EFFECTS OF RESVERATROL SUPPLEMENTATION ON CARDIOVASCULAR RISK FACTORS

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.

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. They are classified into several groups, based on their structure; the main groups are flavonoids, phenolic acids, stilbenes, and lignans.

Resveratrol, or 3,4,5-trihydroxystilbene, is a polyphenol found mainly in grapes, red wine, peanuts, dark chocolate, and wild berries. Food sources and supplements contain both cis and trans isomers of resveratrol; the trans isomer is the most common. It was first identified in 1940 in white hellebore roots, 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. 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. This effect was attributed to the frequent consumption of red wine. In 1992, Siemian and Creasy suggested that the cardioprotective effect of red wine was due to resveratrol.

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%).

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.

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 (59.4%).

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. 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. Aging results in a slow and progressive degeneration of health, with the impairment of cardiac function in the stiffening and thickening of the blood vessels, which are associated with endothelial dysfunction. Evidence shows that aging leads to an increase in the production of reactive oxygen species (ROS) in the heart and the vascular system.

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.

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. 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. For example, grapes are estimated to contain 0.16–3.54 μg/g resveratrol per gram, and dry peels contain approximately 24 μg/g. 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.

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. Supplementation with a low dose of resveratrol (8 mg/day for 1 year) is considered sufficient to significantly reduce cardiovascular risk. 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, but other studies claim that a dose of 450 mg/day would be safe for a person weighing 60 kg 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.

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, five analyzed the glycemic profile, four studied the inflammatory profile, one analyzed lipoproteins, and one investigated the safety of resveratrol consumption in elderly patients.

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, but not that of healthy subjects. In addition, a study of patients with DM did not show significant improvement. 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 and at 500 mg/day in smokers. An anti-inflammatory effect...
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Type of study</th>
<th>Population</th>
<th>n</th>
<th>Dose</th>
<th>Duration</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>Fujitaka et al.</td>
<td>2011</td>
<td>Japan</td>
<td>Double-blind randomized crossover</td>
<td>Patients with metabolic syndrome</td>
<td>34</td>
<td>100 mg/day</td>
<td>3 months</td>
<td>Improvement of endothelial function, without significant changes in BP, IR, lipid profile, and inflammatory markers</td>
</tr>
<tr>
<td>33</td>
<td>Wong et al.</td>
<td>2011</td>
<td>Australia</td>
<td>Double-blind randomized crossover</td>
<td>Men and postmenopausal women with untreated borderline BP</td>
<td>19</td>
<td>Placebo, 30 mg/day, 90 mg/day, and 270 mg/day</td>
<td>1 intervention per week for a total of 4 weeks</td>
<td>Significant dose-dependent effect of resveratrol on flow-mediated dilatation of the brachial artery</td>
</tr>
<tr>
<td>34</td>
<td>Magyar et al.</td>
<td>2012</td>
<td>Hungary</td>
<td>Double-blind placebo-controlled</td>
<td>Post-infarction Caucasian patients</td>
<td>40</td>
<td>10 mg/day</td>
<td>3 months</td>
<td>Significant improvement in left ventricular diastolic function, endothelial function, and LDL-cholesterol levels</td>
</tr>
<tr>
<td>35</td>
<td>Wong et al.</td>
<td>2013</td>
<td>Australia</td>
<td>Double-blind, randomized, crossover controlled</td>
<td>Healthy obese men and obese postmenopausal women</td>
<td>28</td>
<td>75 mg/day</td>
<td>6 weeks</td>
<td>1 flow-mediated dilatation without changes in arterial compliance and BP</td>
</tr>
<tr>
<td>36</td>
<td>Chekalina et al.</td>
<td>2016</td>
<td>Ukraine</td>
<td>Controlled clinical trial</td>
<td>Patients with CAD: stable angina pectoris</td>
<td>93</td>
<td>Basic therapy with beta blockers, statins, and aspirin (control) + 100 mg/day of resveratrol or 3g/day of quercetin</td>
<td>2 months</td>
<td>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</td>
</tr>
<tr>
<td>37</td>
<td>Imamura et al.</td>
<td>2017</td>
<td>Japan</td>
<td>Double-blind randomized controlled</td>
<td>Patients with DM2</td>
<td>50</td>
<td>100 mg/day</td>
<td>12 weeks</td>
<td>Improvement of the ankle-brachial index, arterial stiffness, and oxidative stress</td>
</tr>
<tr>
<td>38</td>
<td>Marques et al.</td>
<td>2017</td>
<td>Brazil</td>
<td>Double-blind randomized controlled</td>
<td>Patients with hypertension</td>
<td>24</td>
<td>Acute dose of 300 mg of resveratrol or placebo, with 1 week washout period, and a crossover</td>
<td>2 days of intervention, 1-week interval between them</td>
<td>Improved endothelial function, more pronounced in women and individuals with high LDL-c</td>
</tr>
<tr>
<td>39</td>
<td>Crandall et al.</td>
<td>2012</td>
<td>USA</td>
<td>Randomized controlled</td>
<td>Elderly overweight or obese patients with IR</td>
<td>10</td>
<td>1 g/day, 1.5 g/day, and 2 g/day</td>
<td>4 weeks</td>
<td>No changes in weight, blood pressure, and lipids, decreased IR</td>
</tr>
<tr>
<td>40</td>
<td>Kumar and Joghee</td>
<td>2013</td>
<td>India</td>
<td>Randomized controlled</td>
<td>Patients with DM2</td>
<td>57</td>
<td>Metformin and/or glibenclamide (control) + 250 mg/day</td>
<td>6 months</td>
<td>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</td>
</tr>
<tr>
<td>41</td>
<td>Movahed et al.</td>
<td>2013</td>
<td>Iran</td>
<td>Double-blind randomized</td>
<td>Patients with DM 2</td>
<td>66</td>
<td>1 g/day</td>
<td>45 days</td>
<td>A significant † in BP, fasting glycemia, glycated hemoglobin, insulin, and IR, and a significant † in HDL</td>
</tr>
<tr>
<td>31</td>
<td>Poulsen et al.</td>
<td>2013</td>
<td>Denmark</td>
<td>Double-blind randomized controlled</td>
<td>Patients with obesity</td>
<td>24</td>
<td>500 mg 3x/day</td>
<td>4 weeks</td>
<td>No significant changes in blood pressure, body composition, glycemic, lipid and inflammatory profile</td>
</tr>
</tbody>
</table>
Table 1. Summary of the studies included in the review by observed outcome.

<table>
<thead>
<tr>
<th>Ref.</th>
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<th>Dose</th>
<th>Duration</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>42</td>
<td>Khodabandehloo et al.</td>
<td>2018</td>
<td>Iran</td>
<td>Double-blind randomized</td>
<td>Patients with DM2</td>
<td>45</td>
<td>2×400 mg/day</td>
<td>8 weeks</td>
<td>A significant decrease in fasting glycemia and BP</td>
</tr>
<tr>
<td>43</td>
<td>Bo et al.</td>
<td>2013</td>
<td>Italy</td>
<td>Double-blind randomized crossover</td>
<td>Healthy adult smokers</td>
<td>50</td>
<td>500 mg/day</td>
<td>90 days</td>
<td>1 TG and 1 anti-inflammatory and antioxidant response</td>
</tr>
<tr>
<td>27</td>
<td>Carneiro et al.</td>
<td>2013</td>
<td>Spain</td>
<td>Triple-blind randomized</td>
<td>Men with hypertension and DM2 and angina pectoris or acute coronary syndrome stable for at least 6 months</td>
<td>35</td>
<td>1 capsule of 330 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</td>
<td>1 year</td>
<td>GE and GE-RES supplementation did not affect body weight, BP, and glycemic profile compared with standard drugs, but there was a significant decrease in alkaline phosphatase and inflammatory profile in the GE-RES group.</td>
</tr>
<tr>
<td>44</td>
<td>Apostolidou et al.</td>
<td>2016</td>
<td>Greece</td>
<td>Randomized controlled crossover</td>
<td>Patients with normal or asymptomatic hypercholesterolemia</td>
<td>33</td>
<td>150 mg/day for 30 days, 30 days, washout, and placebo for 30 days</td>
<td>90 days</td>
<td>In patients with cholesterol at normal levels, resveratrol had an antioxidant effect, whereas in patients with hypercholesterolemia, resveratrol decreased CVD risk.</td>
</tr>
<tr>
<td>45</td>
<td>Seyyedebrahimi et al.</td>
<td>2018</td>
<td>Iran</td>
<td>Double-blind randomized</td>
<td>Patients with DM2</td>
<td>48</td>
<td>800 mg/day</td>
<td>Two months</td>
<td>Significant improvement of the anti-inflammatory profile, significant decrease in fasting glycemia.</td>
</tr>
<tr>
<td>46</td>
<td>Dash et al.</td>
<td>2013</td>
<td>Canada</td>
<td>Double-blind randomized crossover</td>
<td>Overweight or obese individuals with mild hypertriglyceridemia</td>
<td>8</td>
<td>1 g/day in the first week and 2 g/day in the second week</td>
<td>Two weeks</td>
<td>In intestinal and hepatic production of Apo B48 and Apo B100 lipoproteins, without changes in TG and IR.</td>
</tr>
<tr>
<td>47</td>
<td>Anton et al.</td>
<td>2014</td>
<td>USA</td>
<td>Double-blind randomized controlled</td>
<td>Overweight elderly</td>
<td>32</td>
<td>Placebo, 300 mg/day, and 1000 mg/day</td>
<td>12 weeks</td>
<td>Significant decrease in glycemia in the control groups, unrelated to serum markers; good tolerability.</td>
</tr>
</tbody>
</table>

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, which are considered independent risk factors for coronary artery diseases.27

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, untreated borderline blood pressure, obese men and obese postmenopausal women, post-infarction Caucasians, stable angina pectoris, 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 dysfunctions 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.40

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.49 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.\(^{41}\)

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.

**ACKNOWLEDGMENT**

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**CONFLICTS OF INTEREST**

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

**AUTHORS’ CONTRIBUTIONS:** GVS, RTA, ESC, AGPC, and VAM contributed to the concept and design of the study. GVS and RTA performed searches and collected data from articles included in the review and drafted the manuscript. ESC, AGPC, and VAM supervised the study and reviewed the article.

**REFERENCES**


