REVIEW

Resveratrol: How Much Wine Do You Have to Drink to Stay Healthy?[1–3]

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ABSTRACT

Resveratrol is a naturally occurring stilbene endowed with multiple health-promoting effects. It is produced by certain plants including several dietary sources such as grapes, apples, raspberries, blueberries, plums, peanuts, and products derived therefrom (e.g., wine). Resveratrol can be isolated and purified from these biological sources or synthesized in a few steps with an overall high yield. This compound and its glucoside, the *trans*-polydatin piceid, have received worldwide attention for their beneficial effects on cardiovascular, inflammatory, neurodegenerative, metabolic, and age-related diseases. These health-promoting effects are particularly attractive given the prevalence of resveratrol-based nutraceuticals and the paradoxical epidemiologic observation that wine consumption is inversely correlated to the incidence of coronary heart disease. However, the notion of resveratrol as a "magic bullet" was recently challenged by clinical trials showing that this polyphenol does not have a substantial influence on health status and mortality risk. In the present review, we discuss the proposed therapeutic attributes and the mode of molecular actions of resveratrol. We also cover recent pharmacologic efforts to improve the poor bioavailability of resveratrol and influence the transition between body systems in humans. We conclude with some thoughts about future research directions that might be meaningful for resolving controversies surrounding resveratrol. *Adv Nutr* 2016;7:706–18.

Keywords: French paradox, therapy, human trials, liver, SIRT1, pharmacology, nanotechnology

Introduction

Resveratrol is a naturally occurring phytoalexin that is produced by several plants in response to injury. It exerts multiple biological activities, including anti-inflammatory, antiproliferative, and antioxidant effects (1). Structurally, this compound is a stilbenoid that was first isolated in 1939 from the roots of the white hellebore (*Veratrum grandiflorum)* (2) and presumably received its name from the fact that it is a derivative of the benzene-1,3-diol resorcinol and isolated from the *Veratrum* species. Subsequently, resveratrol was isolated from several other plants, fruits, and derivatives, such as grapes, wines, apples, raspberries, blueberries, pistachios, plums, peanuts, and a multitude of medicinal and edible plant species undergoing response to stress conditions (3, 4). Experimental and preclinical studies have attributed several health-promoting effects to this compound, including cardioprotective effects, chemopreventive activity in diverse cancers, and a capacity to extend the lifespan of lower organisms (5, 6).

The hope and hype concerning resveratrol was initiated by the finding that phenolic compounds such as the stilbenes exhibit radical scavenger and antioxidant properties (7, 8). This may account in part for the so-called French paradox originally formulated in 1981 by French epidemiologists who observed a lower mortality incidence of coronary heart disease in France despite high levels of dietary saturated fat and cigarette smoking (9). It was later assumed that moderate drinking of red wine over a long period of time can protect against coronary heart disease and might be the cause of this paradoxical finding (7). Moreover, it was postulated that resveratrol modulates signaling pathways that limit the spread of cancer cells (10), protects nerve cells from damage (11–13), helps to prevent diabetes (14), and acts as an antiaging agent that improves age-related problems (15). Rodent models suggested that this substance might improve consequences of an unhealthy lifestyle resulting from high caloric intake (16). In addition, resveratrol has been shown to mediate therapeutic hepatic effects in acquired and genetic models of iron overload (17).

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However, most of the proposed therapeutic cell- and organ-affecting activities were not confirmed in clinical trials as of yet, and to our knowledge, there are very few data regarding the bioavailability of resveratrol in humans. In healthy subjects, a single dose of resveratrol (100 mg) combined with polyphenols from a muscadine grape extract (75 mg) was shown to suppress oxidative and inflammatory meal-induced stress response (18). Subjects who consumed resveratrol (up to 5 g/d) showed decreased circulating levels of insulin-like growth factor-1 (IGF-1)[4] and IGF-binding protein 3 (19). Consistent with the finding obtained in laboratory animals, a meta-analysis showed that resveratrol improves diabetes (20) and enhances vascular functions in individuals with mildly elevated blood pressure (21). On the other hand, the therapeutic activity of resveratrol on health status and mortality was critically questioned by findings showing that the urinary resveratrol metabolite concentration is not associated with inflammatory markers, cardiovascular disease, cancer, or mortality in older community-dwelling adults (22). Therefore, there is an obvious necessity for more clinical studies addressing the potential preventive and curative effects of resveratrol.

In the present review, we highlight the history of resveratrol, provide some examples of proposed functions, and discuss the presumed molecular resveratrol targets. At the conclusion, we summarize some pharmacologic aspects, speculate about effective therapeutic drug concentrations, and supply clues for potential directions of future resveratrol research.

Current Status

The phenolic compound resveratrol was first isolated in 1939 from the roots of the white hellebore (*V. grandiflorum*) (2) (**Figure 1**A). This perennial, poisonous medicinal plant is mainly found in China and Japan and contains some highly toxic steroidal alkaloids. In traditional Chinese medicine (TCM), the dried roots and rhizomes of hellebores are known as "*li lu*" and are indicated for jaundice, malaria, diarrhea, and headache. Resveratrol is also found in other plants and fruits including grapes, raspberries, blueberries, plums, and peanuts. The highest concentrations of resveratrol are found in the Japanese knotweed *Polygonum japonicum* (formerly known as *Polygonum cruspdatum*) (Figure 1B), which is used in TCM in diverse tea products. Originally this herbaceous plant was endemic in East Asia, Japan, China, and Korea. Nowadays, the Japanese knotweed is also found in many countries in Europe and is classified by the USDA as one of the worst invasive plant species (24). The high content of resveratrol in this plant has inspired scientists to establish a number of strategies for isolation and purification of up to 1 g resveratrol from 100 g of extract acquired from this source (25). In addition, protocols were developed to biotransform polydatin to resveratrol by firmly immobilizing edible *Aspergillus niger* and yeast in roots of these plants, resulting in 11-fold increased yields (26). The use of engineered *Escherichia coli* strains for producing superior resveratrol titers and advanced chemical synthesis protocols is another attractive alternative for providing large quantities of this drug for commercial use (27, 28). In addition to purified resveratrol, unspecified extracts from these plants are also available and marketed as dietary health-promoting supplements. These are generally made from red wine or grape extracts. Red grape varieties and red wines contain roughly 3- to 10-fold more resveratrol than their white counterparts (Figure 1C, **Supplemental Table 1**). Resveratrol exists as 2 geometric isomers in which the 2 phenolic rings are either arranged in *trans*- or *cis*-configuration (**Supplemental Figure 1**).

Although both *cis*- and *trans*-isomers of resveratrol occur in nature, it is generally assumed that the *trans*-form is biologically more active (29). However, there are also conditions in which the *cis*-form showed a higher activity (30). This contradiction may result from the differences in the chemical stability of both isomers (31) or the occurrence of transport proteins (e.g., β-lactoglobulin and albumin) that are viable carriers that stabilize and deliver resveratrol in vivo in the biologically effective *trans*-form (32). In addition, the biological activities of several *trans*-stilbene derivatives are less potent than their corresponding *cis*-isomers (33, 34).

In grapes, both isomers are synthesized almost entirely in the skin with a peak just before the grapes reach maturity. The terminal enzyme that is involved in biosynthesis of resveratrol is the stilbene synthase, which is activated by exogenous stress factors, UV light, and defined chemical signals from pathogenic fungi (35). Therefore, the content of resveratrol and its isomers in the final wine products may significantly differ between countries, cultivation areas, vintages, and production years (Supplemental Table 1). Despite this variability, the concentration of *cis*-resveratrol is generally proportional to the concentration of its *trans*-isomer (35). The average red wine can be expected to contain ~1.9 ± 1.7 mg *trans*-resveratrol/L.

Sources and Recommended Daily Intake of Resveratrol

It is presumed that major dietary sources of resveratrol include grapes, wine, apples, peanuts, and soy (4, 36). In Japan and China, the Itadori tea is another rich source of resveratrol. It is made out of knotweed and applied as a traditional herbal remedy for heart disease and stroke (37). Because the concentration of resveratrol in all of these food products is highly variable, it is somewhat difficult to estimate the average daily intake. According to a study that included 40,685 subjects (aged 35–64 y) from northern and southern regions of Spain, the estimated median and mean dietary intake of total resveratrol and its glucoside *trans*-polydatin piceid is 100 and 933 μg/d, respectively, and the major sources in daily life are wines (98.4%) and grapes or grape juices (1.6%) (38).

[4] Abbreviations used: IGF, insulin-like growth factor; SIRT1, sirtuin-1; TCM, traditional Chinese medicine; tRNA, transfer RNA.

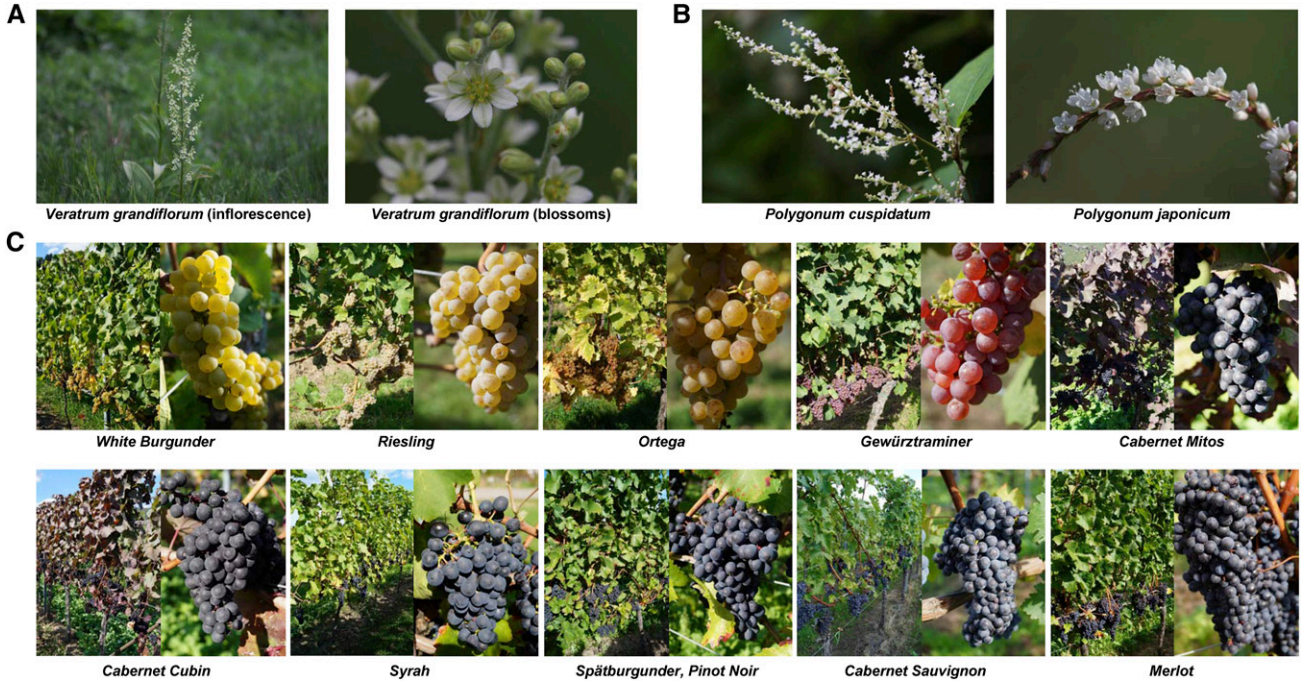

FIGURE 1 Biological sources of resveratrol. (A) Resveratrol was first isolated from the roots of the white hellebore *Veratrum album* var. *grandiflorum* (*Veratrum grandiflorum*). The phenotype of this plant is characterized by strong and leafy stems arranged in inflorescences (left). The 6 petals of that plant are spread, not adherent, and of white or greenish color (right). (B) The highest concentrations of resveratrol are found in the Japanese knotweed *Polygonum japonicum* (synonym *Fallopia japonica*, formerly *Polygonum cruspdatum*). Originally this herbaceous perennial plant was endemic in East Asia (Japan, China, and Korea) and nowadays can be found in Europe classified as one of the worst invasive plant species. It belongs to the genus *Fallopia* and its stems hold lots of distinct raised nodes (left). The small white or cream flowers are arranged in erect racemes (right). (C) The content of resveratrol in wines originating from different grape varieties is highly variable. Typically, white wines (e.g., those produced from the varieties White Burgunder, Riesling, Ortega, and Gewürztraminer) contain ~10 times lower resveratrol quantities than wines made from red grapes varieties [such as Cabernet Mitos, Cabernet Cubin, Syrah, Spätburgunder (Pinot noir), Cabernet Sauvignon, and Merlot]. The photos in panels A and B were reproduced from reference 23 with permission. All grape images were taken in Martinsried, Pfalz, Germany. For typical resveratrol concentrations in depicted wines, please refer to Supplemental Table 1.

This resveratrol intake level might hold true for the Spanish population, but resveratrol intake may be completely different in other countries. As discussed above, exogenous biological and physical stress factors impact the resveratrol content in a specific food or beverage. In addition, there are endogenous factors interfering with the biosynthesis of resveratrol. In peanut kernels, it was shown that germination resulted in increased resveratrol biosynthesis, shifting the concentrations from 2.3–4.5 to 11.7–25.7 μg/g with significantly different concentrations in the cotyledons, roots, and stems (39). Also during the production process of wine, the resveratrol content is modified by various factors, including temperature, pH value, and level of SO_2 (35).

The diverse beneficial effects of resveratrol on a specific disease are strictly dose-dependent, and high doses of resveratrol promote unwanted side effects (40). In this context, it should be mentioned that natural products not only contain the *trans*-resveratrol isomers but also the *cis*-resveratrol isomers. There is a great wealth of other resveratrol dimers and higher molecular weight resveratrol variants (commonly classified as "resveratrol oligomers") occurring in food and beverages. Most often, these compounds have nonsystematic names derived from the name of species from which it was first identified (**Supplemental Table 2**). For example, Ampelopsins, Amurensins, and Hopeaphenol were named after *Ampelopsis brevipedunculata* (a wild grape), *Vitis amurensis*, and plants of the genus *Hopea* (e.g., the evergreen tree *Hopea odorata*), respectively.

In addition to these oligomers, glycosylated resveratrol forms occur in nature. It is assumed that the glycosylation of resveratrol protects this polyphenol from enzymatic oxidation, thereby extending the cellular half-life and preserving the antioxidant capacity (41). All of these factors make it difficult to accurately estimate the exact daily uptake of resveratrol in food products. Therefore, a number of manufacturers sell pharmaceutically produced supplements with the resveratrol content exactly specified. Most often, these "highly potent" drugs are offered with "more is better" recommendations, and some of these "health bomb" formulations are offered with obscure and unscientific instructions suggesting doses of 1 g resveratrol to achieve the best health improvement effects. The recommended amount is equivalent to a dosage of 12.5 mg/kg body weight if an adult of 80 kg is assumed. These concentrations are justified by rough

extrapolations from animal experiments, most of which require daily dosages of 5–100 mg resveratrol/kg body weight in order to reach a specific biological effect.

Clinical trials assessing the effects of resveratrol in humans are rather rare, and some were performed by using grape extracts without precise knowledge of resveratrol concentrations, making it difficult to interpret the results. In one study, resveratrol was administered to healthy volunteers (n = 10) at 1 of 4 daily dosages (0.5, 1.0, 2.5, or 5 g) over the course of 29 d. There was a substantial decrease in circulating IGF-1 and IGF-binding protein 3 among volunteers receiving 2.5 g/d compared with predosing values. In this study, it was further shown that the daily uptake of 2.5 and 5 g caused mild to moderate gastrointestinal symptoms (19). Another clinical study in which 42 healthy volunteers consumed 1 g resveratrol/d for 4 wk showed that this regimen was sufficient to modulate enzyme systems that are involved in carcinogen activation and detoxification pathways (42). Even lower doses (5 mg 2 times/d for 4 wk) of a novel resveratrol formulation termed SRT501 were effective in improving insulin sensitivity in patients with type 2 diabetes, although SRT501 was originally developed for treatment of multiple myeloma (43). Similarly, a previous study suggested that higher doses of 2.5 and 5 g resveratrol/d for 28 d were therapeutically effective in patients with type 2 diabetes (44). Although the last 2 studies (42, 43) are highly encouraging, the observation that different daily doses (10 mg compared with 5 g) applied in human studies are equally effective indicates a scientific dilemma and further raises the question about the necessary amount that should be applied to cure a specific disease. Moreover, the fact that the development of the resveratrol drug SRT501 was halted because of side effects (nausea, vomiting, and diarrhea) raised controversial questions about the overall therapeutic applicability of resveratrol, resveratrol-enriched supplements, and resveratrol formulations.

Nevertheless, safety studies in humans have shown that resveratrol is a safe drug and is reasonably well tolerated at doses of up to 5 g/d (19, 45). Therefore, the overall low toxicity of resveratrol should in principle allow the translation of the encouraging experimental findings to humans. In contrast to this assumption, the overall conclusion of a detailed literature analysis (46) highlighting resveratrol benefits and side effects, proposed resveratrol activities, and issues of relevant resveratrol dose for treatment of human diseases was that the published evidence is not sufficiently strong to justify a recommendation for the administration of resveratrol to humans. In addition, the study indicated that an optimal dose of resveratrol has yet to be established in human studies (46). However, numerous reports describe therapeutic and health-promoting benefits of resveratrol consumption, and these benefits affect many organs (**Figure 2**). However, most of these therapeutic activities were only established in cell culture or in preclinical models. We discuss some of the most important findings of health-promoting effects in the following paragraphs.

Beneficial Effects of Resveratrol

Beneficial effects of resveratrol in heart disease

There are a number of reports describing the beneficial effects of resveratrol on improvement of heart dysfunction,

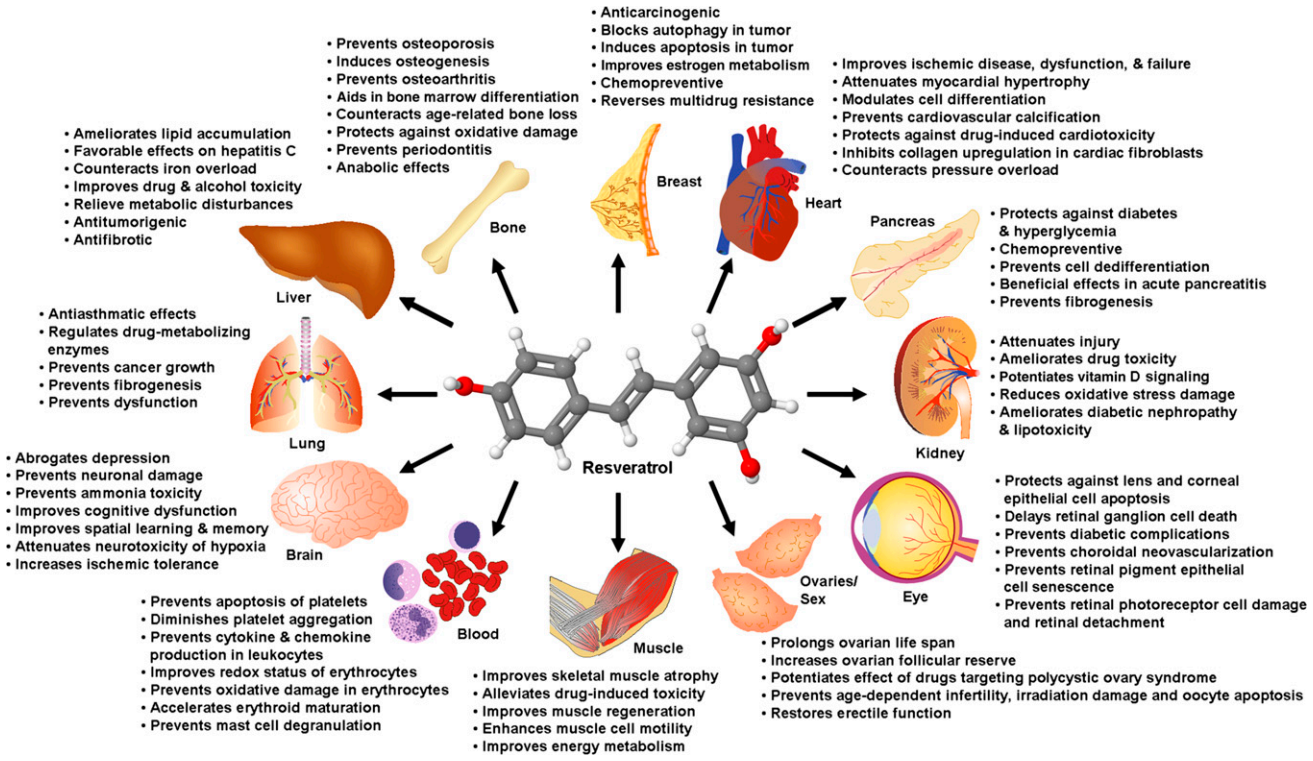

FIGURE 2 Some of the reported beneficial effects of resveratrol on organ function.

failure, calcification, and pressure overload, as well as the attenuation of myocardial hypertrophy by virtue of its antioxidant, antihypertensive, and coronary vasodilating activities (47). At the molecular level, most likely some of these effects are mediated through activation of silent information regulator 1 (SIRT1; also known as Sirtuin 1), 5′-adenosine monophosphate-activated protein kinase, and endogenous antioxidant enzymes (48). A recent study of the pathogenesis of myocardial fibrosis suggested that resveratrol exhibited its therapeutic effects by inhibiting pathways that were driven by reactive oxygen species, extracellular regulated kinases, TGF-β, and periostin (49). In addition, resveratrol was shown to prevent collagen expression in cardiac fibroblasts and to protect against drug-induced cardiotoxicity (50, 51). The therapeutic effects of resveratrol in these models could be attributed to the capacity of resveratrol to protect against drug-induced glutathione depletion and superoxide dismutase activity (51). A recent meta-analysis of 6 randomized controlled trials comprising a total of 247 subjects showed that high levels of resveratrol consumption significantly decreased the systemic blood level, although it had no effect on diastolic blood levels (52).

Beneficial effects of resveratrol in breast cancer

The impact of resveratrol on breast cancer is controversial. Although some reports showed that resveratrol supplementation prevented experimental mammary carcinogenesis (53, 54), other studies found that low concentrations of resveratrol promoted breast cancer (55). Resveratrol decreased breast cancer cell proliferation in a dose-dependent manner (56). Novel aza-resveratrol analogues have already been tested for their potential to inhibit the proliferation of breast cancer cells by impacting the expression of estrogen receptors (57). In a pilot study conducted in 40 postmenopausal women with high BMI, a resveratrol intervention with 1 g resveratrol/d for 12 wk had favorable effects on estrogen metabolisms and increased the concentrations of the sex steroid hormone-binding globulin, which is inversely associated to breast cancer risk (58). Likewise, a randomized double-blind study of 39 adult women with increased breast cancer risk showed decreased methylation of the tumor suppressor gene *RASSF-1α* (Ras association domain family member 1-α) in resveratrol-treated patients compared with nontreated subjects and suppression of expression of the cancer promoting PGE_2 (59). However, this study was conducted with a limited sample size and needs to be validated in larger cohorts.

Beneficial effects of resveratrol on bone homeostasis

Favorable effects of resveratrol on bone homeostasis have also been reported. In one study, it induced osteogenesis, prevented osteoarthritis, and counteracted age-related bone loss (60). Likewise, the oral administration of resveratrol significantly prevented bone loss and osteoclastogenesis in a murine iron overload-induced bone loss model (61). In this model, the application of resveratrol reverted the iron-induced reduction of the bone transcription factor Runx2, the bone-building Osteocalcin, and type I collagen. These data suggest that resveratrol mediates bone building by stimulation of osteoblastic and inhibition of osteoclastic activities. In line with this assumption, a randomized, placebo-controlled trial that enrolled 74 middle-aged obese men showed that oral treatment with 1 g resveratrol/d for 16 wk promoted formation and mineralization of bone (62).

Resveratrol effects on the pancreas and glucose metabolism

Oral gavages of resveratrol in methylglyoxal-treated mice increased pancreatic cellular insulin content, suggesting that this polyphenol may be useful in the treatment of type 2 diabetes by protecting against pancreatic cell dysfunction (63). In humans, there are reports that have shown that resveratrol improves glucose homeostasis, decreases insulin resistance, and decreases metabolic disorders, suggesting that resveratrol has the potential to treat diabetes (64). Based on experimental findings that were established in rats that were maintained on a high-fat diet, it is most likely that some of the therapeutic effects of resveratrol on energy homeostasis and glycemic control were induced by the antioxidant function of resveratrol and its capacity to modulate mitochondrial activities and restore insulin secretion dysfunction (65).

Renal effects of resveratrol

With regard to the kidney, independent reports have shown that resveratrol attenuates renal injury, fibrosis, unwanted drug toxicity, and oxidative and diabetes-associated damage (66–68). Recently, it was demonstrated that resveratrol potentiates vitamin D and nuclear receptor signaling, possibly elucidating a possible molecular pathway of resveratrol activity (69). An inhibitory effect of resveratrol on epithelial-mesenchymal transition, a process that is associated with the progression of fibrosis, was recently demonstrated in the human tubular epithelial cell line HK-2 (66). In the study, it was demonstrated that resveratrol increased expression of SIRT1 and inhibited TGF-β pathway via deacetylation of Smad4, the common intracellular mediator of TGF-β signaling (66).

Resveratrol and the visual system

Similar positive effects were reported in the eye; resveratrol protected lens and corneal epithelium, as well as retinal photoreceptor cells, from diabetic complications and other kinds of damage (70, 71). Comparable to the observations that were found in renal cells, epithelial-mesenchymal transition was significantly inhibited in retinal pigment epithelial cells, suggesting that resveratrol is a potential drug suitable for the treatment of proliferative vitreoretinopathy, a disease marked by retinal detachment and ocular trauma (72). In this model system, resveratrol also leads to a substantial deacetylation of Smad4, which resulted in reduced fibrotic membrane formation. In a diabetic cataract rat model, a protective effect of resveratrol on lens epithelial cell apoptosis

was demonstrated by reduced expression of caspase-3 and lower apoptotic ratios (73).

Resveratrol and fertility

With regard to the ovaries, resveratrol was shown to be an effective therapy for conditions associated with androgen excess, thereby protecting against age-dependent decline in fertility by increasing the ovarian follicular reserve, ovarian life span, and preventing oocyte apoptosis (74). Other reports have shown that resveratrol restores erectile function in experimental models of rats with diabetes, a finding that was mainly reflected by improvement of intracavernous pressure, mean arterial blood pressure, and modulation of cavernous cyclic GMP levels (75). Recently, it was shown that resveratrol supplementation modulates oxidative stress, JNK signaling, and caspase-3 activities, thereby counteracting diabetes-induced decreases in reproductive organ weights, sperm count, and motility (76). Similar effects on spermatogenesis and general testicular germ cell differentiation of resveratrol were also reported in surgically rendered cryptorchid mice (77).

Resveratrol and the blood system

Resveratrol has been shown to affect platelet aggregation and apoptosis, most likely by increasing ATP, ADP, and AMP hydrolysis (78). It was recently demonstrated that this activity by resveratrol is useful in preventing unwanted activation of human platelets during storage for transfusion purposes (79). The study showed that human platelets treated with resveratrol released less thromboxane B_2 and PGE_2 than did control platelets, showed decreased platelet apoptosis in storage, and had a longer half-life following transfusion (79). Furthermore, it could be demonstrated that resveratrol decreases the secretion of PGE_2, CCL5/RANTES, and CXCL8/IL-8 and increases production of IL-1β, IL-6, and IL-10 in LPS-stimulated peripheral blood leukocytes (80). Independent in vitro experiments that were performed in polymorphonuclear leukocytes isolated from healthy, adult dogs also demonstrated that resveratrol increased proinflammatory and decreased anti-inflammatory leukocyte cytokine production in leukocytes (81). These data also show that resveratrol is effective in reducing the robustness of oxidative burst capability in leukocytes (81).

Pulmonary effects of resveratrol

In the lungs, resveratrol has been shown to be effective in preventing dysfunction, fibrogenesis, cancer growth, and injury-induced cell apoptosis and further in displaying antiasthmatic effects and modulating the activity of drug-metabolizing enzymes (82, 83). Novel studies that investigated the effects of resveratrol on hypoxia/reoxygenation-induced alveolar epithelial cell dysfunction suggested that the therapeutic effects of resveratrol are partially mediated by promoting surfactant protein expression and inhibiting the NF-κB signaling pathway, which controls many genes involved in inflammation (84). Also some resveratrol oligomers such as *cis*- and *trans*-gnetin H, which are widely applied in TCM, were tested in vitro; were capable of promoting apoptosis by releasing mitochondria cytochrome *c*, activating caspase 3 and 7, and inhibiting NF-κB activation in 4 human cancer cell lines; and were therapeutically efficient in suppressing the growth of xenograft lung tumors in mice (85).

Neuroprotective effects of resveratrol

Several neuroprotective effects of resveratrol have been reported, including protection against neuronal damage and ammonia toxicity, abrogation of depression, improvement of cognitive dysfunction, and increased ability in spatial learning and memory (86, 87). In a model of rats with middle cerebral artery occlusion, resveratrol reduced ischemia-induced apoptosis in the hippocampus in a dose-dependent manner, indicating that resveratrol is a neuroprotective substance with therapeutic potential (88). In line with these findings, a recent report in which resveratrol's neuroprotective effects were evaluated in neonatal rats showed that resveratrol effects are long lasting, protecting against brain damage, reducing infarct volume, and ameliorating the loss of myelination (89).

Hepatic effects of resveratrol

Other studies have investigated the therapeutic potential of resveratrol in hepatic disease models. Experimentally, there are clear indications that resveratrol ameliorates hepatic lipid accumulation and progression of nonalcoholic steatohepatitis by downregulation of inflammatory signaling pathways and regulation of autophagy (90). In the underlying study, the authors fed mice a methionine-choline deficient diet and found that the daily intragastric administration of resveratrol (100 or 250 mg/kg body weight) attenuated hepatic steatosis and inflammation. In contrast, resveratrol treatment had no consistent therapeutic effects on the alleviation of manifest experimental steatohepatitis (91). Although these findings may suggest that resveratrol treatment has preventive but not curative activities in the pathogenesis of liver diseases, daily supplementation with 500 mg resveratrol for 12 wk improved the outcomes in a randomized, double-blinded, controlled clinical trial that enrolled 50 patients with nonalcoholic fatty liver disease (92).

The resveratrol tetramer vitisin B is a highly potent in vitro inhibitor of the hepatitis C virus helicase (93). Furthermore, in mice that received injections of cancer cells, resveratrol significantly inhibited hepatic retention and metastatic growth of melanoma cells, most likely by interfering with IL-18 secretion, suppressing VCAM-1 expression, and blocking the stimulatory effects of IL-18 on cell adhesion and proliferation (94). Most recently, it was shown that resveratrol protects the liver from iron-mediated injury, which is causative in the formation of acquired and genetic iron-overload diseases (17). The therapeutic potential of resveratrol was also successfully proven in models of colorectal and prostate cancer (95, 96).

Resveratrol and muscle

Several independent reports have found favorable effects of resveratrol on muscle function and injury. In experiments in

which the tibialis region of the hind limbs of rats was subjected to compression injury by 2 cycles of 6-h constant pressure, administration of resveratrol at daily concentrations of 25 mg/kg prevented the compression-induced manifestations of pathohistologic damages and ameliorated oxidative damages in a SIRT1-dependent manner (97). Similarly, the combined dietary intake of 500 mg resveratrol and 10 mg piperine for 4 wk was recently shown to increase skeletal muscle mitochondrial capacity upon low-intensity exercise training (98). Interestingly, resveratrol drastically impacted the muscle fiber characteristics and antioxidative capacity of finished pigs, suggesting that resveratrol is an effective additive to improve pork meat quality (99). Likewise, juvenile Southern flounders that were fed a diet supplemented with 600 μg resveratrol/g of food for 16 wk showed a greater length and body mass than fish fed a control diet (100). Such studies indicate that resveratrol is a new supplement to enhance growth in different agricultural and aquacultural settings.

Molecular Activities of Resveratrol

Potential molecular functions of resveratrol were first reported in 2003 (5). In this pioneering work, it was shown that resveratrol can modulate the activity of SIRT1, a critical deacetylase that impacts the acetylation status of p53, forkhead proteins, and DNA repair enzymes (5). On the other hand, activation of SIRT1 by resveratrol treatment reduced tumorigenesis in a mouse model (101). As a consequence, the binding of resveratrol to SIRT1 is associated with a signal that mimics calorie restriction and increases DNA stability, resulting in extended lifespan of *Saccharomyces cerevisiae* (5). Valuable insights on the structural basis of the resveratrol-SIRT1 interaction and its potential molecular details on SIRT1 activity regulation by resveratrol were recently obtained from crystal structure analysis (**Supplemental Figure 2**) (102). The study suggests that the binding of different resveratrol molecules to the N-terminal domain of SIRT1 is principally responsible for promoting tighter binding between SIRT and a 4-residue acetylated p53 peptide (i.e., 7-amino-4-methylcoumarin), thereby increasing SIRT1 activities.

Other recent findings considered the possibility that the tyrosine-like phenolic ring of resveratrol might fit into the active site pocket of tyrosyl transfer RNA (tRNA) synthetase, which affects downstream activation of key stress signaling pathways (103). In addition, the binding of resveratrol to tyrosyl tRNA synthetase nullifies catalytic activity of this enzyme and redirects the tRNA synthetase to a nuclear function, stimulating NAD^+-dependent auto-poly-ADP-ribosylation of poly(ADP-ribose) polymerase 1 (103). Resveratrol was also shown to bind to the F1-ATPase from heart mitochondria, thereby probably preventing its proper functionality in mitochondrial ATP synthesis (104). Such an activity would explain resveratrol activity on cellular proliferation and apoptosis.

In another study, the authors used a structure-based drug discovery strategy that relies on metabolomics-biased fragment crystallography in which a library is screened against leukotriene A4 hydrolase, an enzyme that is closely linked to arachidonic acid metabolism. Using this screening method, the authors identified resveratrol as an efficient ligand for leukotriene A4 hydrolase (105). This finding might explain the antioxidant activity of resveratrol and further provide some clues about the molecular details of how resveratrol modulates inflammatory responses. Well-designed binding studies using fluorescence spectroscopy and surface plasmon resonance techniques showed that resveratrol also has affinity for phospholipase A_2, another key factor that plays a role in arachidonic acid metabolism and catalyzes the hydrolysis of phospholipids into arachidonic acid and lysophospholipids (106). This in turn provides another good explanation of how resveratrol interferes with inflammatory signaling. Along those lines, crystallographic analysis and functional studies showed that resveratrol acts as a pathway-selective estrogen receptor-α ligand, again offering another pathway by which resveratrol modulates the inflammatory response (107).

During recent years, intensive studies have focused on gaining a better molecular understanding of the proposed insulin-sensitizing function of resveratrol. X-ray crystallographic studies and in vitro transactivation assays showed that resveratrol acts as a PPAR antagonist through its direct interaction with PPARγ and PPARα (108). Other investigations that analyzed crystal protein-resveratrol complexes found an affinity for resveratrol and other polyphenols for insoluble transthyretin, which is relevant in the pathogenesis of diverse amyloid disorders such as familial amyloid polyneuropathy, familial amyloid cardiomyopathy, and senile systemic amyloidosis (109). The precise molecular and structural basis of this interaction was recently determined in high resolution (110). These insights may provide the molecular basis to understand some of the reported beneficial neuro- or cardioprotective effects of resveratrol that are due to increased fibrillogenesis and enable potential new therapeutic intervention strategies for targeting unwanted transthyretin aggregations within a specific tissue.

Biotransformation and Pharmacologic Aspects in Resveratrol Biology

As outlined above, there is a wealth of literature describing beneficial effects of resveratrol in diverse preclinical disease models. However, the clinical potential of resveratrol is somewhat difficult to estimate because there is insufficient information about optimal dosage, biotransformation, potential side effects, and pharmacokinetic parameters. In addition, there are a number of parameters and pharmacologic considerations that affect the rate of active and passive individual absorption in the gastrointestinal tract (111). Unfortunately, most of the studies that investigated pharmacologic aspects of resveratrol were done only in healthy volunteers, and there is no guarantee that these findings can be recapitulated in diseased patients. In addition, compared with its solubility in ethanol (~50 g/L), the aqueous solubility of resveratrol (~3 mg/100 mL) is rather low, suggesting that alcoholic

beverages are beneficial to increase resveratrol's bioavailability and peak plasma concentrations. Likewise, the administration of special galenic formulations of resveratrol is potentially suitable to increase the bioavailability of resveratrol. For example, in patients with colorectal cancer with hepatic metastases scheduled to undergo hepatectomy, the application of the micronized resveratrol formulation SRT501 induced 3.6-fold higher plasma levels than those published for equivalent doses of nonmicronized resveratrol. This drug formulation further extended the mean half-life by over 1 h and almost doubled the time to maximum plasma concentrations (112). Other approaches to increase the bioavailability of resveratrol arose from the finding that the combined application of resveratrol with other molecules such as pterostilbene, a stilbenoid chemically related to resveratrol, can result in synergistic and additive effects in breast cancer cell lines (113). Likewise, the combination of resveratrol and ω-3 PUFAs exerted synergistic effects on CCL5/RANTES expression in LPS-stimulated human peripheral blood leukocytes and additive effects on IL-6 or CXCL8/IL-8 expression in IL-1β-activated chondrocytes (80). Similarly, the synthesis of higher molecular oligomers of resveratrol and analogues is currently studied as an option to increase the selectivity of resveratrol activity. Compared with resveratrol, the triple-bond resveratrol analogue (i.e., 3,4',5-trihydroxy-diphenylacetylene) had weaker antioxidant activity and stronger inhibitory effect on NF-κB activation and on cyclooxygenase-2, TNF-α, and IL-6 production in the mouse leukemic monocyte macrophage cell line RAW 264.7 (114).

On the other hand, methylated resveratrol was shown to increase antitumor activity but failed to mediate beneficial metabolic effects in vitro and mediated its cell growth inhibitory effects at different stages (115). These findings suggest that structural optimization approaches targeting the resveratrol molecule might be suitable to selectively change its activity into a desired direction.

Resveratrol Prodrugs

As discussed above, the therapeutic usage of resveratrol is somewhat hampered by its low bioavailability. As a compound that is poorly soluble in water, resveratrol is effectively absorbed by passive diffusion in the intestine where it is then transported into the liver. Before it reaches the systemic circulation, the presystemic metabolism (i.e., first pass effect) in the liver leads to a substantial reduction of free resveratrol (116). Resveratrol is conjugated in phase II metabolism to higher soluble glucuronides (e.g., resveratrol-3-*O*-glucuronide, resveratrol-4-*O*-glucuronide) and sulfates (e.g., resveratrol-trisulfate) or is bound to albumin and lipoproteins (116). Thus, the therapeutic efficacy of resveratrol after oral administration is rather low. Therefore, efforts that either increase the bioavailability of resveratrol or delay its phase II metabolism by delivering resveratrol as a prodrug are primary targets for the biomedical exploitation of resveratrol (117). Recently, it was demonstrated that the engagement of the free OH groups within resveratrol into an *N*-monosubstituted carbamate linkage with natural amino acids prevents conjugation, increases the stability at low pH values, and decreases the rate of hydrolysis (117). Another strategy that is based on polymer conjugation by using ester- and ether-based polyethylene glycol and polyethylene glycol-polylactide linker chemistry allowed researchers to increase the half-life of resveratrol in rat plasma from 0.13 to 3 h (118). There are also intensive efforts to develop strategies to prepare liposome- or nanotechnology-based resveratrol formulations for enhancing the aqueous solubility and stability or improving the rate and extent of absorption (119, 120). In addition, resveratrol is used as a blueprint for the design and synthesis of novel, more potent drugs. HS-1793, for example, is a resveratrol analogue that is free from the restriction of metabolic instability, bypassing the high-dose requirement in therapeutic use. This substance was shown to induce cell cycle arrest and apoptotic cell death in breast cancer cell lines more effectively than resveratrol and maintain its good compatibility in standard tests of genotoxicity (121, 122). Some innovative soluble galenic forms of resveratrol should, in principle, also improve the bioavailability and efficiency of resveratrol in humans, thereby allowing a decreasing drug burden in humans (123).

Therapeutic Doses of Resveratrol and the French Paradox

Current recommendations for daily consumption of resveratrol are primarily based on arithmetical animal-to-human dosage conversion. Unfortunately, the confirmation of therapeutic effectiveness of these calculated resveratrol concentrations in humans is still pending (124). Independent studies have shown that resveratrol consumption in a daily range of 700–1000 mg/kg body weight is well tolerated without toxicologic effects and that concentrations ≤2 g/d are harmless when applied in the short term (46, 125). Based on these and other findings, various "experts" claim that a daily dosage of 1 g/d is effective for treatment of diverse disorders in humans. In addition, the permanent launch of articles with a lack of scientific background has led to the notion that the consumption of supplements enriched with resveratrol is health-promoting or suitable to alleviate diverse medical conditions. Moreover, the uncritical acceptance and erroneous interpretation of the French paradox, which links a lower incidence of coronary heart disease with the chronic consumption of low doses of red wine or intake of other resveratrol-containing nutrients, have led to the assumption that red wine, grapes, peanuts, chocolate, Itadori tea, or other foods or beverages are a kind of "daily health therapy."

However, one wonders how much of these nutrients must be consumed to reach the RDA of 1 g resveratrol. Typical resveratrol concentrations reported for conventional food products are: peanuts without seed coats, 0.03–0.14 μg/g (126); red wines, 0.361–1.972 mg/L (127); white wines, 0–1.089 mg/L (128); rosé wines, 0.29 mg/L (129); beers, 1.34–77.0 μg/L (130); skin of tomatoes, ~19 μg/g dry weight (131); dark chocolate, 350 μg/kg; milk chocolate, 100 μg/kg (132); Itadori tea, 68 μg/100 mL (37); red grapes, 92–1604 μg/kg fresh weight (133); white grapes,

59–1759 μg/kg fresh weight (133); and apples, 400 μg/kg fresh weight (4). On the basis of these given concentrations, it is not possible to absorb the recommended dose of resveratrol through uptake of any of these nutrients or combinations thereof (**Figure 3**). This inevitably raises the question: how can scientists justify the French paradox by drinking red wine or consuming other foods or beverages? The newest annual report on wine published by the Global Agricultural Information Network reveals that France is the world's biggest wine producer (4.6 billion liters in 2014) and consumer with a per capita consumption of 43.4 L in 2014 (134). Assuming ~73% of these wines are red/rosé wines and 27% are white wines, and further adopting that red/rosé wines contain ~2 mg/L resveratrol and white wines contain ~0.5 mg resveratrol/L, the annual consumption of 31.7 L of red wine and 11.7 L of white wine is equal to an uptake of ~70 mg resveratrol/y (or 0.2 mg/d) or 5000 times less than the proposed therapeutic dose of 1 g/d. Even if further daily resveratrol sources (grapes or peanuts) are considered, these rough calculations clearly document that the consumption of red wine is not a good explanation of the pathologic mechanisms predicting the French paradox.

Of course, we must admit that our calculations only consider the amount of unbound resveratrol in respective beverages and foods. As discussed above, many of the mentioned nutrients contain higher molecular constituents (i.e., resveratrol oligomers) and resveratrol glucosides (e.g., *trans*-polydatin piceid), which often occur in high concentrations and show similar or sometimes higher potency in cell culture and animal studies (135, 136). Unfortunately, the knowledge of these oligomeric entities is poor, and the pharmacologic properties of these compounds are widely unknown. In this regard, the continuous development of databases, such as the Phenol-Explorer, that provide information about the polyphenol content in foods, would be extremely helpful in estimating the daily uptake of resveratrol and resveratrol derivatives (137, 138). In addition, investigation of long-term resveratrol consumption safety, especially in medicated individuals, is urgently needed to estimate the therapeutic potential of resveratrol for clinical significance in the daily care of patients (139).

Another critical issue is the targeting of resveratrol activities to a specific organ. In most of the preclinical studies performed in animals, resveratrol was orally or intraperitoneally administered, resulting in a systemic distribution. Currently, there are several investigations aiming to develop nanotechnology-based formulation, i.e., resveratrol-encapsulated nanoparticles, to improve pharmacokinetic properties and to enhance targetability and bioavailability of resveratrol (140).

In summary, it is certainly valid to argue that it is not possible to take up 1 g of unbound resveratrol/d by consuming conventional food products. Alternatives that are offered by many companies include a variety of (sometimes outrageously expensive) nutritional supplements with precisely defined resveratrol content. Although their clinical usefulness is questionable, they are advertised with extravagant promises. It will be interesting to see how new experimental findings in resveratrol research will be translated into the clinics.

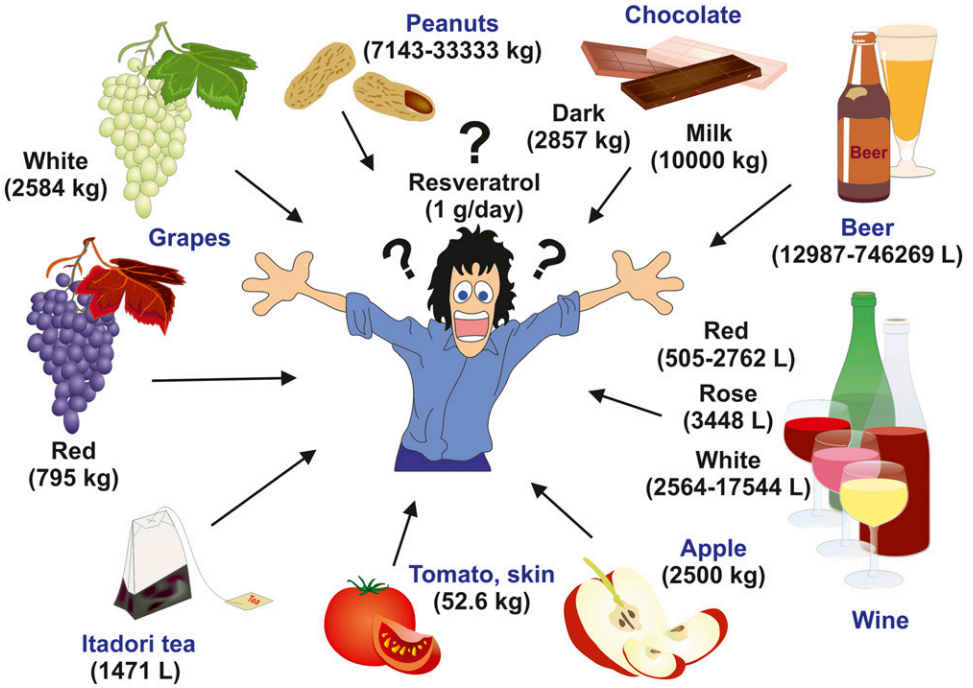

FIGURE 3 Quantities of food and beverages that must be consumed to reach therapeutic doses. Based on animal studies, daily resveratrol doses in the range of hundreds of milligrams to several grams for therapeutic intervention have been proposed. If a person intends to ingest 1 g resveratrol each day, this would require consuming the depicted quantities of foods or beverages. The calculation is based on typical resveratrol contents found in peanuts without seed coats (0.03–0.14 μg/g) (126), red wine (Pinot noir from France, 0.362–1.979 mg/L) (127), white wine (Riesling from Spain, 0.057–0.390 mg/L) (128), rosé wine from Serbia (0.29 mg/L) (129), beer (1.34–77.0 μg/L) (130), skin of tomato (~19 μg/g dry weight) (131), dark chocolate (350 μg/kg), milk chocolate (100 μg/kg) (132), Itadori tea (68 μg/100 mL, when prepared by infusing 1 g of the commercial root prepared with 100 mL of boiling water for 5 min) (37), red Merlot grapes from Japan (1259 μg/kg fresh weight) (133), white Riesling grapes from Japan (387 μg/kg fresh weight) (133), and cultivated apples (estimating a mean total content of 400 μg/kg fresh weight found in 150 different cultivars) (4).

Conclusions

Resveratrol is a polyphenol that is present in the human diet and has a large variety of potential therapeutic properties. However, it is not possible to absorb the recommended therapeutic doses of resveratrol by drinking wine or through dietary sources. In addition, to date, most of the beneficial effects are only established in preclinical models. One of the major challenges in resveratrol research is to determine whether the observed health-promoting effects are transferable to humans. Therefore, clinical trials with the aim of determining the effective dosage regimen for the therapy of specific diseases are urgently needed. These trials must be conducted with well-standardized resveratrol formulations in order to allow the comparison of obtained results. Because previous studies in humans have already consistently shown that the bioavailability of resveratrol after oral intake is rather low, the development of resveratrol formulations with better pharmacologic properties is still a challenging task. Likewise, structural optimization and the development of new galenic resveratrol formulations such as resveratrol-encapsulated nanoparticles should help to physiologically increase resveratrol's activity and overall bioavailability, to lower the necessary dose, to prevent unwanted side effects during therapy, and to target resveratrol activities to specific organs. Resveratrol-enriched supplements might be suitable to allow daily uptake of therapeutically relevant doses (currently presumed to be 1 g) that are not obtainable by conventional foods or beverages. In addition, resveratrol might be a supplement that enhances growth or quality of products cultured in different agricultural and aquacultural settings, thereby developing health-promoting effects. In this regard, the intensification of research of resveratrol oligomer chemistry and biology may also offer some avenues for new therapeutic drugs with better pharmacologic properties. In the long term, such investigations will reveal whether all the hype and hope associated with resveratrol are scientifically justified.

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