LITERATURE REVIEW

Journals BAHIANA
SCHOOL OF MEDICINE AND PUBLIC HEALTH

USE OF RESVERATROL IN CARDIOVASCULAR DISEASES PREVENTION: A SYSTEMATIC REVIEW

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ABSTRACT | Resveratrol, a polyphenolic compound found in blackberry and red wine, has properties that prevent the development of atherosclerosis, and therefore, cardiovascular disease. The aim of this study was, through a systematic review, to assess whether resveratrol reduces the incidence of cardiovascular events and improves inflammation and endothelial dysfunction in individuals at risk. Searches were conducted in databases such as LILACS, PubMed,SCIELO and selected randomized controlled trials in humans, including the use of resveratrol in the prevention of cardiovascular events or in the improvement of inflammation and endothelial function. The final sample consisted of 10 items. Of the four studies that analyzed the flow-mediated dilatation of the brachial artery, all showed significant improvement in endothelial function after the use of resveratrol, compared with placebo. In the 7 studies that evaluated subclinical inflammation, there were differences, 3 studies showed significant decreases in the values of TNF-α, 2 showed significant changes in plasma levels of C-reactive protein and interleukin 6 (IL-6), while 1 didn't showed changes in TNF-α and IL-6. In conclusion, resveratrol is capable of improving endothelial function when compared with placebo. However, it was not possible to infer an improvement or not in the parameters concerning endothelial inflammation, since the data extracted from the studies were insufficient. Moreover, it was not possible to evaluate the use of resveratrol in the improvement of survival, infarction or reduction in mortality, since there were no records in the literature of randomized controlled trials that analyzed the effect of resveratrol use on clinical outcomes in humans.

Keywords: cardiovascular diseases. Inflammation, endothelial cells

Submitted 2017/03/04, accepted for publication 2017/05/13 and published 2017/06/20
DOI: 10.17267/2317-3386bjmhh.v5i2.1309

INTRODUCTION

Cardiovascular Diseases (CVD) are the main cause of death in in developed countries with atherosclerotic disease being considered a public health problem[1,2]. There is an intimate causal relationship between Atherosclerotic diseases and CVD[3], since the main consequences of the former are myocardial infarction, cerebral infarction and aortic aneurysm[4]. Atheromatous plaque formation results from a response to tissue lesions triggered by the endothelium, probably due to the accumulation of low density lipoprotein (LDL), which is later oxidized[5,6]. Accumulation of this lipoprotein occurs as a result of environmental factors, mainly connected with diet and genetic aspects[7]. In this context, resveratrol, a polyphenolic compound found in grape skins, red wine, eucalyptus and peanuts is found, whose benefits have become recognized worldwide, due to its antioxidant and anti-inflammatory properties, in addition to the capacity to inhibit LDL oxidation, and stimulate nitric oxide (NO) production, which characterize it as a cardiovascular protector[8]. From this perspective, the "French paradox" - an expression attributed to the low incidence of coronary diseases in the French population - is inserted, in spite of its diet rich in fats, due to the moderate consumption of red wine[9]. Therefore, one perceives that the possible effects of resveratrol are closely connected to CVD, since endothelial dysfunction and accumulation of LDL are the first steps towards the formation of atheromatous plaque[10,11,12]. As resveratrol has anti-oxidant, anti-thrombotic and anti-atherosclerotic properties, it may represent a substance of great potential use in clinical practice, with a view to better control of CVD[13]. Therefore, the aim of the present study was to evaluate the effect of the use of resveratrol on the prevention of cardiovascular events, endothelial function and the inflammatory response in human beings.

METHODS

Search in the literature

The electronic databases used to conduct this research were PubMed (Public Medical Literature Analysis and Retrieval System Online), LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde), Scielo (Scientific Electronic Library Online) and the DOAJ (Directory of Open Access Journals). The uniterms were consulted in DECS (Descriptors in Health Science), with the purpose of determining the ideal descriptors to be researched in titles, abstracts and subjects of the referenced articles. The following expressions and their corresponding translations: cardiovascular disease or inflammation or coronary artery disease, were selected for combination with the term resveratrol, using the conjunction AND. Specifically, in PubMed, the filter for the type of study was used, selecting only randomized clinical trials.

After reading the respective titles and abstracts with reference to each article found, only studies that presented the following characteristics were included: English, Portuguese or Spanish language, period of publication between 2000 and 2016, study design: randomized clinical trial in human beings, which evaluated the use of resveratrol in the prevention of cardiovascular diseases, including directs effects on the development of atherosclerosis and endothelial dysfunction. Studies with explicit methodological biases (bias of selection, follow-up and data analysis), presentation of insufficient or ambiguous and nonspecific results with regard to the topic proposed, were excluded.

The variables extracted in compilation of the data of each study selected by means of the eligibility criteria were information with reference to the authors, titles, periodicals, profile of the population, sample size, outcomes considered, follow-up period, mean variation of the studied outcomes, when continuous and/or relative risk, and when the outcomes were dichotomized.

Outcomes Evaluated

For the selection of articles, the clinical outcomes

such as longer survival, better quality of life, reduction in acute myocardial infarction, sudden death, cerebral vascular accident and coronary artery disease, or substitute outcomes, such as the reduction in inflammation and endothelial function, were considered.

Criterion for evaluation of quality of studies

The relevance test, by means of which the studies were submitted to and evaluated with regard to quality, consisted of the following criteria: date on which the research was conducted (2000-2016), presence of blinding, time of follow-up. type of outcome presented (clinical or substitute), presentation of original results (in absolute values about endothelial dysfunction, after the use of resveratrol), presence of biases and specific definition of the research participants. The relevance test was applied and later the studies considered low quality were excluded. The stage described was carried out by two different researchers, and when there was disagreement about whether or not a study should be included, the choice was made by consensus. Furthermore, the quality of evidences was evaluated by means of the Grade Approach, adapted by The Cochrane Collaboration[14].

RESULTS

Selection of Studies

Initially, 54 studies were identified in PubMed, 60 in LILACS, 2 in SCIELO, and none in DOAJ. In this first stage, 14 articles were selected because the fulfilled the inclusion criteria, and were read in full. The reasons for non-inclusion of studies were: articles that had explicit methodological biases (bias of selection, follow-up, data analysis - they were analyzed observing the conclusion and methodology of studies), presentation of insufficient or ambiguous and nonspecific results with regard to the proposed topic. Having done this, 10 articles eligible for the review in question were identified. The stages of selection of records identified are disposed in the diagram, drawn up according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) protocol[15]. (Figure 1).

After making the selection, the final set was composed of 10 articles (Table 1), all in the English language, from the PubMed database. The studies selected were about adult individuals of both sexes, with risk for CVD. The period of publication was between 2005[16] and 2016[17].

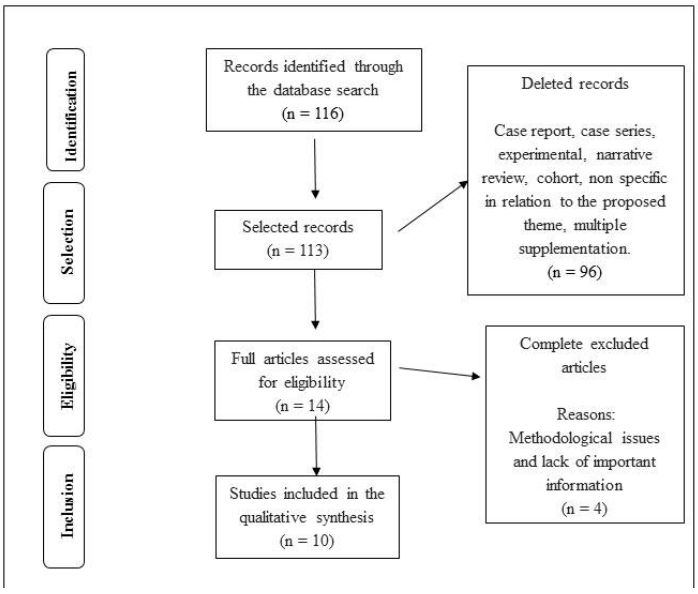

Figure 1. Diagram of selected articles for systematic review

Table 1. Characteristics of clinical trials that evaluated the effect of resveratrol on endothelial function

Author Journal Country Year	Population's profile	Sequence	mg	Average variation	Blinding	Comment Outcomes
K. Magyar. et al. Clinical Hermorheology and Microcirculation Hungary 2014	Adults with previous IAM History and DAC Age = 42-80 n= 40	12 weeks	10 mg	Refers significance but does not present exact numeric values	Dual-blind	Increased VMF brachial artery and preventing platelet aggregation
John Lekakis et al. European Journal of Cardiovascular prevention and Rehabilitation Greece 2005	Men with DAC Age = (n=15): 59.7 ± 9.3 e (n=15): 62.2 ± 8.6 n= 30	Non informed	0.54 mg/day	4.52 ± 1.34% versus 2.6 ± 1.5%; P <0.001	Dual-blind	Increased VMF of brachial artery
Keisuke Fujitaka et al. Nutrition Research Japan 2011	Patients with SM Age: A: 63 ± 9 e B: 62 ± 14 n= 34	24 weeks	100mg/day	4.4% ± 2.4 % for 10.0% ± 3.4 %	Non informed	Increase of VMF the brachial artery. PCR and IL-6 unchanged
R. H. X. Wong et al. Nutrition, Metabolism & Cardiovascular Disease Australia 2010	Obese adults and women in postmenopause Age = 55±2 n= 19	Non informed	30, 90 e 270 mg	4.1 ± 0.8% for 7.7 ± 1.5% after 270 mg of RES	Dual-blind	Increased VMF of brachial artery
Tosca L. Zern et al. J. Nutr. New York 2005	Pre-and postmenopausal women Age = (24 = 39.7 + or – 8.5 and 20= 58.5 + or – 7.5) n= 44	11 weeks	7µmol/kg (36g/day)	1.53 ± 1.03 (placebo) and 1.36 ± 0.89 (LPG); 2.45 ± 1.78 (placebo) and 2.20 ± 1.97 (LPG)	Simple-blind	Reduction of TNF α values (oxidative stress); IL-6 and PCR unchanged
Silvie Timmers et al. Cell Metabolism Sweden 2011	Healthy obese adults Age= 52.5±2.1 n= 11	4 weeks	150 mg/day	3.13 ± 0.67 e 2.42 ± 0.38 ng/mL, p= 0.09 (IL-6); 16.15 ± 2.27 e 15.14 ± 2.03 pg/mL, p= 0.04 (TNF-α)	Dual-blind	Reduction of the values of TNFα and IL-6; PCR with no significant reduction
João Tomé-Carneiro et al. Am J Cardiol Spain 2010	Patients in primary prevention of DCV Age= A: 63 ± 9, B: 56 ± 11, C: 62 ± 9. n= 75	48 weeks	8mg/day during 6 months and 16mg/day in the following 6 months	-26%, p=0.03 (PCR); -19.8%, p=0.01 (TNF-α); 19,8%, p=0.01 (IL-10)	Triple-blind	Reduction of highly sensitive PCR, and Pro-Inflammatory Cytokines and TNFα.
Anette Karlsen et al. Eur J Nutr LOCAL 2010	Adults with high risk for DCV Age = group water: 30-68 and bilberry group 34-68. n= 62	4 weeks	0,03-3,96 mg/day	-0.30 mg/L (PCR); -6.0 mg/mL (IL-6); 1.9 pg/mL (TNF-α)	No report	Reduction of PCR, IL-6 and TNF α increase
Gertruud CM Bakker et al. Am J Clin Nutr USA 2010	Healthy obese adults Age = 22-58 n=36	20 weeks	25.2mg/day	-3% (ICAM-1) and -4% (VCAM-1)	Dual-blind	Reduction of ICAM -1 and VCAM-1. PCR unchanged
Sanne M, Van der Made et al. PLoS One. Italy 2015	Obese adults and women Age = 61 ± 7 n= 45	04 weeks	150 mg/day	-0.05 ± 0.91 p=0.455 (TNFα- pg/mL) 0.23 ± 1.26 p=0.718 IL-6 (pg/mL) -2 ± 64 p=0.829 sICAM-1 (ng/mL) 8 ± 105 p=0.595 sVCAM-1 (ng/mL)	Dual-blind	IL-6, TNFα, sICAM-1, and sVCAM-1 unchanged

ICAM-1, intercellular adhesion molecule; VCAM-1, vascular adhesion molecule; PCR, protein c reactive; IAM, acute myocardial infarction; DAC, coronary artery disease; VMF, flow-mediated vasodilation; LPG, *lyophilized grape powder*; TNF-α, tumor necrosis factor α; IL-6, Interleukin -6; SM, metabolic syndrome.

Characteristics of Study

The population samples ranged from 11 to 75 participants18,19, in total 396, aged between 22 and 69 years20,21.

Characteristics of participants:

In all the studies, 396 adults of both sexes were recruited. In three of the studies, the sample was composed of overweight/obese adults (BMI between 25.5 and 35.5 kg⁄m2 20, BMI 22,23), however, in three, the individuals were healthy (low degree of inflammation - CRP of 1-10mg⁄L - fasting glycemia ≤ 6.9 mmol⁄L, fasting cholesterol ≤ 8mmol⁄L, blood hemoglobin concentration ≥ 8mmol⁄L, consumption of ≤ 28 units of alcohol per week42; without family history of diabetes, other endocrine disease, or use of medications[18]), and in one, in addition to being overweight, the subjects were hypertensive, included post-menopausal women

Only one research was composed exclusively of pre- and post-menopausal women[16]. In two studies, the participants had angiographically documented[17].21 coronary artery diseases (CAD), with one of these being composed of a population with previous AMI[16]. Another four publications selected participants at risk for CVD (PAS between 135-160 mmHg and PAD 90-100 mmHg, LDL ≥ 3.4 mmol⁄L, CT⁄HDL ratio >4, elevated hematocrit - ≥0.4 for women and ≥0.42 for men - or smoking at least 3 cigarettes daily)23,24 , with the sample being under primary prevention in only one (statin treatment for over 3 months before inclusion) and defined as being metabolic syndrome, according to the criteria of the Japan Society for Study of Obesity[25] in the other[26].

Characteristics of Interventions

The follow-up period ranged from 4 to 48 weeks18,19, and in spite of all the studies being randomized clinical trials, six were of the cross-over type[16,18,20,22,23,26],and four were parallel studies[17,19,21,24]. Of the ten studies selected, six used capsules composed of resveratrol only[17,18,19,22,23,26], in different doses (10 mg, 150 mg, 8 or 16 mg, 100mg, 30 or 90 or 270mg or 150mg respectively) and four made use of capsules mixed with different compounds[16,20,21,24], including resveratrol. The quantity of resveratrol used in the intervention fluctuated from minimum concentrations of 0.54 mg⁄day21, to doses of 36g⁄day16.

As regards the composition of the placebo used in each trial, two articles did not provide this information[17,18], one article only discontinued the use of resveratrol[25], and the other used water[24]. The remainder made use of inert substances with similarities as regards appearance and energy value.

Seven studies warned the participants not to change their lifestyle[16,18,19,22,23,26], five allowed the medications previously used to be continued[16,17,19,20,26] and four studies informed that the ingestion of polyphenolic compounds was not permitted during the follow-up period[16,18,22,24].

Access to the Outcome

The use of the correct methodology for the measurement of dependent endothelial vasodilatation (as predictor of endothelial function), and the biochemical methods for the collection and analysis of the blood inflammatory parameters (IL-6, CRP and TNF- α) performed in fasting, did not undergo significant variation among the studies, with the exception of the use of nitrate, or not, for measurement of nondependent endothelial dilatation, present in only one of the articles[19].

Outcomes

The outcomes considered in the studies in question were as follows: lipid alterations, alterations in the inflammatory markers such as ultrasensitive CRP, TNF-α and IL-6, and in endothelial function, measured by means of the vasodilatation mediated by brachial artery flow.

Risk of bias of studies included.

The studies presented had a satisfactory quality, judging by the inclusion of important covariables and methodological analysis. With regard to the presence of blinding, six studies were double-blind[17,18,21,22,23], one simple-blind[20], one triple-blind[19] and two had

no blinding[25,26]. None of the publications related having significant imbalances as regards the initial characteristics of the allocated groups. With respect to blinding about allocation of the participants, three studies were not explicit about[17,18,20] whether or not there was blinding, four had low risk[16,21,22,26] and two high risk[19,24], for bias of selection. The articles that were double-blind presented low risk for bias of performance[17,18,20,21,22,23]. Of the simple-blind type, one also had low risk16, since the composition of the placebo and the substance tested was similar, the other had high risk[24], since the composition of the placebo was different and the other had an uncertain risk[26]. As regards bias of detection, seven studies presented low risk[17,18,19,20,21], and three uncertain risk[16,24,26], since the existence of blinding or not of the researchers responsible for collection of the exams was not informed. All the studies were considered low risk for bias of loss, since the articles that presented loss during follow-up[18,20,22,23,24], had a value lower than 20% in comparison with the beginning of randomization. They also had low risk of bias for selection of the outcome, because all the studies described the results that were proposed in the methodology.

Grading the quality of evidence

According to the Grade Approach[14], the evidences of the selected studies were of higher quality, since they all concerned randomized clinical trials.

Studies that evaluated FMV

The evidences in the studies that evaluated the FMV of the brachial artery[17,21,22,26], were considered moderate quality, since they had a clinical variability with respect to the characteristics of the participants and the doses administered. Only one article had evidences considered low quality[26], because it did not inform about the type of blinding.

Studies that evaluated endothelial inflammation

The fact that the studies included[16,18,19,20,23,24] had a clinical variability with respect to the characteristics of the participants, doses administered and outcomes, lowered the value of the evidences extracted from them, and thus they were of a moderate quality. Furthermore, the lack of information of one of the studies[24] as regards blinding, led to its evidence being of low quality, as was that of one of the other studies[16], due to the fact of being simple blind.

Effects of Interventions

The majority of the individuals who received resveratrol presented a more beneficial development with regard to the improvement in endothelial function and lipid markers, in comparison with those submitted to the placebo treatment. Of the nine studies, four evaluated the FMV of the brachial artery[17,21,22,26], and all showed a significant improvement ($p < 0.05$) in endothelial function in the Group with the use of resveratrol. Whereas, not all the trials that evaluated the blood inflammatory markers obtained an improvement in these parameters. For example, there were no significant alterations in the plasma values of CRP in four of the six studies analyzed[17,8,20,26].

DISCUSSION

In individuals with high risk for CVD it is desirable to use therapies in addition to those recommended, with a view to interrupting the evolution of the disease in the direction towards unfavorable outcomes. Therefore, substances with the possible anti-thrombotic and anti-sclerotic capacity, such as resveratrol, may assume an important role in the family therapy of these diseases. However, there are records in the literature of randomized clinical trials, in which the participants at cardiovascular risk, with the use of resveratrol either obtained improvement in clinical outcomes, or did not, such as longer survival, improvement in quality of life or reduction of infarctions[13].

In this systematic review, it could be observed by analysis of the results of four randomized clinical trials included[17,21,22,26], that there was significant improvement ($p<0.0$) in flow mediated vasodilatation of the brachial artery, in individuals

using resveratrol, compared with those who received placebo. Similar outcomes have been demonstrated in the literature with the use of red wine and grape juice in previously health men[27]. However, in this study the use of substances present in the drinks in question were evaluated and not only resveratrol.

Pace-Asciak et al[28] also suggested that the polyphenolic compounds of red wine have protective properties against coronary arterial disease. Since then the use of polyphenolic substances have been evaluated in human beings[29,30,31].

The improvement in endothelial dependent vasodilatation may result from the fact that resveratrol is capable of activating the enzyme SIRT[1,18] which forms part of the family of silent information regulation (sirtuins)[32] and is responsible for the increase in the endothelial nitric oxide synthetase endothelial enzyme (eNOS)[33]. Thereby, an increase in the endothelial production of NO17 occurs, which promotes vascular relaxation, with consequent dilatation of the blood vessel, and is in agreement with a study[33], which demonstrated the fundamental role of the deacetylase protein SIRT1 in endothelial NO regulation and of endothelial dependent vascular tonus by eNOS. On the other hand, there are records in the literature, which demonstrate[32] that resveratrol is not responsible for directly activating SIRT1, having little or no action on it.

Whereas Orallo et al[34], demonstrated a clear effect of trans-resveratrol on endothelial dependent vasodilatation in rat aortas, which did not occur in arteries in which the endothelium had been removed. This finding strengthens the potential effect of this substance on endothelial dependent vasodilatation. Moreover, it is important to point out that the technique use for measurement of endothelial function in the studies included, is based on the increase in blood flow, causing dilatation of the vessels locally[35]. In spite of being a mechanical and observer dependent method, it is reliable and accurate[36].

There were no records in the literature of randomized clinical trials that carried out biochemical evaluation of endothelial function, by means of parameters such as the measurement of endothelial NO and arginase. However, the degree of dilatation of the brachial artery is routinely used in clinical studies to measure endothelial function, and this noninvasive technique has been correlated with that of invasive evaluation of endothelial function of the coronary artery by means of Acetylcholine infusion[35,37].

Although endothelial dysfunction is a substitute outcome, it is intimately related to subclinical atherosclerosis, and by means of the FMV of the brachial artery technique, allows physiopathological and important diagnostic information to be provided for the probable prognosis of the patient at risk for CVD[38].

A prospective cohort study conducted with a sample of 3026 persons, in 6 communities of the United States showed that FMV of the brachial artery is a predictor of the incidence of cardiovascular events in previously healthy individuals. It is worth emphasizing that only one study included in the final sample of articles evaluated and identified the reduction in the concentrations of VCAM-1 and ICAM-120 after the use of resveratrol. These data show evidence of the improvement in endothelial function promoted by resveratrol, as has been demonstrated in records documented in the literature[39,40]. However, in spite of the reduction in these parameters (VCAM-1 and ICAM-1) having been obtained from a double-blind, randomized study, present in the final sample of articles, it is necessary to evaluate the relevance of this result, since it does not represent the main objective of the clinical trial analyzed, thus, making it impossible to evaluate its statistical power.

With respect to the inflammatory response, it was not possible to find an improvement in the parameters analyzed, such as TNF-α, CRP and IL-6 41. However, TNF-α presented an important reduction in three of the four articles that evaluated this outcome. With regard to IL-6, in two clinical trials there was a beneficial change in the outcome, but in another two, the parameters remained unchanged. Therefore, the data obtained are inconclusive with regard to inflammatory response. This finding differs from those of Kelley et al[30] (2013), who verified the reduction in CRP after the consumption of sweet cherries, which are rich in polyphenolic compounds. However, in the mentioned study there was no placebo group and the parameters evaluated may have been influenced by

factors other than the substance analyzed. Csiszar et al[40] (2013) also showed evidence that resveratrol is responsible for attenuating not only TNF-α and IL-6, as was found in one of the studies included. Furthermore, Sampaio et al[42] (2013) found that the response to CRP is a situation variable and may not always reflect an association with endothelial function.

The reduction in inflammatory parameters, when present, may be explained by the capacity of resveratrol to reduce the oxidation of LDL, as has been demonstrated by Zou et al[43], and inhibit the expression of adhesion molecules, such as VCAM-1 and ICAM-144,[45]. Therefore, resveratrol has properties that would be capable of impeding the progression of the inflammatory cascade, responsible for increasing the peripheral inflammatory parameters such as PCR, IL-6 and TNF-α, could be the result of reduction in lipid peroxidation[46]. However, one of the studies demonstrated an increase in this inflammatory parameter, a situation which may occur with the purpose of stimulating the increase in interleukin 10 (IL-10), an anti-inflammatory cytokine[24]. The decreasing values of IL-6 may be explained by the action of resveratrol in inhibiting the acute stage of inflammation. Whereas, the absence of alterations in the levels of inflammatory markers in one of the studies included16, may be owing to the fact that the blood samples were not collected at the same time of day.In addition, the data may have been conditioned to a diurnal variation in IL-6, because glycocorticoids and catecholamines elevate these values.

The disagreements in the results of studies with respect to the alteration or not of endothelial inflammation parameters may also be justified by the heterogeneity of the populations studied, different periods of follow-up, and variability of the doses administered. Moreover, the maintenance of the parameters may occur because of the low concentrations of these markers in the initially healthy participants of the studies evaluated, low sensitivity of the methods used for analysis or limitation of the effect of resveratrol on the specific inflammatory pathway.

Therefore, it could be concluded that there was an improvement in endothelial function, evaluated by means of FMV of the brachial artery after the use of resveratrol in comparison with the placebo. However, the conclusion is still limited with regard to its possible effects on endothelial inflammation, since the data of the studies were insufficient to prove whether or not there was improvement.

The method used in the present study is adequate for the evaluation of scientific evidence, considering that in addition to the method having good accuracy[47], it contemplates the purpose of responding the question raised. Nevertheless, it is important to point out the possible limitations of this review that although randomization was adequate in all the studies, these presented heterogeneity as regards blinding, follow-up time, doses recommended, parameters evaluated in each outcome, in addition to variability in the methods used to obtain the outcomes. Added to this is the fact that the studies selected for the present review had a reduced sample size.

There are no demonstrations that the use of resveratrol may modify the existent and recommended therapies, and its clinical usefulness in the prevention of cardiovascular events could not be proved. Therefore further studies are necessary, which evaluate resveratrol as a coadjuvant therapy in the prevention of cardiovascular diseases in patients at low and medium risk, analyzing their respective clinical outcomes.

The present study demonstrated, by means of alterations in the FMV of the brachial artery, that resveratrol is capable of improving endothelial function, when compared with the placebo. Nevertheless, it is not possible to infer improvement in the parameters concerning endothelial inflammation, since the data extracted from the studies were shown to be inconclusive. Furthermore, it was not possible to evaluate the use of resveratrol in the improvement or not of survival, infarction, or reduction in mortality, since there were no records in the literature of randomized clinical trials that analyzed the influence of the use of resveratrol on the clinical outcomes in human beings.

AUTHOR CONTRIBUTIONS

GOES GM participated in the study design, collecting research data, interpreting data and writing the manuscript. FRAGA AS participated in the collection of research data, interpretation of data and writing of the manuscript. LADEIA AMT contributed in the critical review of the intellectual content, supervised the writing, approved and revised the final draft of the manuscript.

COMPETING INTERESTS

No financial, legal or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).

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