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EFFECTS OF RESVERATROL SUPPLEMENTATION ON CARDIOVASCULAR RISK FACTORS

EFEITOS DA SUPLEMENTAÇÃO DE RESVERATROL SOBRE FATORES DE RISCO CARDIOVASCULAR

Gabriela Vatavuk-Serrati[1]
Renata Torres Alves[1]
Edna Silva Costa[2]
Adriana Garcia Peloggia de Castro[1]
Valéria Arruda Machado[2]

1. Centro Universitário São Camilo, São Paulo, SP, Brazil
2. Universidade Federal de São Paulo, São Paulo, SP, Brazil

Correspondência:
Gabriela Vatavuk-Serrati.
Rua Padre Manoel de Paiva, 401 – Santo André, SP, Brazil.
gabrielavserrati@gmail.com

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ABSTRACT

Resveratrol, or 3,4,5-trihydroxystilbene, is a polyphenol found mainly in grapes, red wine, peanuts, dark chocolate and some berries. Several studies have investigated the impact of resveratrol on cardiovascular diseases, cancer, neurodegenerative diseases, diabetes and hyperglycemia, as well as its potential effects on longevity. However, the results are still inconclusive, especially regarding the necessary dosage, which is unlikely to be achieved through diet alone. Therefore, we have reviewed the recent literature on resveratrol supplementation in humans and its effects on risk factors for the development of cardiovascular diseases. We included fifteen studies that evaluated the endothelial function, glycemic profile, inflammatory profile, lipoproteins, and the safety of its consumption by the elderly. Resveratrol supplementation was proven to be safe for use in the elderly and mainly benefits endothelial function in different populations, also having a positive effect on the glycemic profile of patients with insulin resistance and inflammation. A significant reduction in the intestinal and hepatic production of lipoproteins Apo B-48 and Apo B-100 was also observed. Due to all these aspects, supplementation with resveratrol could play a protective role in the development of cardiovascular diseases.

Keywords: Polyphenols; Dietary Supplementation; Cardiovascular Diseases.

RESUMO

O resveratrol, ou 3,5,4-triidroxiestilbeno, é um polifenol encontrado principalmente em uvas, vinho tinto, amendoins, chocolate amargo e algumas frutas silvestres. Diversos estudos investigaram sua ação sobre doenças cardiovasculares, câncer, doenças neurodegenerativas, diabetes, hiperglicemia, bem como seus possíveis efeitos sobre a longevidade. No entanto, os resultados ainda são inconclusivos, principalmente no que se refere à dose necessária, que dificilmente é atingida só com a alimentação. Portanto, foi feita uma revisão da literatura recente quanto à suplementação de resveratrol em seres humanos e seus efeitos sobre os fatores de risco para desenvolvimento de doenças cardiovasculares. Foram incluídos 15 estudos que avaliaram a função endotelial, o perfil glicêmico, o perfil inflamatório, lipoproteínas, bem como a segurança do consumo por idosos. A suplementação de resveratrol mostrou-se segura em idosos e benéfica principalmente para a função endotelial em diferentes populações, tendo efeito positivo também sobre o perfil glicêmico de pacientes com resistência à insulina e inflamação. Além disso, verificou-se redução significativa da produção intestinal e hepática das lipoproteínas Apo B-48 e Apo B-100. Devido a todos esses aspectos, a suplementação com resveratrol pode exercer papel protetor contra o desenvolvimento de doenças cardiovasculares.

Descritores: *Polifenóis; Suplementação Nutricional; Doenças Cardiovasculares.*

INTRODUCTION

Polyphenols, chemical compounds that contain more than one hydroxyl group in an aromatic ring, can be found in fruits, vegetables, oilseeds, grains, tea, and coffee, and are known for their antioxidant properties.[1-3] They are classified into several groups, based on their structure; the main groups are flavonoids, phenolic acids, stilbenes, and lignans.

Resveratrol, or 3,5,4-trihydroxystilbene, is a polyphenol found mainly in grapes, red wine, peanuts, dark chocolate, and wild berries.[4,5] Food sources and supplements contain both cis and trans isomers of resveratrol; the trans isomer is the most common.[6,7] It was first identified in 1940 in white hellebore roots,[8] and later in 1963, in roots used in Chinese and Japanese medicine for the treatment of diseases related

to the liver, skin, heart, circulation, and lipid metabolism.[9] In 1976, resveratrol was synthesized in grape leaves after fungal infection and exposure to ultraviolet rays.[10] However, the number of studies on resveratrol increased greatly after the so-called "French paradox", when researchers observed a low incidence of cardiovascular diseases among the French population, despite a diet high in cholesterol and saturated fats.[11] This effect was attributed to the frequent consumption of red wine.[12] In 1992, Siemann and Creasy suggested that the cardioprotective effect of red wine was due to resveratrol.[13]

According to the World Health Organization (WHO), chronic non-communicable diseases (NCDs) accounted for 39.5 million deaths worldwide in 2015, which represent 70% of the total deaths. Cardiovascular diseases (CVD) were the main cause of NCD-related deaths (45%), followed by neoplasms (22%), chronic respiratory diseases (10.7%), and diabetes mellitus (DM) (4%).[14]

This trend has also been observed in Brazil. In 2010, NCDs accounted for 73.9% of deaths in the country; 31.3% were due to CVD, 16.7% due to neoplasms, 6.0% due to chronic respiratory diseases, and 5.3% due to DM.[15]

Data from the National Health Survey (*Pesquisa Nacional de Saúde*; PNS) conducted in 2013 indicate that approximately 66 million people (45.1% of the Brazilian population) were diagnosed with at least one NCD; moreover, the prevalence was higher among women (50.4%).[16]

Factors such as hypertension, hypercholesterolemia, hyperglycemia, obesity, smoking, a sedentary lifestyle, and a diet low in nutrients and high in saturated fats and refined carbohydrates are considered risk factors for the development of CVD.[17] However, there is evidence that aging also plays a role in the development of these diseases, even in individuals who do not present with these risk factors.[18] Aging results in a slow and progressive degeneration of health, with the impairment of cardiac function[19] in addition to the stiffening and thickening of the blood vessels, which are associated with endothelial dysfunction.[20] Evidence shows that aging leads to an increase in the production of reactive oxygen species (ROS) in the heart and the vascular system.[21,22] It is known that oxidative stress causes a decrease in nitric oxide (NO) synthesis, which is essential for endothelium-dependent dilatation and, consequently, for the prevention of thrombosis and platelet aggregation that are characteristic of atherosclerosis.[23,24]

Moreover, several animal models and *in vitro* studies have shown the protective effects of resveratrol against cancer, neurodegenerative diseases, DM, hyperglycemia, as well as the possible effects on longevity.[25] However, studies on resveratrol in humans have reported inconclusive results, mainly due to difficulties related to bioavailability. Resveratrol is metabolized rapidly and is degraded on exposure to light and air.[25] For example, grapes are estimated to contain 0.16–3.54 μg resveratrol per gram, and dry peels contain approximately 24 μg/g.[26] However, peels are not usually chewed, which impairs the release of resveratrol. Leifer and Barberio proposed that the leaves and fruit should be ingested directly from the vine and that the grape peels should be chewed slowly, thereby increasing the bioavailability by up to 100-fold.[25]

Red wine contains more polyphenols than white wine, with up to six times more resveratrol and a concentration of up to 14.3 mg/L.[26] Supplementation with a low dose of resveratrol (8 mg/day for 1 year) is considered sufficient to significantly reduce cardiovascular risk.[27] However, this concentration cannot be reached by dietary means, as it would require the daily consumption of 1–3 L wine, depending on the type.

Furthermore, no conclusive data are available on the toxicity of resveratrol. Some studies have indicated that it is safe to consume up to 5 g resveratrol per day,[28] but other studies claim that a dose of 450 mg/day would be safe for a person weighing 60 kg[29] and that supplementation with a higher dose could be toxic. In addition, studies have shown dose-independent adverse effects, such as nephrotoxicity and gastrointestinal tract problems.[30,31]

Owing to the divergence of the applicability of resveratrol to clinical practice and potential health benefits and/or harms, the evidence obtained from recent human studies is extremely important. Therefore, we have conducted a review of the relationship between the consumption of resveratrol and the risk factors for the development of cardiovascular diseases.

OBJECTIVE

To describe and discuss the relationships between the consumption of resveratrol and the risk factors for cardiovascular diseases that are presented in the literature.

METHODS

A narrative review was performed to search for articles in the MEDLINE, LILACS, JAMA, SciELO, and Scopus databases using the following keywords: resveratrol, cardiovascular, heart, and disease, using the Boolean operators "AND" and "OR". The data were collected between April and May 2018, with priority given to articles published within the past 10 years. Articles considered relevant by related literature reviews and meta-analyses were also included.

RESULTS AND DISCUSSION

Fifteen original studies that investigated the effects of resveratrol supplementation in humans were included. The studies were conducted in 12 different countries in North America, Europe, Asia and Oceania.

Seven studies assessed endothelial function,[32-38] five analyzed the glycemic profile,[31,39-42] four studied the inflammatory profile,[27,43-45] one analyzed lipoproteins,[46] and one investigated the safety of resveratrol consumption in elderly patients.[47]

A summary of the studies included in this review is presented in Table 1.

Supplementation with resveratrol is apparently beneficial in improving the glycemic profile of individuals with glucose metabolic dysfunction,[39,41,42] but not that of healthy subjects[31]. In addition, a study of patients with DM did not show significant improvement.[40] One of the possible explanations could be that a hypoglycemic individual is already undergoing treatment and, thus, supplementation with resveratrol has no additional benefits; moreover, the dose used in this study was lower than that used in other studies.

Studies that assessed inflammation suggest that resveratrol exerted anti-inflammatory effects at doses of 150 mg/day in healthy individuals and patients with hypercholesterolemia[44,45] and at 500 mg/day in smokers.[43] An anti-inflammatory effect

Table 1. Summary of the studies included in the review by observed outcome.

Ref.	Author	Year	Country	Type of study	Population	n	Dose	Duration	Result
32	Fujitaka et al.	2011	Japan	Double-blind randomized crossover	Patients with metabolic syndrome	34	100 mg/day	3 months	Improvement of endothelial function, without significant changes in BP, IR, lipid profile, and inflammatory markers
33	Wong et al.	2011	Australia	Double-blind randomized crossover	Men and postmenopausal women with untreated borderline BP	19	Placebo, 30 mg/day, 90 mg/day, and 270 mg/day	1 intervention per week for a total of 4 weeks	Significant dose--dependent effect of resveratrol on flow--mediated dilatation of the brachial artery
34	Magyar et al.	2012	Hungary	Double-blind placebo-controlled	Post-infarction Caucasian patients	40	10 mg/day	3 months	Significant improvement in left ventricular diastolic function, endothelial function, and LDL-cholesterol levels
35	Wong et al.	2013	Australia	Double-blind, randomized, crossover controlled	Healthy obese men and obese postmenopausal women	28	75 mg/day	6 weeks	↑ flow-mediated dilatation without changes in arterial compliance and BP
36	Chekalina et al.	2016	Ukraine	Controlled clinical trial	Patients with CAD: stable angina pectoris	93	Basic therapy with beta blockers, statins, and aspirin (control) + 100 mg/day of resveratrol or 3g/day of quercetin	2 months	All groups showed a ↓ in total and LDL cholesterol, without significant differences between them; in the resveratrol group there was a ↓ of systemic inflammation and improvement of endothelial function
37	Imamura et al.	2017	Japan	Double-blind randomized controlled	Patients with DM2	50	100 mg/day	12 weeks	Improvement of the ankle-brachial index, arterial stiffness, and oxidative stress
38	Marques et al.	2017	Brazil	Double-blind randomized crossover	Patients with hypertension	24	Acute dose of 300 mg of resveratrol or placebo, with 1 week washout period, and a crossover	2 days of intervention, 1-week interval between them	Improved endothelial function, more pronounced in women and individuals with high LDL-c
39	Crandall et al.	2012	USA	Randomized controlled	Elderly overweight or obese patients with IR	10	1 g/day, 1.5 g/day, and 2 g/day	4 weeks	No changes in weight, blood pressure, and lipids, decreased IR
40	Kumar and Joghee	2013	India	Randomized controlled	Patients with DM2	57	Metformin and/or glibenclamide (control) + 250 mg/day	6 months	In the intervention group, there was significant ↓ in body weight, BMI, systolic blood pressure, inflammatory profile, total cholesterol, TG and total protein, and a non-significant ↓ in glycemia and glycated hemoglobin
41	Movahed et al.	2013	Iran	Double-blind randomized	Patients with DM 2	66	1 g/day	45 days	A significant ↓ in BP, fasting glycemia, glycated hemoglobin, insulin, and IR, and a significant ↑ in HDL
31	Poulsen et al.	2013	Denmark	Double-blind randomized controlled	Patients with obesity	24	500 mg 3×/day	4 weeks	No significant changes in blood pressure, body composition, glycemic, lipid and inflammatory profile

Table 1. Summary of the studies included in the review by observed outcome.

Ref.	Author	Year	Country	Type of study	Population	n	Dose	Duration	Result
42	Khodabandehloo et al.	2018	Iran	Double blind randomized	Patients with DM2	45	2× 400 mg/ day	8 weeks	A significant ↓ in fasting glycemia and BP
43	Bo et al.	2013	Italy	Double-blind randomized crossover controlled	Healthy adult smokers	50	500 mg/day	90 days	↓ TG and ↑ anti-inflammatory and antioxidant response
27	Carneiro et al.	2013	Spain	Triple-blind randomized controlled	Men with hypertension and DM2 with angina pectoris or acute coronary syndrome stable for at least 6 months	35	1 capsule of 350 mg/day of grape extract (GE) or GE+8 mg of resveratrol (GE-RES) or maltodextrin (control) for 6 months, and 2 capsules/day for 6 months	1 year	GE and GE-RES supplementation did not affect body weight, BP, and glycemic profile compared with standard drugs, but there was a significant ↓ in alkaline phosphatase and inflammatory profile in the GE-RES group.
44	Apostolidou et al.	2016	Greece	Randomized controlled crossover	Patients with normal or asymptomatic hypercholesterolemia	33	150 mg/day for 30 days, 30 days, washout, and placebo for 30 days	90 days	In patients with cholesterol at normal levels, resveratrol had an antioxidant effect, whereas in patients with hypercholesterolemia, resveratrol ↑ vitamin E and ↓ the risk of CVD
45	Seyyedebrahimi et al.	2018	Iran	Double-blind randomized	Patients with DM2	48	800 mg/day	Two months	Significant improvement of the anti-inflammatory profile, significant ↓ BP and non-significant decrease in fasting glycemia
46	Dash et al.	2013	Canada	Double-blind randomized crossover	Overweight or obese individuals with mild hypertriglyceridemia	8	1 g/day in the first week and 2 g/day in the second week	Two weeks	↓ Intestinal and hepatic production of Apo B48 and Apo B100 lipoproteins, without changes in TG and IR
47	Anton et al.	2014	USA	Double-blind randomized controlled	Overweight elderly	32	Placebo, 300 mg/day, and 1000 mg/day	12 weeks	Significant ↓ in glycemia in the control groups, unrelated to serum markers; good tolerance

IR = insulin resistance; BP = blood pressure; TG = triglycerides; CVD = cardiovascular disease; CAD = coronary artery disease; DM = diabetes mellitus; BMI = body mass Index.

was also observed in a study that used a low daily dose (8 mg) of resveratrol combined with 350 mg of grape extract, possibly due to the synergistic effect between different polyphenols.[27]

In overweight or obese individuals with mild hypertriglyceridemia, resveratrol supplementation resulted in lower intestinal and hepatic production of Apo B-48 and Apo B-100 lipoproteins[46], which are considered independent risk factors for coronary artery diseases[48].

With regard to endothelial function, several studies indicate that doses between 10 and 100 mg/day were sufficient to confer positive effects in patients with metabolic syndrome,[32] untreated borderline blood pressure,[33] obese men and obese postmenopausal women,[35] post-infarction Caucasians,[34] stable angina pectoris,[36] and DM.[37] A study that analyzed the acute supplementation of 300 mg resveratrol showed that there was a more pronounced response in women, suggesting that there were sex differences in the response to resveratrol, and in patients with high LDL cholesterol, possibly owing to their increased production of ROS, and, subsequently, increased endothelial impairment.[38]

The vascular wall has several enzyme systems that produce reactive oxygen species (ROS), including NADPH oxidase, xanthine oxidase, mitochondrial respiratory chain enzymes, and dysfunction in endothelial nitric oxide synthase (eNOS). In physiological conditions, eNOS produces nitric oxide, which has a vasoprotective function on the endothelium. However, under pathological conditions, this enzyme can become dysfunctional, producing ROS. Resveratrol is a polyphenol and, thus, sequesters a series of oxidants, such as hydroxyl radicals, hydrogen peroxide, and peroxynitrite.[49]

In elderly individuals, who are more susceptible to the development of cardiovascular diseases, no positive relationship was found between resveratrol levels induced by a Western diet and protection against all-cause mortality in a cohort study conducted over 9 years.[50] Although no benefits were observed, a study that administered supplements to elderly individuals for 12 weeks showed no deleterious effects on serum markers or side effects, characterizing it as a safe supplement for this population.[47]

A major limitation of this work was the scarcity of research assessing cardiovascular risk factors in humans, mainly from 2014 onwards. Most studies were reviews, described animal models or *in vitro* cell studies, or analyzed the effects of resveratrol on diseases, especially cancer. In addition, the studies included in this review show wide variations in both the dose and the duration of the interventions, which makes it difficult to achieve an accurate comparisons of results; thus, it is impossible to reach a consensus on the applicability of resveratrol in clinical practice. However, this also occurs with other bioactive compounds.[51]

According to the study of Tomé-Carneiro et al., it is difficult to conduct larger or multicentric studies on resveratrol supplementation in humans due to the lack of funding, mainly by the pharmaceutical industry: as resveratrol is not a patented molecule, clinical trials are only conducted using analogous compounds or patented formulations.[52]

CONCLUSION

Resveratrol supplementation was shown to be safe for elderly individuals and mainly has beneficial endothelial function in different populations. Additionally, it had a positive effect on the glycemic profile of patients with insulin resistance and inflammation. Moreover, it caused a significant reduction in the intestinal and hepatic production of lipoproteins.

These reports show that resveratrol supplementation may have a protective role in the development of cardiovascular diseases.

However, further studies are required to fully elucidate the mechanisms through which resveratrol can be beneficial in disease prevention as well as the doses required to safely achieve these positive effects.

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CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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