heat (thermogenesis) in two specific body tissues: skeletal muscle and interscapular brown adipose tissue (IBAT). The results of this research could provide insights into the potential health benefits of *trans*-Resveratrol supplementation and its impact on reducing obesity. Thermogenesis, particularly in brown adipose tissue, plays a role in burning calories and regulating body weight, so any enhancement in this process could potentially contribute to a reduction in obesity. They showed that the anti-obesity effect of *trans*-Resveratrol in the body is related to notable changes in health-related factors. Specifically, it triggered an increase in the expression of several important genes and proteins known to have positive effects on health. These included mitochondrial-*trans*cription-factor-A (TFAM), mitochondrial-protein-cytochrome-C-oxidase subunit-2 (COX2), SIRT1, and peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α). Additionally, *trans*-Resveratrol promoted the upregulation of uncoupling proteins (UCP1 and UCP3) expression in the IBAT. These changes indicate that Resveratrol may contribute to improved health by enhancing the expression of genes and proteins associated with mitochondrial function, cellular energy metabolism, and thermogenesis in IBAT [37].

These findings underscore the scientific significance of *trans*-Resveratrol as a potential tool in the fight against obesity and its associated metabolic disorders. While the research is ongoing, the incorporation of *trans*-Resveratrol into the daily diet through the consumption of foods and beverages rich in this compound may offer a complementary strategy in the fight against obesity.

Neuroprotective properties

Preventing neurodegenerative diseases represents a critical constraint in healthcare, given the devastating impact these conditions have on individuals and society as a whole. In

recent years, there has been a growing interest in harnessing the potential of natural molecules such as *trans*-Resveratrol as a promising potential for neuroprotection [17]. Emerging research suggests that *trans*-Resveratrol may have neuroprotective effects, including the modulation of neuroinflammation and the enhancement of synaptic plasticity. *Trans*-Resveratrol exhibits neuroprotective activity through its interaction with specific molecular targets. When *trans*-Resveratrol is introduced into the body, it engages with the AMP-activated protein kinase (AMPK) within muscle tissue. AMPK is an enzyme that plays a crucial role in cellular energy regulation. Activation of AMPK by *trans*-Resveratrol triggers a cascade of events, including the upregulation of SIRT1 and PGC-1α (Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha). SIRT1 is involved in cellular energy production and metabolism, while PGC-1α is associated with mitochondrial biogenesis and oxidative metabolism. These combined effects suggest that *trans*-Resveratrol has the potential to enhance the body metabolic activity and energy production, which can be vital for individuals seeking neuroprotection [37, 38]. Additionally, *trans*-Resveratrol has been found to decrease adipose tissue lipolysis, the process by which fat is broken down into fatty acids, potentially contributing to neuroprotection by limiting the release of fatty acids from fat stores, thereby reducing the risk of neurodegenerative diseases. These mechanisms illustrate how *trans*-Resveratrol may exert its neuroprotective effects at the molecular level [11, 39]. Its ability to modulate cellular pathways associated with neurodegeneration, including the reduction of oxidative stress and inflammation, as well as the promotion of autophagy and mitochondrial function, makes it a compelling candidate for therapeutic intervention. Furthermore, its low toxicity profile and accessibility from dietary sources make it an attractive avenue for preventive measures [10, 39]. Resveratrol has demonstrated neuroprotective effects, particularly in animal models such as rats. Regular moderate consumption of red wine has been associated with a substantial reduction in amyloid-AD neuropathology and the mitigation of Aβ-related memory loss in Tg2576 mice [40]. Recent studies involving Tg2576 mice have suggested that soluble Aβ oligomers in the extracellular space contribute significantly to AD dementia and memory deficits. Treatment with polyphenolic compounds from grape seed extract (GPSE) rich in *trans*-Resveratrol has shown promise in reducing Aβ peptide oligomerization and cognitive loss in Tg2576 mice, as demonstrated by Wang et al. in 2008 [41].

In the context of Resveratrol treatment in APP/PS1 mouse model of Alzheimer's Disease (AD), it was observed that activated microglia decreased considerably, implying that Resveratrol may reduce inflammation, irrespective of its effects on amyloid deposition. Studies conducted in a C57Bl/6J mice model also indicated a substantial reduction in the number of rears during ambulatory locomotion in high-grade mice treated with Resveratrol [41]. These

findings suggested that Resveratrol impact on both muscle and brown adipose tissues could enhance mitochondrial activity, leading to increased energy expenditure, improved aerobic efficiency, and enhanced sensorimotor function [42]. Furthermore, Sharma and Gupta reported that treated rats with streptozocin (STZ) administered through intracerebroventricular (ICV) with *trans*-Resveratrol resulted in significantly increased retention latencies and shorter transfer latencies in the elevated plus-maze test, a test used to assess anxiety-related behavior in rodent models. However, no significant differences were observed in the locomotor activity of the sham group. Their study focused on an icv-STZ model in various rat types with Alzheimer's-type dementia. Rats treated with Resveratrol at doses of 10 and 20 mg/kg for 21 days exhibited elevated brain glutathione levels and increased levels of MDA (malondialdehyde) in the brain, as observed in ICV STZ-treated rats. These results suggest that Resveratrol may hold potential in the treatment of neurodegenerative diseases like Alzheimer's disease [26].

As we continue to unravel the complex biology of neurodegeneration, exploring the potential of natural molecules like *trans*-Resveratrol may offer new hope in our quest to combat these debilitating conditions.

Dietary sources of *trans*-Resveratrol

The primary dietary sources of *trans*-Resveratrol include grapes (*Vitis vinifera*), berries (such as blueberries and cranberries), certain nuts (like peanuts), and their derived products. The concentration of *trans*-Resveratrol varies widely among different species, cultivars, and plant parts (Table 1). Environmental factors, UV radiation, and stressors like pathogens influence its production [43].

The rich source of resveratrol is, first of all red grape (*Vitis*) skin (50-100 μg/g of fresh weight, according to the cultivar and cultivation conditions. Another sources of these molecule are also red wine, blueberries, raspberries, and strawberries (1-12 μg/g, 1-9 μg/g, 1-4 μg/g and 0.2-2.0 μg/g respectively). Trans-resveratrol is also present in another natural sources, however at lower concentrations, below 1.0 μg/g of fresh weight (for instance peanuts, peanut butter, pistachios, cashews, as well as dark chocolate and Japanese knotweed.

It's important to note that these values are approximate and can vary based on factors such as the specific variety of the plant, growing conditions, processing methods, and more. Additionally, the concentrations are often quite low, which is why Resveratrol supplements are often used to achieve higher doses for potential health benefits [44].

Table 1. The content of trans-Resveratrol in various natural sources

Sources	*trans*-Resveratrol concentrations	References
Red grape skin	50-100 micrograms (µg) of *trans*-Resveratrol per gram of fresh weight	[45]
Red grape wine	1-12 milligrams (mg) of *trans*-Resveratrol per liter	[46]
Blueberries	1-9 µg of *trans*-Resveratrol per gram of fresh weight.	[47]
Raspberries	1-4 µg of *trans*-Resveratrol per gram of fresh weight.	[47]
Strawberries	0.2-2 µg of *trans*-Resveratrol per gram of fresh weight.	[48]
Raw Peanuts	0.01-1.2 µg of *trans*-Resveratrol per gram	[49]
Peanut butter	0.04-0.13 µg of *trans*-Resveratrol per gram	[49]
Pistachios	0.06-0.07 µg of *trans*-Resveratrol per gram	[50]
Cashews	0.05-0.09 µg of *trans*-Resveratrol per gram	[50]
Dark chocolate (cocoa beans)	0.001-0.6 µg of *trans*-Resveratrol per gram	[51]
Japanese Knotweed (*Polygonum cuspidatum*)	20-360 mg of *trans*-Resveratrol per gram of dry weight	[52]

Methods of analysis

Accurate quantification of *trans*-Resveratrol is essential for evaluating its presence in various matrices and studying its health benefits. Analytical methods encompass high-performance liquid chromatography (HPLC), usually coupled to diode array detection (DAD) and/or mass spectrometry (MS), and nuclear magnetic resonance (NMR) spectroscopy. These methods differ in terms of sensitivity, selectivity, and complexity, accommodating to diverse research needs [14, 44].

Spectrophotometry (UV-VIS)

The analysis of *trans*-Resveratrol using UV/VIS spectroscopy is a widely employed technique in the quantification and characterization of this important polyphenolic compound. UV/VIS spectroscopy relies on the measurement of the absorbance or transmission of ultraviolet and visible light by a sample. *Trans*-Resveratrol exhibits characteristic absorption peaks in the UV/VIS range, particularly around 305 nm, which is attributed to its conjugated double bond system [13]. To perform the analysis, a sample containing *trans*-Resveratrol is prepared, often through solvent extraction or dilution in a suitable solvent. The prepared

sample is then placed in a UV/VIS spectrophotometer, and the absorbance of light at the characteristic wavelength is measured. By applying Beer-Lambert's law, which correlates absorbance with concentration, the concentration of *trans*-Resveratrol in the sample can be determined. UV/VIS spectroscopy is advantageous for its simplicity, speed, and cost-effectiveness, making it a valuable tool for routine analysis of *trans*-Resveratrol in various biological, pharmaceutical, and food samples [53]. Furthermore, it enables rapid screening of samples for the presence of trans-Resveratrol, aiding in research endeavors focused on exploring its potential health benefits and applications in different industries.

High/Ultra Performance Liquid Chromatography coupled with Mass Spectrometry (HPLC/UPLC)

High-Performance Liquid Chromatography (HPLC) and Ultra-Performance Liquid Chromatography-Mass Spectrometry (UPLC-MS) represent powerful analytical techniques employed in the precise and comprehensive analysis of *trans*-Resveratrol. These methodologies enable the separation, identification, and quantification of this bioactive compound with remarkable precision and sensitivity [18].

In HPLC analysis, a chromatographic column effectively resolves the *trans*-Resveratrol separation in complex mixtures, allowing its accurate quantification. UV-visible detection is commonly used in conjunction with HPLC, relying on the compound characteristic absorbance at specific wavelengths for quantification. HPLC is ideal for routine analysis of *trans*-Resveratrol due to its reliability and accessibility [54].

UPLC-MS, on the other hand, combines the UPLC power of chromatographic separation with the mass spectrometry detection capabilities. This cutting-edge approach not only enhances the speed and efficiency of separation but also provides unparalleled specificity and sensitivity in identifying *trans*-Resveratrol and its derivatives. The mass spectrometry component not only confirms the compound identity but also offers valuable structural information and the ability to detect trace levels in complex biological samples [45].

Together, HPLC and UPLC-MS represent a dynamic duo in the realm of *trans*-Resveratrol analysis, offering scientists a versatile toolkit to explore its presence, concentration, and structural attributes in various matrices, including foods, beverages, dietary supplements, and biological samples. These techniques play a pivotal role in advancing our understanding of the compound distribution, metabolism, and potential therapeutic applications.

Gas chromatography

The analysis of trans-Resveratrol by gas chromatography (GC) is a critical analytical technique employed in the quantification and characterization of this bioactive polyphenolic compound. GC offers several advantages for the analysis of trans-Resveratrol, including its ability to provide high sensitivity and precision. In this method, trans-Resveratrol is first extracted from the sample matrix, often utilizing techniques such as solid-phase extraction (SPE) or liquid-liquid extraction (LLE). Subsequently, the extracted compound is derivatized to enhance its volatility and thermal stability, which is crucial for successful GC analysis. Common derivatization agents include trimethylsilyl (TMS) derivatives or acetylation reagents. The derivatized trans-Resveratrol is then injected into the GC system, equipped with a capillary column and a suitable detector, typically a flame ionization detector (FID) or a mass spectrometer (MS). The separation of trans-Resveratrol is achieved based on its vapor pressure and affinity for the stationary phase within the column. The resulting chromatogram provides quantitative and qualitative information about the trans-Resveratrol content in the sample, allowing for precise determination and assessment of this compound in various biological, pharmaceutical, and food-related matrices. The GC analysis of trans-Resveratrol plays a pivotal role in elucidating its presence and concentration, facilitating research endeavors aimed at exploring its therapeutic and health-promoting properties [55].

Nuclear Magnetic Resonance

Nuclear Magnetic Resonance (NMR) spectroscopy stands as an indispensable analytical technique in the precise analysis of *trans*-Resveratrol, a prominent member of the stilbenoid family. In the realm of stilbenoid analysis, NMR offers a multifaceted array of applications crucial for elucidating the structural, quantitative, and functional aspects of this bioactive compound. Foremost among its applications, NMR enables the rigorous structural elucidation of *trans*-Resveratrol. It empowers researchers to unravel the intricate arrangement of atoms within the molecule, providing invaluable insights into its chemical structure. Beyond structural insights, NMR serves as a robust tool for quantitative analysis. By comparing NMR signal integrals to known standards, researchers can accurately determine the concentration of *trans*-Resveratrol in complex mixtures, facilitating precise quantification. NMR spectroscopy plays a crucial role in assessing the purity of synthesized or isolated *trans*-Resveratrol. It has the capability to detect impurities or conversion residues, ensuring the compound high purity [56]. In the context of stilbenoids, isomer differentiation is of paramount importance, and NMR excels in this regard. It can readily distinguish between various isomeric forms, such as *cis* and *trans* isomers, based on distinctive chemical shifts, aiding in the identification of specific

isomeric configurations [57]. Conformational analysis, another pivotal application, delves into the three-dimensional structure of *trans*-Resveratrol in solution. This sheds light on the molecule flexibility or rigidity, essential for understanding its interactions and biological activities [58]. NMR versatility extends to the investigation of *trans*-Resveratrol interactions with other molecules, a crucial aspect in elucidating its mechanisms of action and binding affinities, particularly in biological systems [2]. Moreover, NMR can serve in stability studies, tracking *trans*-Resveratrol resilience under diverse conditions, including exposure to light, heat, or varying pH levels, thereby informing storage and shelf-life considerations [59]. In conclusion, NMR spectroscopy emerges as an indispensable tool for the comprehensive analysis of *trans*-Resveratrol, offering a wealth of applications to probe its structural, quantitative, and functional attributes, ultimately enriching our understanding of this bioactive compound and its potential therapeutic applications.

Conclusions

Trans-Resveratrol, a natural polyphenol abundant in various plant sources, holds immense potential for improving human health. Its multifaceted biological activities, ranging from antioxidant and anti-inflammatory effects to potential anticancer and neuroprotective properties, highlight its significance as a health-promoting molecule [10]. First and foremost, *trans*-Resveratrol demonstrates potent antiaging properties by mitigating cellular senescence and apoptosis, safeguarding skin cells from UV-induced damage, and modulating key apoptotic pathways. These attributes position it as a promising candidate for age-related health concerns [60]. Furthermore, *trans*-Resveratrol robust antioxidant activity, as demonstrated through various assays and comparisons with other antioxidants, underscores its efficacy in neutralizing free radicals and combating oxidative stress. This property is pivotal in protecting cells and tissues from oxidative damage, which is implicated in various chronic diseases [11]. *Trans*-Resveratrol anti-inflammatory effects, elucidated through the downregulation of proinflammatory cytokines and mediators, hold substantial therapeutic potential. By mitigating the inflammatory response, it may contribute to the management of inflammatory conditions and promote overall well-being [61]. In the realm of diabetes, *trans*-Resveratrol has displayed promise in modulating glucose metabolism and insulin sensitivity, offering potential avenues for the prevention and management of diabetes mellitus [35]. Moreover, its anticancer properties, as evidenced by its influence on cell proliferation, apoptosis, and inflammatory pathways, underscore its potential role in cancer prevention and adjuvant therapy [62].

Research into the use of *trans*-Resveratrol to mitigate the risk of neurodegenerative diseases holds the promise of not only enhancing our understanding of disease mechanisms

but also potentially offering cost-effective, natural, and safe strategies to protect and support brain health as individuals age. A deeper understanding of its sources, variability, and mechanisms of action, along with the development of accurate analytical methods, will continue to unveil the full spectrum of its benefits. Nonetheless, further research is needed to translate its potential into effective therapeutic interventions for various diseases.

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