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# Resveratrol and exercise (Review)

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**Abstract.** Although it is recommended for a healthy lifestyle, moderate exercise is known to lead to oxidative stress, inflammation and muscle injury. Hence there are efforts to develop dietary strategies to counter the oxidative stress caused by physical activity. Recently, there has been an interest in the capability of resveratrol (RES) to modulate physical performance and prevent oxidative stress. Despite the inconsistency among reports regarding the topic, it has been suggested that RES delays fatigue by hindering lipid peroxidation. It is hypothesized that RES administration produces favorable effects on hepatic cell rejuvenation, exerts a regulatory effect on glucose metabolism, and preserves liver glycogen reserves that are diminished during physical activity. Consequently, there is a growing interest in the association between RES and exercise. The aim of the current review is to interpret the association between RES and exercise.

**Contents**



## 1. Introduction

The notion of nutrition has extended beyond its contribution to survival and regulation of food intake to assume a role in the prevention and treatment of diseases. Polyphenols are compounds that are synthesized by plants and have a wide variety of functions ranging from defense to pollination. Recently, these compounds have become of increasing interest in medical research. Within this group, the most commonly evaluated polyphenol has been resveratrol (RES), found in grapes and berries (3,5,4-trihydroxy-stilbene) (1). It is naturally present in grapes and various types of food and beverage, including red wine (2). RES (trans-3,4',5-trihidroksistilben) is produced by plants in response to different stress conditions and infections (3). It is found in assorted types of plants, such as strawberries, grapes, peanuts and pine; with the skin of fresh grapes containing ~50-100 $\mu$g/g wet-weight RES (4). Chemically, RES, a non-steroid compound ($C_{14}H_{12}O_3$) exerts an estrogen-like biological activity.

RES is usually found in a glycosylated or conjugate form in plants. It has been demonstrated that glycosylation protects compounds against impairment and increases gastrointestinal absorption (5). Following oral administration, RES is metabolized to water-soluble forms, including RES-3-O glucuronide and RES-3-O sulfate, by liver phase II drug-metabolizing enzymes. As the more dominant forms, which are excreted through the urine, these metabolites have longer serum half-lives than the main compound, RES (6). However, the efficiency and bioavailability of these RES metabolites remain unknown (7). The absorption of orally administered RES is more effective than that of other known polyphenols, quercetin and catechin (8). Recently, numerous pharmacological activities of RES (anti-diabetic, -oxidative, -inflammatory, -cancerous and -asthmatic, and pain killing) have been elucidated through *in vitro* and *in vivo* studies (3). Additionally, RES is a major activator of the protein and gene family of sirtuins (SIRTs; silent information regulators) (9). RES increases energy use by activating the SIRT1 signaling pathway and, hence, reinforcing mitochondrial function. Silent, but significant regulators of metabolism, cancer, aging and longevity, SIRTs are significantly associated with signal transduction pathways that are linked to stress (10).

## 2. RES metabolism

When consumed by healthy individuals, RES, which has low bioavailability, reaches its peak level in the plasma within 30-60 min (6), and accumulates in organs, such as the heart, liver and kidneys (11). It has been established that RES administered to rats reached its maximum concentration at 60 min in the plasma and kidneys, 30 min in the liver, and 120 min in the

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heart (12). Additionally, RES is modified by the glucuronidation reaction in liver microsomes (13). RES, which is rapidly absorbed and transferred to the tissues, is primarily excreted in the urine (12). The majority of RES is absorbed by the jejunum and a smaller quantity by the ileum (14). It is found in dietary products in cis and trans forms, and its glycosylated form is 3-O-β-D-glucoside. Preventing the enzymatic oxidation of RES, glycosylation preserves the biological efficiency of RES, and enhances its stability and bioavailability. As the intestinal cells absorb only non-glycosylated RES, glycosidases are required in the absorption process. The relative ratio between glycosylated and non-glycosylated resveratrol in food regulates its absorption rate. There are two signaling pathways associated with the transfer of trans-piceid to enterocytes: The first signaling pathway is via lactase phlorizin hydrolase found on the apical membrane. It is released to the lumen as non-glycosylated trans-RES and subsequently diffuses to the luminal side . The second signaling pathway is the destruction of glycosides by cytosolic β-glucosidase after passing through the brush border membrane by sodium-dependent glucose transporter 1. After de-glycosylation, trans-RES is formed from trans-piceid. Trans-RES is further metabolized in erythrocytes, forming a novel compound, which is a glucuronide conjugate. The major glucuronate is the trans-RES-3-O-β-glucuronide. This glucuro-conjugate is released from the enterocytes into the intestinal lumen (15).

Results from rat studies demonstrated that the half-life of orally administered RES in the circulation varies between 12 and 15 min. In these studies, RES was administered to the rats at doses of 2 mg/kg (16) and 50 mg/kg (17) and at a dose of 20 mg/kg to mice (18) through the intragastric route, and the peak concentration values in the plasma were found to be 0.5, 1.2 and 6.6 $\mu$M, respectively. Rat and mouse studies have demonstrated that RES is absorbed well, and is rapidly transformed to glucuronide and sulfate conjugates in the epithelial cells of the liver and intestines (8,19,20). When labelled RES is orally administered to rats, 50-75% of the dose is absorbed. The peak plasma concentration of RES glucuronide was found to be 105 $\mu$M and it was shown that RES was strongly subject to enterohepatic circulation (8). In perfused rat small intestines, 16.8% of RES was found as RES glucuronide, 3.4% as RES sulfate, and 0.3% as free RES (18). It was demonstrated that following the perfusion of 200 $\mu$M RES in isolated rat small intestines, the majority of the RES was converted to glucuronide conjugate and entered circulation (21). Similarly, RES was shown to be converted to glucuronide and sulfate conjugates in human and rodent liver and intestine cells (20). According to these studies, it appears that RES is absorbed in considerable quantities through the gastrointestinal tract in rats and mice, and is metabolized in the liver and intestines through conjugation. When administered orally at a high dose (such as 50 mg/kg) to rats, the peak concentration of unmetabolized RES drops to <10 $\mu$M and it is eliminated very rapidly. Conversely, the conjugates of RES reach higher plasma levels when compared with RES (17).

In a study with male volunteers aged 30-50 years, Meng *et al* (22) administered a group 0.03, 0.5 or 1 mg/kg RES dissolved in whisky. Another group was administered 200, 400, 600 and 12,00 ml grape juice containing 0.16/100 ml RES, and RES was identified in the urine samples in the group given just grape juice. It was shown that at the dose of 0.03 mg/kg, the majority of the RES was eliminated within 2-3 h, while at the dose of 1 mg/kg, RES elimination took 7-10 h (22). Since its water solubility is quite low, RES has to be either conjugated or bound to proteins to be found in high concentrations in the serum (23). Albumin is one of the plasma proteins that carry RES (24). In addition, plasma RES was shown to interact with lipoproteins (25). In order to investigate the toxic effects of RES, Sprague-Dawley rats were orally administered 20 mg/kg RES for 28 days and hematologic, biochemical and histopathologic analyses were conducted. The study found that alanine transaminase and aspartate aminotransferase enzyme levels, which are indicators of hepatic toxicity, did not change as a result of RES administration; similarly, the hematologic, biochemical and histopathological parameters remained unchanged (26).

## 3. RES transport to tissues

The hydrophilic conjugation of RES facilitates its transfer to blood, its distribution in the body and its expression. RES and its metabolites are filtered from the blood by the liver and gall bladder, discharged to the intestines with bile, and subsequently re-absorbed. RES is found in the colon shortly after its oral administration; however, its distribution to tissues takes a couple of hours. RES is conjugated with glucuronic acid in the liver, and with sulfates in the liver and duodenum (6).

## 4. RES excretion

The time of excretion depends on the plasma concentration of RES. However, there is no correlation between the quantity produced and the quantity excreted. A particularly small quantity of non-glycosylated RES is present in the urine. Although it is found predominantly in its natural form in the kidneys, the urine primarily contains its conjugated form (14).

## 5. RES and exercise

In addition to dietary habits, physical exercise is considered to be a major component of a healthy lifestyle. Moderate exercise has been demonstrated to be useful in the prevention of primary and secondary diseases, including cardiovascular diseases (27), type II diabetes (28), metabolic syndrome (29) and neurodegenerative diseases, such as Alzheimer's (30,31). The term hormesis has been proposed to explain the phenomenon of surviving exposure to small concentrations of toxic substances and adapting to them (32). The adaptive response that the metabolism produces to physical exercise is explained in this framework. In response to the increase in free radical production resulting from intense physical exercise, the metabolism activates its antioxidant system (33). Commonly accepted to be a calorie-limiting factor (34), RES affects adaptations in the $O_2$ transport system to meet the increased $O_2$ requirements in exercise. In many cases, RES activates molecule pathways during exercise (35,36) and produces a performance enhancing effect (37). Conversely, human studies demonstrate that RES curbs the beneficial effects of exercise in certain groups of patients, such as those with cardiovascular disease (38,39). Consequently, the effects of RES on exercise are debatable and require further investigation.

## 6. RES and exercise in experimental animals

An active lifestyle is regarded as a major component of healthy aging. Since RES was claimed to have a performance-boosting effect in exercise, it has been assumed that RES may contribute to maintaining health in aging and increasing the quality of life (35,36). Accordingly, RES was shown to increase endurance in exercise (40) and longevity (41,42) in an old mouse model. It is clear that in these events, RES therapy activates skeletal muscle function to a great extent (43). To illustrate, when sedentary mice fed on a high-fat diet were administered RES, their skeletal muscle stamina and strength increased (41,42). Different reports have shown that RES prevents muscle breakdown (44), recovery of atrophic muscle mass in mice (45) and improves muscle function in muscular dystrophy in mice (46). Furthermore, it has been reported that RES increased exercise capabilities and sketletal muscular endurance (20,37). Consistently, RES was shown to elevate the muscle strength and aerobic endurance in rats specifically bred for types of exercise requiring stamina (47). Notably, in addition to its beneficial effects on exercise (48), RES was shown to exert significant effects on the heart tissue in two different rodent models. Consequently, when administered in combination with regular exercise (37), RES is proposed to have additional beneficial effects on the heart and skeletal muscle. One-month administration of RES (15 mg/kg/day) together with swimming exercise in old rats (age, 18 months) demonstrated that RES had a positive impact on the cardiac functions of old rats via activation of the SIRT1 signaling pathway (49). It was reported that 100 mg/kg RES administration to young mice (age, 4-5 months) with muscular dystrophy for 8 weeks improved muscle functions, although oxidative parameters remained unchanged (46). A notable finding, with regard to the association between aging and RES, was that even short-term administration of RES was demonstrated to elevate antioxidant activity and the proteins associated with it in old mice (50). Similarly, RES therapy prevented bone loss associated with the skeletal system and aging in old male rats (51). In contrast to the above-mentioned results, it has been reported that RES may not always have beneficial effects in all rodent models. For example, RES administration did not improve endurance in the case of a single-session exercise in genetically obese mice (52). Similarly, it was reported that RES administration did not boost treadmill stamina over the 12-week training period in mice specifically bred for low-capacity exercise types (47). In contrast to exercise, RES supplementation did not affect peritoneal macrophages in mice (53). An overall evaluation of these results (all of which are animal experiments) indicates that the performance-boosting effects of RES in exercise are inconsistent.

## 7. Resveratrol in muscle tissue and exercise

During physical exercise muscle tissues require large quantities of energy (in the form of ATP) to fulfill their contraction functions. The required energy (ATP) is produced by muscle mitochondria through oxidative phosphorylation. Thus, a useful adaptation of the muscle to exercise training is increased mitochondrial function and content (54,55). As with exercise, RES enables mitochondrial biogenesis in the skeletal muscle and cardiac tissues (56,57), as well as in endothelial cells (58). Metabolic and cardiovascular diseases (59,60), and aging restrict the exercise capacity of muscle tissues by diminishing their mitochondrial function and content. However, exercise training and RES enhance mitochondrial function and content in aging, and prevent the aging-associated reduction in the mitochondrial content of the skeletal muscle (61,62).

## 8. Resveratrol and exercise in humans

An examination of the effects of RES or placebo together with high-intensity aerobic exercise in physically inactive, but healthy men, aged between 60 and 75 years showed that exercise reduced oxidative stress and inflammation, while increasing muscular endurance and maximal oxygen intake in the skeletal muscle in the placebo group (38,39). Notably, the positive exercise-induced effects on the concerned parameters were not observed in the RES group (38,39). However, it should be noted that the dose of RES used in the study (3.1 mg/kg/day) (38,39) was significantly lower than the RES dose bringing about favorable effects in animal studies (10 mg/kg/day) (37,47). Arguably, the most significant study regarding the association between RES and exercise is one involving athletes who ran in the London marathon. The study investigated the effects of administration of 600 mg/day RES or placebo to athletes during the week prior to the run on the inflammatory response and muscle injury. No significant difference was found between the RES and placebo groups (63). Similarly, daily administration of 150 mg RES for four weeks did not alter performance adaptation and muscle function response to low-dose high intensity exercise (3 days per week) (64). Olesen *et al* (39) reported that exercise improved metabolic functions of muscles in older men (aged 60-72 years), while administration of 250 mg RES daily over a period of 8 weeks did not produce a positive impact. Likewise, Voduc *et al* (2) showed that RES supplementation did not alter exercise duration and aerobic capacity, and that despite the slight decrease in fasting blood glucose and slight (not statistically significant) increase in liver enzymes, the results were within the normal range; while total blood parameters, immunity parameters, and liver functions remained unaffected by RES. Consequently, unlike animal studies, the results of studies investigating the association between RES and exercise in humans are not promising.

## 9. Antioxidant effect of RES in exercise

Although it is recommended to contribute to a healthy lifestyle, moderate physical exercise leads to tissue damage (32). Therefore, efforts to develop dietary strategies against oxidative stress caused by physical activity are being made (33). Recently, there has been a growing interest in investigating the potential of RES to modulate physical performance and prevent oxidative stress (34). RES was shown to prevent lipid peroxidation in mice that were 12-months-old (40). Dal-Ros *et al* (65) also presented similar results. In a study involving 14 athletes, RES supplementation was shown to inhibit the lipid peroxidation caused by exercise (66). Furthermore, regular exercise training improves vascular functions by reducing

reactive oxygen species (67). Exercise training results in an increased antioxidant activity (68,69). Similar to exercise, RES increases the expression of these antioxidant enzymes in endothelial (70,71) and smooth muscle (69) cells. Recently, RES was shown to reduce vascular damage by elevating superoxide dismutase 2, mitochondrial expression in isolated vessels of hypertensive patients (72). Unlike exercise, RES eliminates reactive oxygen species (71,73). Although SIRT1 overexpression was shown to reduce the mitochondrial oxidative stress in endothelial cells, RES also elevates the levels of SIRT1, in a dose-dependent manner, which may lead to a marked benefit in exercise (74,75).

Besides preventing ischemic attacks (76,77), regular physical activity reduces the infarct tendency, by conditioning the heart for ischemic attacks, and encourages post-ischemic functional recovery (78). It has been shown that pharmacological doses of RES exerts a regenerative affect on heart function in mice (79,80). As a result, RES has curative affect on myocardial function due to reduced free radical production (81,82) and increased antioxidant activity (83,84). Thus, it has been concluded that RES is a crucial protector of the heart during post-ischemic recovery.

## 10. Conclusion

Various studies examining the association between RES and exercise have been performed at the Physiology Department of Selçuk University's School of Medicine. One of these is the study by Duran *et al* (85). The study examined the effect of RES supplementation on plasma leptin and liver glycogen levels in rats that were subjected to an acute swimming exercise regime. In the study, RES supplementation to rats subjected to the acute swimming exercise regime prevented the reduction in liver glycogen resulting from exercise. This result indicates that RES exerts a protective effect on liver glycogen. Arslangil (86) investigated how RES supplementation to rats subjected to an acute swimming exercise regime affected element metabolism in the blood and tissues. The study demonstrated that swimming exercise and RES supplementation produced changes in the element distribution in the rat blood and tissues. Furthermore, it was demonstrated that RES supplementation exerts a protective and/or regulatory effect on bone metabolism, independent of exercise. Thus, examination of these studies regarding the association between RES and exercise indicates that the current results of published studies are inconsistent, and a standard is yet to be established regarding the association between dose and duration in RES administration. Furthermore, due to its positive effects on muscle functions, antioxidant activity, liver glycogen, carbohydrate metabolism and bone metabolism, RES is undeniably correlated with exercise. However, future studies are required to reveal the effects of RES on exercise.

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