Polyphenols in exercise performance and prevention of exercise-induced muscle damage.

Malaguti M, Angeloni C, Hrelia S.

Source

Department for Life Quality Studies-Alma Mater Studiorum-University of Bologna, Via Irnerio 48, 40126 Bologna, Italy.

Abstract

Although moderate physical exercise is considered an essential component of a healthy lifestyle that leads the organism to adapt itself to different stresses, exercise, especially when exhaustive, is also known to induce oxidative stress, inflammation, and muscle damage. Many efforts have been carried out to identify dietary strategies or micronutrients able to prevent or at least attenuate the exercise-induced muscle damage and stress. Unfortunately most studies have failed to show protection, and at the present time data supporting the protective effect of micronutrients, as antioxidant vitamins, are weak and trivial. This review focuses on those polyphenols, present in the plant kingdom, that have been recently suggested to exert some positive effects on exercise-induced muscle damage and oxidative stress. In the last decade flavonoids as quercetin, catechins, and other polyphenols as resveratrol have caught the scientists attention. However, at the present time drawing a clear and definitive conclusion seems to be untimely.

Effect of resveratrol and quercetin supplementation on redox status and inflammation after exercise.

McAnulty LS, Miller LE, Hosick PA, Utter AC, Quindry JC, McAnulty SR.

Source

a Department of Nutrition and Health Care Management, Appalachian State University, Boone, NC 28608, USA.

Abstract

Resveratrol and quercetin function as antioxidants and anti-inflammatories in vitro, but these mechanisms have been minimally examined in combination in exercising humans. The purpose of this investigation was to examine supplementation as a countermeasure against oxidative stress and inflammation in response to exercise. Fourteen athletes were randomly assigned, in a double-blind crossover design, to a resveratrol and quercetin combination (RQ) (120 mg resveratrol and 225 mg quercetin for 6 days and 240 mg resveratrol and 450 mg quercetin on day 7 just prior to exercise) or to placebo (P). There was a 1-week washout between trials. Blood was taken at baseline, pre-exercise, immediately after exercise, and 1 h after exercise. Plasma was analyzed for oxidative stress (F2-isoprostanes and protein carbonyls), antioxidant capacity (ferric-reducing ability of plasma (FRAP), Trolox equivalent antioxidant capacity (TEAC), oxygen radical absorptive capacity (ORAC)), and inflammation (cytokine interleukin (IL)-8 and C-reactive protein (CRP)).
Statistical design utilized a $\times 3$ ANOVA and Student's t test. Pre-exercise values were not different from baseline for any measure. The postexercise increase in F2-isoprostanes was significantly less ($p = 0.039$ interaction) with RQ (68%) than with P (137%). Protein carbonyls, FRAP, ORAC, and TEAC significantly increased after exercise but were not affected by treatment. IL-8 and CRP increased significantly immediately after exercise but were not affected by treatment. These data indicate that RQ significantly reduces exercise-induced lipid peroxidation without associated changes in inflammation or plasma antioxidant status.


**Resveratrol mitigates isoflurane-induced neuroapoptosis by inhibiting the activation of the Akt-regulated mitochondrial apoptotic signaling pathway.**

Bai T, Dong DS, Pei L.

**Source**

Department of Anaesthesiology, the First Hospital of China Medical University, Shenyang, Liaoning 110001, P.R. China.

**Abstract**

The inhalation anesthetic, isoflurane, induces learning and memory impairment. Mitochondrial dysfunction and oxidative stress are thought to play important roles in isoflurane-induced neuroapoptosis. In this study, we treated neuronal cells with isoflurane for 6 h. We found that isoflurane induced the opening of mitochondrial permeability transition pores, increased the levels of reactive oxygen species and the activation of caspase-3, and decreased the mitochondrial membrane potential and the intracellular calcium ion concentration. Resveratrol (RESV; trans-3,5,4'-trihydroxystilbene), a naturally occurring phytoalexin, is found at high concentrations in the skin of red grapes and red wine and has been demonstrated to have anti-infective, antioxidant and cardioprotective functions. Our findings demonstrated that the neuroprotective effects of RESV were independent on its direct radical scavenging properties. Following treatment of the cells with various concentrations of RESV, we found that RESV induced the expression of mitochondrial superoxide dismutase and catalase activity, and reduced mitochondrial oxidative stress and damage. The data from the present study demonstrate that RESV effectively protects neuronal cells from isoflurane-induced cytotoxicity by activating the Akt signaling pathway.


**Protective effect of resveratrol against endotoxemia-induced lung injury involves the reduction of oxidative/nitrative stress.**

Zhang HX, Duan GL, Wang CN, Zhang YQ, Zhu XY, Liu YJ.

**Source**

Department of Physiology, Second Military Medical University, 800 Xiangyan Road, Shanghai 200433, China; Department of Respiration, Kongjiang Hospital, Shanghai 200093, China.

**Abstract**

**BACKGROUND:**

Resveratrol, a natural plant polyphenol, has received increasing attention because its varied bioactivities, including the inhibition of tumorigenesis, lipid modification and calorie-restriction. We aimed to investigate the effect of resveratrol on oxidative/nitrative stress in endotoxemia-associated acute lung injury.
METHODS:

Mice were injected with lipopolysaccharide (LPS, 5 mg/kg, ip). Resveratrol at a dose of 0.3 mg/kg was administered alone or immediately before injection of LPS. Twenty four hours later, lung tissues were collected for histopathologic examination, and determination of malondialdehyde (MDA), H$_2$O$_2$, reduced/oxidized glutathione (GSH/GSSG) ratio, total antioxidant capacity (T-AOC), superoxide dismutase (SOD) activity, catalase (CAT) activity, inducible nitric oxide synthase (iNOS) expression, nitric oxide (NO) and peroxynitrite production.

RESULTS:

Resveratrol treatment improves histopathological changes in the lung during endotoxemia. Increased oxidative stress in endotoxemic lung was reversed by resveratrol treatment, as evidenced by the decreases of pro-oxidant biomarker (MDA and H$_2$O$_2$), and the increases of anti-oxidant biomarkers (GSH/GSSG ratio, T-AOC, CAT and SOD activity). Treatment with resveratrol inhibited endotoxemia-induced iNOS expression and NO production. Moreover, peroxynitrite formation in endotoxemic lung was significantly attenuated after resveratrol treatment.

CONCLUSIONS:

Resveratrol exerts protective effects against acute endotoxemia-associated lung injury. These beneficial effects may be due to both the anti-oxidant and anti-nitrative properties of resveratrol. These findings support the potential for resveratrol as a possible pharmacological agent to reduce acute lung injury resulting from oxidative/nitrative damage.

J Recept Signal Transduct Res. 2013 Aug 5. [Epub ahead of print]

Differential modulation of ROS signals and other mitochondrial parameters by the antioxidants MitoQ, resveratrol and curcumin in human adipocytes.


Source

Laboratory of Endocrinology, Department of Biomedicine, University Hospital and University Children's Hospital.

Abstract

Abstract Mitochondrial reactive oxygen species (ROS) have been demonstrated to play an important role as signaling and regulating molecules in human adipocytes. In order to evaluate the differential modulating roles of antioxidants, we treated human adipocytes differentiated from human bone marrow-derived mesenchymal stem cells with MitoQ, resveratrol and curcumin. The effects on ROS, viability, mitochondrial respiration and intracellular ATP levels were examined. MitoQ lowered both oxidizing and reducing ROS. Resveratrol decreased reducing and curcumin oxidizing radicals only. All three substances slightly decreased state III respiration immediately after addition. After 24 h of treatment, MitoQ inhibited both basal and uncoupled oxygen consumption, whereas curcumin and resveratrol had no effect. Intracellular ATP levels were not altered. This demonstrates that MitoQ, resveratrol and curcumin exert potent modulating effects on ROS signaling in human adipocyte with marginal effects on metabolic parameters.


Resveratrol Protects Against Functional Impairment and Cardiac Structural Protein Degradation Induced by Secondhand Smoke Exposure.
Arcand S, Sharma K, Al-Dissi AN, Cadete VJ, Sawicki G, Weber LP.

Abstract

BACKGROUND:

Secondhand smoke (SHS) impairs cardiac function and resveratrol is cardioprotective, possibly via antioxidant and anti-inflammatory capabilities. Previously, it was shown that resveratrol protects against SHS-induced cardiac dysfunction, but the molecular mechanism is not clear.

METHODS:

We measured cardiac function in pigs exposed to SHS alone in a first experiment or with and without resveratrol (5 mg/kg/day) in a second experiment using echocardiography and compared this with proteomic changes.

RESULTS:

In the first experiment after 28 days, end-diastolic volume, end-systolic volume, and stroke volume were all impaired in SHS pigs compared with control pigs, with cardiac output significantly depressed as early as 14 days. Depressed function corresponded to increased inflammation, oxidative stress, and matrix metalloproteinase-2, but decreased intact myosin light chain 1 in SHS compared with control pigs at 28 days. In our second study after 14 days, two-dimensional electrophoresis detected 6 significantly increased protein spots in SHS compared with control pigs. Mass spectrometry identified 4 spots as fragments of sarcomeric protein (1 myosin light chain 1, 1 β-myosin heavy chain, and 2 myosin-7), and 2 spots as glucose metabolism enzymes (lactate and pyruvate dehydrogenases). Resveratrol normalized the fragmented protein levels, but not the metabolic enzymes. At 14 days, matrix metalloproteinase-2 activity almost doubled in cardiac tissue from SHS compared with control pigs, and resveratrol appeared to normalize it.

CONCLUSIONS:

Thus, the ventricular differences in protein expression might explain the mechanism by which SHS reduces critical hemodynamic parameters through the degradation of sarcomeres, appearing to be prevented by resveratrol administration.


Resveratrol Blunts the Positive Effects of Exercise Training on Cardiovascular Health in Aged Men.

Gliemann L, Schmidt JF, Olesen J, Biensø RS, Peronard SL, Grandjean SU, Mortensen SP, Nyberg M, Bangsbo J, Pilegaard H, Hellsten Y.

Abstract

Aging is thought to be associated with decreased vascular function partly due to oxidative stress. Resveratrol is a polyphenol, which, in animal studies has been shown to decrease atherosclerosis, improve cardiovascular health and physical capacity, in part through its effects on Sirtuin 1 signaling and through an
improved antioxidant capacity. We tested the hypothesis that resveratrol supplementation enhances training-induced improvements in cardiovascular health parameters in aged men. Twenty-seven healthy physically inactive aged men (age: 65 ± 1 years; BMI: 25.4 ± 0.7 kg/m2; MAP: 95.8 ± 2.2 mmHg; maximal oxygen uptake: 2488 ± 72 ml O2 min-1) were randomized into 8 weeks of either daily intake of either 250 mg trans resveratrol (n = 14) or of placebo (n = 13) concomitant with high-intensity exercise training. Exercise training lead to a 45% greater (P < 0.05) increase in maximal oxygen uptake in the placebo group than in the resveratrol group and to a decrease in MAP in the placebo group only (-4.8 ± 1.7 mmHg; P < 0.05). The interstitial level of vasodilator prostacyclin was lower in the resveratrol than in the placebo group after training (980 ± 90 versus 1174 ± 121 pg ml-1; P < 0.02) and muscle TBX synthase was higher in the resveratrol group after training (P < 0.05). Resveratrol administration also abolished the positive effects of exercise on LDL, TC/HDL ratio and triglycerides concentrations in blood (P < 0.05). Resveratrol did not potentiate the effect of exercise training on atherosclerosis marker VCAM-1. Sirtuin 1 protein levels were not affected by resveratrol supplementation. These findings indicate that, whereas exercise training effectively improves several cardiovascular health parameters in aged men, concomitant resveratrol supplementation blunts most of these effects.


Antioxidant effects of resveratrol in cardiovascular, cerebral and metabolic diseases.


Source

Vascular Physiopathology Unit, IRCCS INM Neuromed, Pozzilli (IS), Italy.

Abstract

Resveratrol-a natural polyphenolic compound-was first discovered in the 1940s. Although initially used for cancer therapy, it has shown beneficial effects against most cardiovascular and cerebrovascular diseases. A large part of these effects are related to its antioxidant properties. Here we review: (a) the sources, the metabolism, and the bioavailability of resveratrol; (b) the ability of resveratrol to modulate redox signalling and to interact with multiple molecular targets of diverse intracellular pathways; (c) its protective effects against oxidative damage in cardio-cerebro-vascular districts and metabolic disorders such as diabetes; and (d) the evidence for its efficacy and toxicity in humans. The overall aim of this review is to discuss the frontiers in the field of resveratrol's mechanisms, bioactivity, biology, and healthrelated use.


Modulation of Endogenous Antioxidant Activity by Resveratrol and Exercise in Mouse Liver Is Age Dependent.

Tung BT, Rodríguez-Bies E, Ballesteros-Simarro M, Motilva V, Navas P, López-Lluch G.

Source

Centro Andaluz de Biología del Desarrollo, Universidad Pablo de Olavide, Carretera de Utrera Km. 1, 41013 Sevilla, Spain. glopllu@upo.es.

Abstract

Aging is a multifactorial process in which oxidative damage plays an important role. Resveratrol (RSV) and exercise delay some of the damages occurring during aging and increase life span and health span. We treated mice at different ages with RSV during 6 months and trained them during the last 6 weeks to determine if RSV and exercise induce changes in endogenous antioxidant activities in liver and if their effects depend on the age of the animal at the beginning of the intervention. Aging was accompanied by the
increase in oxidative damage in liver especially affecting the glutathione-dependent system. Both RSV and exercise reversed the effect of aging and maintained high activities of glutathione, glutathione peroxidase, and glutathione transferase activities in old animals. NAD(P)H:quinone acceptor oxidoreductase activity was also increased. Modulation of antioxidant activities was not completely accompanied by changes at the protein level. Whereas glutathione peroxidase 1 protein increased in parallel to the higher activity in old animals, NAD(P)H:quinone acceptor oxidoreductase protein decreased by RSV although the activity was enhanced. Our results indicate that RSV and exercise revert the effect of aging in liver of old animals maintaining higher antioxidant activities and decreasing oxidative damage. Short-term interventions are enough to produce beneficial effects of RSV or exercise at later ages.


**The role of polyphenols in the modulation of sirtuins and other pathways involved in Alzheimer's disease.**

Jayasena T, Poljak A, Smythe G, Braidy N, Münch G, Sachdev P.

**Source**

Centre for Healthy Brain Ageing (CHeBA), School of Psychiatry, University of New South Wales, Sydney, Australia.

**Abstract**

Alzheimer's disease (AD) is characterised by extracellular amyloid deposits, neurofibrillary tangles, synaptic loss, inflammation and extensive oxidative stress. Polyphenols, which include resveratrol, epigallocatechin gallate and curcumin, have gained considerable interest for their ability to reduce these hallmarks of disease and their potential to slow down cognitive decline. Although their antioxidant and free radical scavenging properties are well established, more recently polyphenols have been shown to produce other important effects including anti-amyloidogenic activity, cell signalling modulation, effects on telomere length and modulation of the sirtuin proteins. Brain accessible polyphenols with multiple effects on pathways involved in neurodegeneration and ageing may therefore prove efficacious in the treatment of age-related diseases such as AD, although the evidence for this so far is limited. This review aims to explore the known effects of polyphenols from various natural and synthetic sources on brain ageing and neurodegeneration, and to examine their multiple mechanisms of action, with an emphasis on the role that the sirtuin pathway may play and the implications this may have for the treatment of AD.


**Food, Nutrigenomics, and Neurodegeneration-Neuroprotection by What You Eat!**

Virmani A, Pinto L, Binienda Z, Ali S.

**Source**

Research, Innovation and Development, Sigma-tau SpA, Via Pontina km 30,400, 00040, Pomezia, Rome, Italy, ashraf.virmani@sigma-tau.it.

**Abstract**

Diet in human health is no longer simple nutrition, but in light of recent research, especially nutrigenomics, it is linked via evolution and genetics to cell health status capable of modulating apoptosis, detoxification, and appropriate gene response. Nutritional deficiency and disease especially lack of vitamins and minerals is well known, but more recently, epidemiological studies suggest a role of fruits and vegetables, as well as essential fatty acids and even red wine (French paradox), in protection against disease. In the early 1990s, various research groups started considering the use of antioxidants (e.g., melatonin, resveratrol, green tea, lipoic acid) and metabolic compounds (e.g., nicotinamide, acetyl-L-carnitine, creatine, coenzyme Q10) as
possible candidates in neuroprotection. They were of course considered on par with snake oil salesman (women) at the time. The positive actions of nutritional supplements, minerals, and plant extracts in disease prevention are now mainstream and commercial health claims being made are subject to regulation in most countries. Apart from efficacy and finding, the right dosages, the safety, and especially the level of purification and lack of contamination are all issues that are important as their use becomes widespread. From the mechanistic point of view, most of the time these substances replenish the body's deficiency and restore normal function. However, they also exert actions that are not sensu stricto nutritive and could be considered pharmacological especially that, at times, higher intake than recommended (RDA) is needed to see these effects. Free radicals and neuroinflammation processes underlie many neurodegenerative conditions, even Parkinson's disease and Alzheimer's disease. Curcumin, carotenoids, acetyl-L-carnitine, coenzyme Q₁₀, vitamin D, and polyphenols and other nutraceuticals have the potential to target multiple pathways in these conditions. In summary, augmenting neuroprotective pathways using diet and finding new natural substances that can be more efficacious, i.e., induction of health-promoting genes and reduction of the expression of disease-promoting genes, could be incorporated into neuroprotective strategies of the future.


Resveratrol induced neuroprotection is mediated via both estrogen receptor subtypes, ERα and ERβ.

Saleh MC, Connell BJ, Saleh TM.

Source

Department of Biomedical Sciences, Atlantic Veterinary College, University of Prince Edward Island, P.E.I., Charlottetown, C1A 4P3, Canada.

Abstract

Resveratrol, a dietary polyphenol with antioxidant and anti-inflammatory activity, has been shown to provide neuroprotection in models of ischemia. However, the mechanism of action of resveratrol-induced neuroprotection remains unclear. Previous work in our laboratory has provided evidence that acute, systemic administration of resveratrol is neuroprotective in a permanent model of cerebral ischemia, an effect that was blocked when animals received the non-selective estrogen receptor antagonist, ICI, 182,780. The present study was designed to investigate whether the source of neuroprotection afforded by resveratrol action within the cerebral cortex itself is mediated preferentially via selective activation of either α or β estrogen receptor subtype. Intracortical injection of resveratrol (0.1 and 1.0µM) 10min prior to 30min of ischemia followed by 5.5h of reperfusion significantly reduced infarct volume in the prefrontal cortex. This neuroprotective effect was significantly attenuated when resveratrol injection (1.0µM) was preceded by injection of a selective estrogen receptor α antagonist, 1,3-bis(4-hydroxyphenyl)-4-methyl-5-[4-(2-piperidinylethoxy)phenol]-1N-pyrazole dihydrochloride (MPP) or a selective estrogen receptor beta (ERβ) antagonist, 4-[2-phenyo-5,7-bis(trifluoromrthyl)pyrazolo(1,5-a)pyrimidin-3-yl]phenol (PHTPP). These results provide evidence for rapidly induced neuroprotection mediated by resveratrol activation of either estrogen receptor subtype within the ischemic cortex of rats.


[Advance of studies on effect of resveratrol on activity of cytochrome P450].

[Article in Chinese]

Lu Y, Huang ZJ, Yuan H.

Source

Third Hospital of Xiangya, Central South University, Changsha 410013, China. luyao0719@163.com
Abstract

Resveratrol is a natural antioxidant, with such effects of anti-tumor, anti-inflammation, and relief and prevention of cardiovascular disease. Studies on the effect of resveratrol on the activity of cytochrome P450 are of positive significance to combined clinical administration of resveratrol and other drugs. As there are many in vivo and in vitro experiments proving the effect of resveratrol on the activity of cytochrome P450 at present, the essay summarizes relevant studies in recent years.


Resveratrol, a natural chemopreventive agent against degenerative diseases.

Ignatowicz E, Baer-Dubowska W.

Source

Department of Pharmaceutical Biochemistry, Karol Marcinkowski University of Medical Sciences, Poznań, Poland.

Abstract

Resveratrol (3,5,4'-trihydroxystilbene) is a naturally occurring compound shown to modulate the risk of cardiovascular degenerative diseases (atherosclerosis) and inhibit chemical carcinogenesis in rodents. Various studies have demonstrated the effect of this phytoalexin on biological mechanisms involved in cardioprotection. These include modulation of lipid turnover, inhibition of eicosanoid production, prevention of the low-density lipoprotein oxidation and inhibition of platelet aggregation. Carcinogenesis in animal models can be divided at least into three stages: initiation, promotion and progression. Initiation occurs as result of interaction of a reactive form of carcinogen with DNA. Chemical carcinogens like polycyclic aromatic hydrocarbons are metabolized to reactive species by cytochrome P450 dependent enzymes activated through aryl hydrocarbon (Ah) receptor. The inhibition of tumor initiation by resveratrol most probably occurs through preventing the activation of Ah receptor. Resveratrol affects also several factors involved in tumor promotion and progression. Since tumor promoting agents alter the expression of genes whose products are associated with inflammation, chemoprevention of cardiovascular diseases and cancer may share the same common mechanisms. This includes principally modulation of the expression of growth factors and cytokines. Recently, chemopreventive properties of resveratrol have been associated with the inhibition of NF-kappaB. This transcription factor is strongly linked to inflammatory and immune responses, regulation of cell proliferation and apoptosis, thus it is important for tumor development and many other diseases including atherosclerosis. Although the mechanisms by which resveratrol interferes with the activation of NF-KB are not clear, it seems that inhibition of its degradation which is necessary for its cellular activation is the principal target. Based on the quantity and diversity of data available on the biological activity of resveratrol, it has to be considered a very promising chemoprotector and chemotherapeutic. Urgent investigations on its bioavailability and effects on in vivo systems, especially in humans, are necessary.


Role of resveratrol in prevention and therapy of cancer: preclinical and clinical studies.

Aggarwal BB, Bhardwaj A, Aggarwal RS, Seeram NP, Shishodia S, Takada Y.

Source

Cytokine Research Laboratory, Department of Bioimmunotherapy, The University of Texas M. D. Anderson Cancer Center, Box 143, 1515 Holcombe Boulevard, Houston, Texas 77030, USA. aggarwal@mdanderson.org

Abstract
Resveratrol, trans-3,5,4′-trihydroxy stilbene, was first isolated in 1940 as a constituent of the roots of white hellebore (Veratrum grandiflorum O. Loes), but has since been found in various plants, including grapes, berries and peanuts. Besides cardioprotective effects, resveratrol exhibits anticancer properties, as suggested by its ability to suppress proliferation of a wide variety of tumor cells, including lymphoid and myeloid cancers; multiple myeloma; cancers of the breast, prostate, stomach, colon, pancreas, and thyroid; melanoma; head and neck squamous cell carcinoma; ovarian carcinoma; and cervical carcinoma. The growth-inhibitory effects of resveratrol are mediated through cell-cycle arrest; upregulation of p21Cip1/WAF1, p53 and Bax; down-regulation of survivin, cyclin D1, cyclin E, Bcl-2, Bcl-xL and cIAPs; and activation of caspases. Resveratrol has been shown to suppress the activation of several transcription factors, including NF-kappaB, AP-1 and Egr-1; to inhibit protein kinases including IkappaBalpha kinase, JNK, MAPK, Akt, PKC, PKD and casein kinase II; and to down-regulate products of genes such as COX-2, 5-LOX, VEGF, IL-1, IL-6, IL-8, AR and PSA. These activities account for the suppression of angiogenesis by this stilbene. Resveratrol also has been shown to potentiate the apoptotic effects of cytokines (e.g., TRAIL), chemotherapeutic agents and gamma-radiation. Pharmacokinetic studies revealed that the target organs of resveratrol are liver and kidney, where it is concentrated after absorption and is mainly converted to a sulfated form and a glucuronide conjugate. In vivo, resveratrol blocks the multistep process of carcinogenesis at various stages: it blocks carcinogen activation by inhibiting aryl hydrocarbon-induced CYP1A1 expression and activity, and suppresses tumor initiation, promotion and progression. Besides chemopreventive effects, resveratrol appears to exhibit therapeutic effects against cancer. Limited data in humans have revealed that resveratrol is pharmacologically quite safe. Currently, structural analogues of resveratrol with improved bioavailability are being pursued as potential therapeutic agents for cancer.

Influence of glucuronidation and reduction modifications of resveratrol on its biological activities.


**Source**

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, 222 Tianshui Street S., Lanzhou 730000, China.

**Abstract**

Resveratrol (3,5,4′-trihydroxystilbene, RES), a star among dietary polyphenols, shows a wide range of biological activities, but it is rapidly and extensively metabolized into its glucuronide and sulfate conjugates as well as to the corresponding reduced products. This begs the question of whether the metabolites of RES contribute to its in vivo biological activity. To explore this possibility, we synthesized its glucuronidation (3-GR and 4′-GR) and reduction (DHR) metabolites, and evaluated the effect of these structure modifications on biological activities, including binding ability with human serum albumin (HSA), antioxidant activity in homogeneous solutions and heterogeneous media, anti-inflammatory activity, and cytotoxicity against various cancer cell lines. We found that 1) 4′-GR, DHR and RES show nearly equal binding to HSA, mainly through hydrogen bonding, whereas 3-GR adopts a quite different orientation mode upon binding, thereby resulting in reduced ability; 2) 3-GR shows comparable (even equal) ability to RES in FRAP- and AAPH-induced DNA strand breakage assays; DHR, 3-GR, and 4′-GR exhibit anti-hemolysis activity comparable to that of RES; additionally, 3-GR and DHR retain some degree activity of the parent molecule in DPPH-scavenging and cupric ion-initiated oxidation of LDL assays, respectively; 3) compared to RES, 4′-GR displays equipotent ability in the inhibition of COX-2, and DHR presents comparable activity in inhibiting NO production and growth of SMMC-7721 cells. Relative to RES, its glucuronidation and reduction metabolites showed equal, comparable, or some degree of activity in the above assays, depending on the specific compound and test model, which probably supports their roles in contributing to the in vivo biological activities of the parent molecule.

**J Bone Miner Metab.** 2013 May 19. [Epub ahead of print]

Resveratrol supplementation preserves long bone mass, microstructure, and strength in hindlimb-suspended old male rats.
Durbin SM, Jackson JR, Ryan MJ, Gigliotti JC, Alway SE, Tou JC.

Abstract

Resveratrol has gained popularity as an "anti-aging" compound due to its antioxidant and anti-inflammatory properties. Few studies have investigated the role of resveratrol supplementation in the prevention of age-related bone loss and skeletal disuse despite increased inactivity and age-related bone loss in the elderly. The objective of the study was to investigate the effect of resveratrol supplementation on disuse and age-related bone loss. Old (age 33 months) Fischer 344 × Brown Norway male rats were provided either trans-resveratrol (12.5 mg/kg bw/day) or deionized distilled water by oral gavage for 21 days. Rats were hindlimb-suspended (HLS) or kept ambulatory (AMB) for 14 days. Both femora and tibiae were collected. Bone mass was measured by dual-energy X-ray absorptiometry and bone microstructure was determined by micro-computed tomography. HLS of old male rats accelerated loss of bone mineral content, decreased trabecular bone volume per unit of total volume, and increased trabecular separation. Resveratrol supplementation ameliorated bone demineralization and loss of bone microarchitecture in HLS old male rats. The peak force measured by the three-point bending test was reduced (P = 0.007) in HLS/control compared to AMB/control rats. Resveratrol supplementation ameliorated HLS-induced loss of femur strength. Plasma osteocalcin and alkaline phosphatase was higher (P < 0.04) and C-reactive protein was lower (P = 0.04) in old male rats given resveratrol. The bone protective effects of resveratrol appeared to be mediated through increased osteoblast bone formation, possibly due to reduced inflammation. Based on the results, resveratrol supplementation appeared to provide a feasible dietary therapy for preserving the skeletal system during disuse and age-related bone loss.

Santos JA, de Carvaho GS, Oliveira V, Raposo NR, da Silva AD.

Abstract

Resveratrol has been extensively researched for its powerful antioxidant capacity and other biological effects. The number of patents involving this compound has been growing in recent years. However, the biggest problem associated with this molecule, a limited bioavailability due to its fast metabolism in the liver, has led to obtaining its analogues or derivatives. In this work, we selected patents which describe the application of the antioxidant activity of resveratrol and its analogues as food for the human segment.

Barger JL.
Adipose tissue is an active endocrine organ that responds to changes in energy balance and influences whole-body physiology. Adipose tissue dysfunction with obesity is associated with metabolic disease, neurodegeneration, inflammation, and cancer, whereas calorie restriction (CR) decreases both adiposity and disease risk. Although resveratrol does not affect obesity, it mimics long-term CR by increasing both life span in model organisms and health span in rodents. Because resveratrol's benefits in experimental animals are reminiscent of improved adipose tissue function under CR, this review synthesizes existing data to assess if resveratrol's effects may be mediated by mimicking CR in adipose tissue. In metabolically unhealthy humans, resveratrol consumption recapitulates the health benefits of CR, whereas short-term resveratrol in otherwise healthy humans mimics CR at the transcriptional, but not physiological, level. This latter observation (neutral effect of short-term resveratrol) may be protective against future disease risk; however, long-term studies in healthy humans will be needed to support this hypothesis.

**Metabolic benefits of inhibiting cAMP-PDEs with resveratrol.**

Chung JH.

Laboratory of Obesity and Aging Research; Genetics and Developmental Biology Center; National Heart Lung and Blood Institute; National Institutes of Health; Bethesda, MD USA.

**Abstract**

Calorie restriction (CR) extends lifespan in species ranging from yeast to mammals. There is evidence that CR also protects against aging-related diseases in non-human primates. This has led to an intense interest in the development of CR-mimetics to harness the beneficial effects of CR to treat aging-related diseases. One CR-mimetic that has received a great deal of attention is resveratrol. Resveratrol extends the lifespan of obese mice and protects against obesity-related diseases such as type 2 diabetes. The specific mechanism of resveratrol action has been difficult to elucidate because resveratrol has a promiscuous target profile. A recent finding indicates that the metabolic effects of resveratrol may result from competitive inhibition of cAMP-degrading phosphodiesterases (PDEs), which increases cAMP levels. The cAMP-dependent pathways activate AMP-activated protein kinase (AMPK), which is essential for the metabolic effects of resveratrol. Inhibiting PDE4 with rolipram reproduces all of the metabolic benefits of resveratrol, including protection against diet-induced obesity and an increase in mitochondrial function, physical stamina and glucose tolerance in mice. This discovery suggests that PDE inhibitors may be useful for treating metabolic diseases associated with aging.

**Evidence for circulatory benefits of resveratrol in humans.**

Wong RH, Coates AM, Buckley JD, Howe PR.

Nutritional Physiology Research Centre, Sansom Institute for Health Research, University of South Australia, Adelaide, Australia.

**Abstract**
Impairments of endothelial function, which can be assessed noninvasively by flow-mediated dilation (FMD) of the brachial artery, contribute to the development of cardiovascular disease. Associations between FMD and cognition suggest a vascular component in the loss of cognitive function. Certain vasoactive nutrients that have been shown to improve FMD may also have the potential to enhance cerebral perfusion and cognition. Preclinical studies show that trans-resveratrol can enhance nitric oxide bioavailability, thereby increasing endothelium-dependent vasodilation. We have now shown that acute administration of resveratrol elicits dose-dependent increases of FMD with greater potency than other vasoactive nutrients and that this benefit is sustained following regular consumption. We describe the potential implications of this vasodilator benefit of resveratrol and its role in enhancing cerebrovascular and cognitive functions.

**J Hypertens.** 2013 Jun 5. [Epub ahead of print]

**Chronic resveratrol consumption improves brachial flow-mediated dilatation in healthy obese adults.**

Wong RH, Berry NM, Coates AM, Buckley JD, Bryan J, Kunz I, Howe PR.

**Source**

aNutritional Physiology Research Centre, Sansom Institute for Health Research bSchool of Psychology, Social Work and Social Policy, University of South Australia, Adelaide, South Australia, Australia cR&D Human Nutrition and Health, DSM Nutritional Products Ltd, Kaiseraugst, Switzerland dClinical Nutrition Research Centre, University of Newcastle, Callaghan, New South Wales, Australia.

**Abstract**

BACKGROUND:: We have previously demonstrated acute dose-dependent increases of flow-mediated dilatation (FMD) in the brachial artery after resveratrol consumption in mildly hypertensive, overweight/obese adults. Resveratrol supplementation has also been shown to increase cerebral blood flow acutely, without affecting cognition. OBJECTIVES:: To evaluate the effects of chronic resveratrol supplementation on both FMD and cognitive performance. METHOD:: Twenty-eight obese but otherwise healthy adults (BMI: 33.3±0.6kg/m) were randomized to take a single 75mg capsule of trans-resveratrol (Resvida) or placebo daily for 6 weeks each in a double-blind crossover supplementation trial. Blood pressure, arterial compliance, FMD, and performance on the Stroop Color-Word Test were assessed at the end of each 6-week intervention period while fasted and at least 18h after taking the last daily capsule. An additional capsule of the same supplement was then taken. FMD assessment was repeated 1h later. RESULTS:: Chronic resveratrol supplementation for 6 weeks was well tolerated and resulted in a 23% increase in FMD compared with placebo (P=0.021, paired t-test). The extent of increase correlated negatively with baseline FMD (r=-0.47, P=0.01). A single dose of resveratrol (75mg) following chronic resveratrol supplementation resulted in a 35% greater acute FMD response than the equivalent placebo supplementation. These FMD improvements remained significant after adjusting for baseline FMD. Blood pressure, arterial compliance, and all components of the Stroop Color-Word Test were unaffected by chronic resveratrol supplementation. CONCLUSION:: Daily resveratrol consumption was well tolerated and has the potential to maintain healthy circulatory function in obese adults.


**Effects of resveratrol on cerebral blood flow variables and cognitive performance in humans: a double-blind, placebo-controlled, crossover investigation.**

Kennedy DO, Wightman EL, Reay JL, Lietz G, Okello EJ, Wilde A, Haskell CF.

**Source**
Abstract

BACKGROUND:

The many putative beneficial effects of the polyphenol resveratrol include an ability to bolster endogenous antioxidant defenses, modulate nitric oxide synthesis, and promote vasodilation, which thereby improves blood flow. Resveratrol may therefore modulate aspects of brain function in humans.

OBJECTIVE:

The current study assessed the effects of oral resveratrol on cognitive performance and localized cerebral blood flow variables in healthy human adults.

DESIGN:

In this randomized, double-blind, placebo-controlled, crossover study, 22 healthy adults received placebo and 2 doses (250 and 500 mg) of trans-resveratrol in counterbalanced order on separate days. After a 45-min resting absorption period, the participants performed a selection of cognitive tasks that activate the frontal cortex for an additional 36 min. Cerebral blood flow and hemodynamics, as indexed by concentration changes in oxygenated and deoxygenated hemoglobin, were assessed in the frontal cortex throughout the posttreatment period with the use of near-infrared spectroscopy. The presence of resveratrol and its conjugates in plasma was confirmed by HPLC after the same doses in a separate cohort (n = 9).

RESULTS:

Resveratrol administration resulted in dose-dependent increases in cerebral blood flow during task performance, as indexed by total concentrations of hemoglobin. There was also an increase in deoxyhemoglobin after both doses of resveratrol, which suggested enhanced oxygen extraction, that became apparent toward the end of the 45-min absorption phase and was sustained throughout task performance. Cognitive function was not affected. Resveratrol metabolites were present in plasma throughout the cognitive task period.

CONCLUSION:

These results showed that single doses of orally administered resveratrol can modulate cerebral blood flow variables.