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Exploring the impact of bioactive compounds on endothelial dysfunction in hypertensive individuals: a comprehensive systematic review

Explorando o impacto de compostos bioativos na disfunção endotelial em indivíduos hipertensos: uma revisão sistemática.

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ABSTRACT

Systemic Arterial Hypertension is considered the main risk factor for cardiovascular diseases and is also associated with a pro-oxidative environment and endothelial alterations. The objective of this review was to evaluate the evidence available in the literature regarding the impact of resveratrol, quercetin, and catechin consumption on endothelial function in individuals with arterial hypertension. The search was conducted using the PICOS strategy across the following databases: Science Direct, Pubmed, Scielo, and Lilacs. The inclusion criteria comprised adults and the elderly of both sexes, with a body mass index above 18.5 kg/m², diagnosed with arterial hypertension. Resveratrol and quercetin were found to have a positive effect on the vascular endothelium by increasing flow-mediated dilation. Additionally, quercetin alone led to a reduction in blood pressure among hypertensive individuals. However, due to limitations in the available studies, it was not possible to reach a conclusive result regarding catechin. Further studies are needed to evaluate its effect. Therefore, including food sources rich in resveratrol and quercetin may prove beneficial for individuals with this chronic non-communicable disease.

Keywords: Resveratrol; Quercetin; Catechin; Endothelium; Hypertension.

RESUMO

A hipertensão arterial sistêmica é considerada o principal fator de risco para doenças cardiovasculares e também está associada a um ambiente pró-oxidativo e alterações endoteliais. O objetivo desta revisão foi avaliar as evidências disponíveis na literatura sobre o impacto do consumo de resveratrol, quercetina e catequina na função endotelial em indivíduos com hipertensão arterial. A busca foi conduzida utilizando a estratégia PICOS nas seguintes bases de dados: Science Direct, Pubmed, Scielo e Lilacs. Os critérios de inclusão abrangeram adultos e idosos de ambos os sexos, com índice de massa corporal acima de 18,5 kg/m², diagnosticados com hipertensão arterial. O resveratrol e a quercetina demonstraram ter um efeito positivo no endotélio vascular, aumentando a dilatação mediada pelo fluxo. Além disso, a quercetina, isoladamente, levou à redução da pressão arterial em indivíduos hipertensos. No entanto, devido às limitações dos estudos disponíveis, não foi possível obter um resultado conclusivo em relação à catequina. Estudos adicionais são necessários para avaliar seu efeito. Portanto, a inclusão de fontes alimentares ricas em resveratrol e quercetina pode ser benéfica para indivíduos com esta doença crônica não transmissível.

Palavras-chave: Resveratrol; Quercetina; Catequina; Endotélio; Hipertensão.

INTRODUCTION

Systemic Arterial Hypertension (SAH) is defined by the Brazilian Hypertension Guideline (2020) as a multifactorial condition characterized by persistent elevation of blood pressure, with systolic blood pressure greater than or equal to 140 mmHg and/or diastolic blood pressure greater than or equal to 90 mmHg. SAH affects approximately 1.13 billion people worldwide, accounting for nearly 14.5% of the population, almost double the number in 1975 (BARROSO et al., 2021; ZHOU et al., 2017).

This chronic non-communicable disease is a circulatory disorder associated with metabolic and structural changes in blood vessels, including endothelial dysfunction, which may contribute to its development (YUGAR-TOLEDO et al., 2015). Endothelial dysfunction leads to decreased nitric oxide (NO) production by the endothelial NO synthase enzyme and an increase in inflammatory cytokines. These imbalances result in increased endothelial permeability and blood vessel constriction, negatively impacting cardiovascular homeostasis and contributing to disease progression (BARROSO et al., 2021).

Healthy eating habits, with an emphasis on fresh foods such as fruits and vegetables, while avoiding ultra-processed foods and low concentrations of saturated fat, are considered essential for preventing and treating SAH and its complications (BARROSO et al., 2021). These foods serve as sources of bioactive compounds (REIS et al., 2015). Notably, resveratrol, quercetin, and catechin have been identified as bioactive compounds that promote endothelial health and blood pressure control through various mechanisms (BEHLING et al., 2008; CAVALCANTE et al., 2021; SENGER; SCHWANKE; GOTTLIEB, 2010).

For the first time in the scientific literature, research has compiled information on these specific bioactive compounds and their effects on the aforementioned conditions. The objective of this systematic review, therefore, is to investigate the effects of resveratrol, quercetin, and catechin consumption on endothelial function in patients with SAH.

MATERIALS AND METHODS

Design, search strategy and eligibility criteria

The search was conducted using the PICOS strategy, which includes population, intervention, comparison, outcome, and study design. Keywords were selected from Health Sciences Descriptors (MeSH and DeCS), including endothelium, hypertension, resveratrol, quercetin, and catechin. Boolean operators (AND and OR) were used to combine these keywords. The search was performed in the following databases: Science Direct, PubMed (Medline), Scielo, and Lilacs. The articles were limited to English, Portuguese, and Spanish languages.

The inclusion criteria were as follows: adult and elderly individuals of both sexes with a body mass index greater than or equal to 18.5 kg/m², diagnosed with SAH, and studies that solely focused on the supplementation of the mentioned compounds. Exclusion criteria encompassed experimental studies, meta-analyses, systematic reviews, letters to the editor, studies involving healthy individuals, individuals with severe liver and pancreatic diseases, heart failure, inflammatory diseases, chronic kidney disease undergoing hemodialysis, neoplasms, articles discussing the use of food and alcoholic beverages, and those lacking clear presentation of bioactive food compounds dosage.

Protocol and registration

This study comprises a systematic review investigating the effects of resveratrol, quercetin, and catechin on endothelial function in individuals with SAH. The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, detailed in supplemental file S1. The study protocol was not previously registered.

Primary and secondary outcomes

The primary outcome was assessing the effects of resveratrol, quercetin, and catechin on endothelial changes in individuals with SAH, based on randomized clinical trials. The secondary outcome was to analyze the dosages of these compounds used in the studies.

Data extraction

Data extraction was carried out by two independent reviewers and recorded in a Microsoft Excel spreadsheet. Duplicate articles were removed. Articles were then assessed based on their titles and abstracts for eligibility. Selected articles were fully read, and those not meeting the inclusion criteria were excluded.

Risk of bias assessment

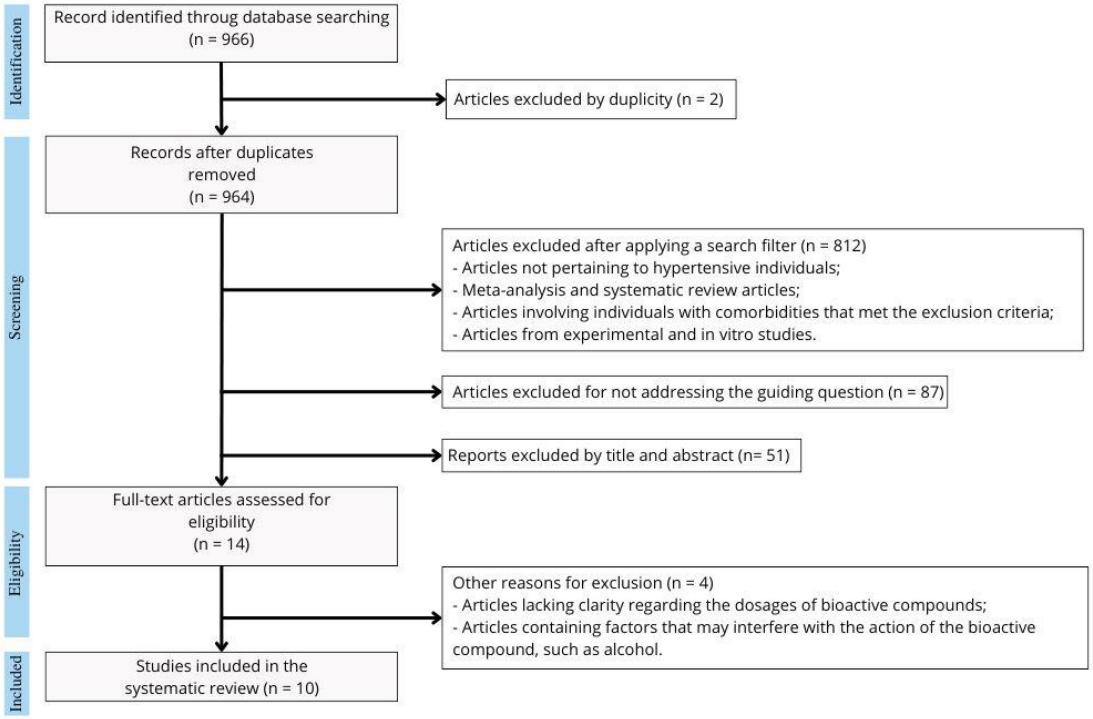
The risk of bias assessment was conducted independently by two reviewers, with any discrepancies resolved by a third researcher from the study team. Randomized clinical trial articles selected for evaluation were assessed using the Cochrane Collaboration Risk of Bias (ROB) tool, employing a simplified framework outlined by Carvalho et al. (2013) (CARVALHO; SILVA; GRANDE, 2013). This tool covers seven aspects: sequence generation, allocation concealment, blinding of participants and personnel, detection bias, attrition bias, reporting bias, and overall risk of bias. Articles were categorized as having low, uncertain, or high risk of bias based on these criteria.

RESULTS

Studies selection

The search was carried out between August 2021 and April 2024, yielding 966 articles. Following a rigorous screening process, 14 articles were selected for full review. Eligibility assessment based on predetermined criteria led to the inclusion of 10 articles in the systematic review. Further details are available in Figure 1.

Figure 1. PRISMA flow diagram.



Source: Author, 2024.

Studies characteristics

The studies selected for this systematic review were published between 2007 and 2018 and focused on adults of both genders diagnosed with SAH. All included articles were intervention studies conducted as randomized clinical trials, involving a total of 395 individuals. These studies investigated the effects of the bioactive compounds under scrutiny (resveratrol, quercetin, and catechin) on blood pressure and endothelial function. There was notable variation in sample size and gender distribution across the studies, although the age ranges were similar. Table 1 presents details of the 10 studies included in this review, indicating a beneficial impact of resveratrol and quercetin on enhancing endothelial function in individuals with SAH. However, no significant effect was observed in normotensive individuals.

Table 1: Characterization of the studies included in the systematic review (n = 10).

	Author/ Year	Study design	n	Sex	Mean age (years)	Exposure/ Intervention	Outcome
Resveratrol	Marques, et al / 2018(MARQUES et al., 2018)	RCT	24	14 women and 10 men	54	300 mg of resveratrol in a single dose.	The group that received trans-resveratrol showed a significant increase in FMD, despite no change in blood pressure.
	Wong, *et al* / 2011(WONG et al., 2011)	RCT	19	5 women and 14 men	55	A placebo dose plus 3 single doses of resveratrol were evaluated: 30, 90, 270 mg at 4 weekly intervals.	All three dosages significantly increased FMD when compared to placebo.
	Silva-e-Oliveira, *et al* / 2016(SILVA-E-OLIVEIRA et al., 2016)	RCT	17	11 women and 6 men	35	100 mg of resveratrol for 30 days.	There was no significant difference between the placebo and supplemented groups.
	Fujitaka, *et al* / 2011(FUJITAKA et al., 2011)	RCT	34	9 women and 25 men	63	100 mg/day of resveratrol for 3 months.	Supplementation improved endothelial function.
Quercet	Edwards, *et al* / 2007(EDWARDS et al., 2007)	RCT	41	15 women and 26 men with hypertension	49,2	365 mg of quercetin twice daily for 28 days.	Supplementation reduced blood pressure.
	Brüll, *et al* / 2015(BRÜLL et al., 2015)	RCT	68	34 women and 34 men	47,4	162 mg/day of quercetin for 6 weeks.	Improvement in blood pressure in individuals with SAH, however, there

in						were no changes in endothelial function.
	Egert, *et al* / 2009(EGERT et al., 2009)	RCT	93	51 women and 42 men	45,3	150 mg/day of quercetin for 6 weeks.	Supplementation improved endothelial function.
	Brull, *et al* / 2017(BRÜLL et al., 2017)	RCT	22	11 women and 11 men	48	54 mg of quercetin with a high-calorie, high-fat and high-carbohydrate diet for 6 weeks.	Study-induced postprandial metabolic responses were not attenuated by concomitant intake of quercetin.
	Larson, *et al* / 2012(LARSON et al., 2012)	RCT	17	17 men	41	1095 mg of quercetin for 7 days.	It resulted in a decrease in FMD, however, there was no change in blood pressure.
Catechin	Saarenhovi, *et al* / 2017(SAARENHOVI et al., 2017)	RCT	60	34 women and 26 men	55	100 mg/day of catechin for 4 weeks.	Supplementation improved endothelial function.

FMD: flow-mediated dilation; RCT: randomized clinical trial; SAH: systemic arterial hypertension.

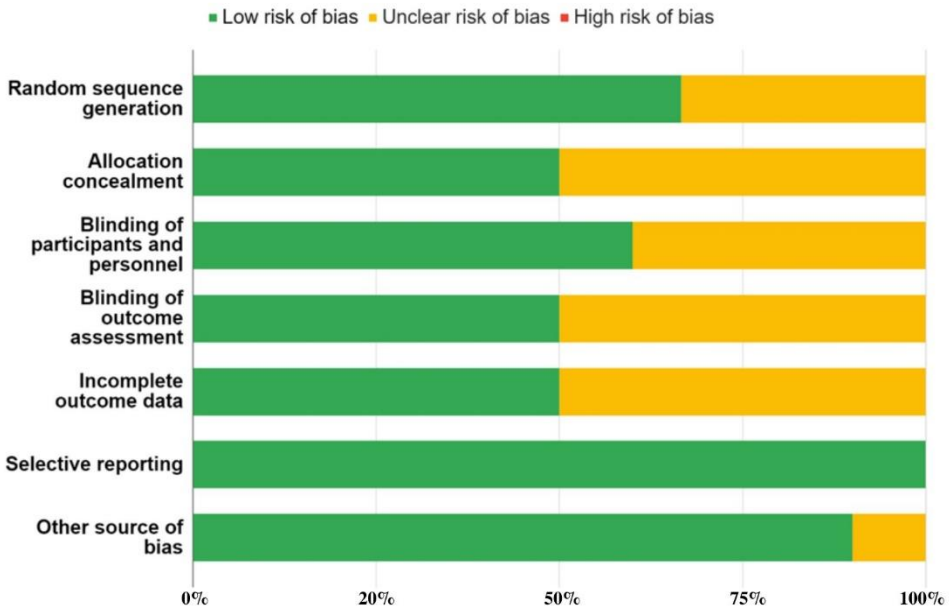
Source: Author, 2024.

Regarding catechin, only one study meeting our inclusion criteria was identified, demonstrating promising improvements in endothelial function. Therefore, further randomized clinical trials are needed to evaluate the role of this bioactive compound in endothelial function among individuals with SAH.

Risk of bias

Figure 2 presents the risk of bias assessment of the randomized clinical trials included in the systematic review, utilizing the Cochrane Risk of Bias (ROB) tool. The majority of articles showed a low risk of bias across the seven aspects evaluated by the tool. Particularly noteworthy is the aspect of "selective outcome report," which displayed a low risk of bias in all included articles, indicating a high level of reporting integrity.

Figure 2. Assessment of risk of bias in randomized clinical trial studies selected for the present systematic review according to the Cochrane Risk of Bias - ROB tool.



Source: Author, 2024.

DISCUSSION

Endothelial dysfunction can arise from inflammatory processes associated with conditions like SAH (BARROSO et al., 2021). Research has explored certain bioactive compounds that can influence flow-mediated dilation (FMD) of the brachial artery, a non-invasive method for assessing endothelial health, to mitigate potential negative impacts (MARQUES et al., 2018).

Resveratrol, quercetin, and catechin are bioactive compounds found in plant-based foods, recognized for their antioxidant and anti-inflammatory properties. Numerous studies have investigated their cardiovascular health implications, particularly concerning SAH and endothelial function, aiming to evaluate their effectiveness in maintaining vascular homeostasis.

Resveratrol, primarily found in the skin and seeds of Vitis vinifera L. (grape), as well as in red wine, almonds, peanuts, blackberries, blueberries, and cocoa, exists in both cis and trans isomeric forms, with trans-resveratrol being the biologically active form (CASEIRO et al., 2019; CAVALCANTE et al., 2021). Resveratrol has garnered attention for its cardioprotective effects, notably in relation to SAH and atherosclerosis. It positively impacts vascular endothelium and inhibits platelet aggregation. This cardiovascular protective effect is believed to stem from the activation of sirtuin molecules by resveratrol, an enzyme complex that plays a role in safeguarding against cardiac hypertrophy when present at higher levels in the body (CASTALDO et al., 2019; DAI et al., 2018).

The findings of this systematic review include a study by Wong et al. (2011), which observed a significant increase in FMD with three different doses of resveratrol (30mg, 90mg, and 270mg), indicating an improvement in endothelial function. Interestingly, there was no significant difference between the doses, suggesting that even the lowest dose was effective (WONG et al., 2011). Similarly, Marques et al. (2018) found that 300mg of trans-resveratrol significantly increased FMD, indicating improved endothelial function in patients with SAH, although it did not affect blood pressure (MARQUES et al., 2018). In contrast, Silva-e-Oliveira et al. (2016) did not observe significant improvements in endothelial function with low doses of resveratrol (100mg daily for 30 days), suggesting that higher doses and longer treatment duration may be necessary (SILVA-E-OLIVEIRA et al., 2016). This is supported by a study by Fujitaka et al. (2011), where endothelial improvement was observed using 100mg of resveratrol for three months (FUJITAKA et al., 2011).

Red wine is a widely consumed beverage extensively studied in relation to cardiovascular health. It has a complex composition, containing a wide variety of phenolic compounds, including resveratrol, which can range from 2000 to 6000 mg/L (MINZER; ESTRUCH; CASAS, 2020). In his thesis, Andrade (2006)* conducted a study

involving red wine and observed an increase in sympathetic activity in hypertensive and hypercholesterolemic patients. However, only the hypercholesterolemic patients demonstrated an improvement in endothelial function, as indicated by an increase in FMD. This improvement may be attributed to the increase in endothelial NO synthase and the inhibition of endothelin-1 production. The absence of significant changes in FMD in hypertensive patients suggests different mechanisms regulating endothelial function between various health conditions, possibly influenced by the medications used by hypertensive individuals. It is believed that hypertensive individuals may have lower bioavailability of NO.

The dosages of resveratrol used in the analyzed studies ranged from 30 to 300mg, either administered as a single dose or divided into fractions. In 75% of the studies, Quercetin is a flavonoid widely found in vegetables, fruits, seeds, nuts, black tea, red wine, and beer. However, onions, apples, and broccoli are considered its primary sources [5]. Its cardioprotective effects are attributed to various mechanisms, including the inhibition of low-density lipoprotein oxidation, platelet aggregation, and protein kinase C activity. Inhibited protein kinase C promotes vasodilation by reducing endothelin-1 expression and increasing NO synthesis (SCHAAN, 2003). Additionally, quercetin has been shown to activate β-adrenergic receptors, contributing to vasodilation by aiding in the production of NO by endothelial cells (SILVA; ZANESCO, 2010).

Our findings indicate that quercetin demonstrated a reduction in blood pressure in hypertensive individuals, as observed in studies by Edwards et al. (2007), Larson et al. (2012), and Brull et al. (2015). However, its impact on blood pressure regulation in normotensive individuals has not been significant (BRÜLL et al., 2015; EDWARDS et al., 2007; LARSON et al., 2012). Egert et al. (2009) reported a potential beneficial effect of quercetin on the vascular endothelium, which can be attributed to the inhibition of NADPH oxidase and activation of endothelial NO synthase (EGERT et al., 2009). Brull et al. (2017) conducted an interesting study involving supplementation of 54mg/day of quercetin in combination with a hypercaloric, hyperlipidic, and hyperglycemic diet, aiming to assess the effect of this compound on postprandial parameters such as blood pressure and endothelium-derived adhesion molecules. However, the observed parameters were not attenuated by the concurrent ingestion of quercetin with the provided diet, suggesting the importance of proper nutrition in conjunction with supplementation

to achieve positive results for endothelial function and blood pressure (BRÜLL et al., 2017).

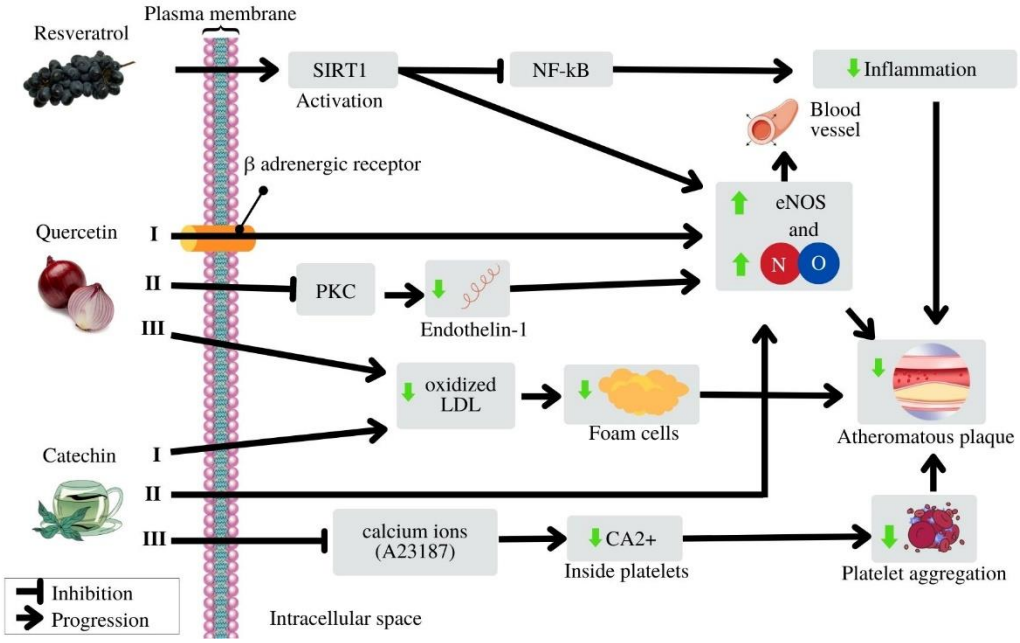
The mechanisms underlying blood pressure regulation are not fully understood, but it is believed that factors influencing endothelial function differ, at least partially, from those regulating blood pressure (BRÜLL et al., 2015). Larson et al. (2012) support this notion in their study, where they observed that a dose of 1095 mg of quercetin for 7 days reduced blood pressure in hypertensive men through a mechanism independent of changes in angiotensin-converting enzyme activity, endothelin-1, or NO bioavailability. Furthermore, this reduction in blood pressure did not affect vascular reactivity, leaving the specific reason for the blood pressure reduction unknown. Larson et al. (2012) reported that their study was the first to demonstrate that a single dose of quercetin can reduce blood pressure in individuals with SAH, and that acute doses may yield similar results to chronic usage (LARSON et al., 2012).

In the analyzed studies, quercetin doses ranged from 54 to 1095 mg, with considerable variations in the duration of follow-up, ranging from 7 days to 6 weeks. Most studies reported a significant increase in FMD and improvement in blood pressure.

The therapeutic potential of catechin has primarily been investigated through herbal treatment using the medicinal herb *Camellia sinensis* in patients with various comorbidities, including cardiovascular diseases (PIRES et al., 2021). This compound can improve endothelial function and blood pressure levels by promoting a balance between vasodilators (e.g., NO) and vasoconstrictors (e.g., thromboxanes and isoprostanes).[6] This effect may be attributed to catechin's inhibition of calcium ion A23187, which reduces intraplatelet Ca2+ levels and prevents platelet aggregation. Additionally, flavonoids such as catechin can reduce atherosclerosis by inhibiting LDL oxidation (OLIVEIRA, 2009; PIRES et al., 2021). The mechanisms of action of both compounds are best represented in Figure 3.

Figure 3. Ways of action of resveratrol, quercetin and catechin on vascular endothelium. After being ingested and absorbed by cells, resveratrol is able to: after ingestion and absorption already in the intracellular space, activates sirtuin molecules. These molecules, in turn, stimulate the production of nitric oxide by the endothelial nitric oxide synthase enzyme and cause the inhibition of the NF-kB inflammatory pathway, resulting in the vasodilation of blood vessels and the reduction of inflammatory processes such as atherosclerosis. Catechin: I)

Promote the improvement of endothelial function promotes the improvement of endothelial function by reducing oxidized LDL and consequently the process of atherosclerosis; II) Increase vasodilating substances such as nitric oxide and reduce vasoconstrictors such as thromboxanes and isopropanes by stimulating the action of the endothelial nitric oxide synthase enzyme; III) Positively influence the reduction of platelet aggregation by inhibiting calcium ions A23187, and thus reduce the process of atherosclerosis. Quercetin: I) induces the activation of β-adrenergic receptors, which in turn contributes to the vasodilation of blood vessels by increasing the expression of nitric oxide; II) The second pathway is that of protein kinase C (PKC), this protein induces vasodilation by reducing the expression of endothelin-1 and increasing the synthesis of nitric oxide; III) Quercetin promotes the improvement of endothelial function by reducing oxidized LDL and consequently the process of atherosclerosis. PKC: protein kinase C; eNOS: endothelial nitric oxide synthase enzyme; NO: nitric oxide; LDL: low density lipoprotein; SIRT1: sirtuin 1; NF-kB: nuclear factor kappa B.



Source: Author, 2024.

A study conducted by Saarenhovi et al. in 2017 investigated the use of catechin and demonstrated a positive effect on endothelial function with the administration of 100mg of epicatechin from apples, as it acutely improved FMD in hypertensive individuals. However, no significant effect on blood pressure was observed. The same study found that the long-term effect of epicatechin on FMD did not significantly differ from the placebo, suggesting a possible reduction in the compound's vascular effects with prolonged exposure (SAARENHOVI et al., 2017).

In contrast, Grassi et al. (2016) conducted research involving black tea polyphenols, which contain 24mg of catechins, in hypertensive patients divided into a control group and a placebo group. Both groups consumed cream to assess whether the compounds present in tea could mitigate the impact of dietary fat. Unlike the placebo group, the tea group exhibited a reduction in FMD after 7 days. On the eighth day, when fat was administered, it was observed that the intervention group did not experience a significant change in FMD when consuming fat concurrently with tea, indicating vascular protection. Compared to the placebo, ingestion of black tea increased circulating angiogenic cells and helped maintain and repair the endothelium, thus aiding in its regulation. These results suggest that the flavonoids in tea can enhance or preserve the bioavailability of NO, decrease the production of reactive oxygen and nitrogen species, and increase NO synthase activity (GRASSI et al., 2016).

The findings from studies involving resveratrol, quercetin, and catechin suggest potential clinical improvements in individuals with cardiovascular diseases, particularly those with SAH, by focusing on endothelial health. These compounds may serve as adjuncts in the treatment of this condition, mitigating its severity and progression. The mechanisms of action for those compounds are depicted in central illustration.

However, it is important to note that only one study on catechin met the inclusion criteria for this review, limiting our ability to draw specific conclusions about this compound. Therefore, further studies on catechin are necessary to provide more specific results for its use in improving endothelial function in hypertensive individuals.

CONCLUSION

Based on the findings of this review, it is recommended that a healthy diet comprising foods rich in resveratrol and quercetin, or their supplementation alongside a well-balanced diet, is beneficial for the health, treatment, and prevention of individuals with SAH. These compounds have shown favourable effects on vascular endothelium in individuals with this condition. However, further studies are needed to draw a definitive conclusion regarding the impact of catechin on the vascular endothelium of hypertensive individuals.

REFERÊNCIAS

BARROSO, W. K. S. et al. Diretrizes Brasileiras de Hipertensão Arterial – 2020. **Arquivos Brasileiros de Cardiologia**, v. 116, n. 3, p. 516–658, 3 mar. 2021.

BEHLING, E. et al. Flavonóide quercetina: aspectos gerais e ações biológicas. **Alimentos e Nutrição**, v. 15, 1 set. 2008.

BRÜLL, V. et al. Effects of a quercetin-rich onion skin extract on 24 h ambulatory blood pressure and endothelial function in overweight-to-obese patients with (pre-)hypertension: a randomised double-blinded placebo-controlled cross-over trial. **British Journal of Nutrition**, v. 114, n. 8, p. 1263–1277, 28 out. 2015.

BRÜLL, V. et al. Acute intake of quercetin from onion skin extract does not influence postprandial blood pressure and endothelial function in overweight-to-obese adults with hypertension: a randomized, double-blind, placebo-controlled, crossover trial. **European Journal of Nutrition**, v. 56, n. 3, p. 1347–1357, abr. 2017.

CARVALHO, A. P. V.; SILVA, V.; GRANDE, A. J. Avaliação do risco de viés de ensaios clínicos randomizados pela ferramenta da colaboração Cochrane. **Diagn Tratamento**, v. 18, p. 38–44, 1 jan. 2013.

CASEIRO, A. et al. Avaliação laboratorial do efeito antioxidante e anti-inflamatório do Resveratrol na função vascular. **RevSALUS - Revista Científica da Rede Académica das Ciências da Saúde da Lusofonia**, v. 1, n. 2, p. 37–46, 27 nov. 2019.

CASTALDO et al. Red Wine Consumption and Cardiovascular Health. **Molecules**, v. 24, n. 19, p. 3626, 8 out. 2019.

CAVALCANTE, L. G. D. S. et al. Papel antiaterogênico do Resveratrol e seu efeito sobre a pressão arterial. **Research, Society and Development**, v. 10, n. 10, p. e213101018873, 8 ago. 2021.

DAI, H. et al. Sirtuin activators and inhibitors: Promises, achievements, and challenges. **Pharmacology & Therapeutics**, v. 188, p. 140–154, ago. 2018.

EDWARDS, R. L. et al. Quercetin Reduces Blood Pressure in Hypertensive Subjects1,. **The Journal of Nutrition**, v. 137, n. 11, p. 2405–2411, nov. 2007.

EGERT, S. et al. Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: a double-blinded, placebo-controlled cross-over study. **British Journal of Nutrition**, v. 102, n. 7, p. 1065–1074, 14 out. 2009.

FUJITAKA, K. et al. Modified resveratrol Longevinex improves endothelial function in adults with metabolic syndrome receiving standard treatment. **Nutrition Research**, v. 31, n. 11, p. 842–847, nov. 2011.

GRASSI, D. et al. Black Tea Increases Circulating Endothelial Progenitor Cells and Improves Flow Mediated Dilatation Counteracting Deleterious Effects from a Fat Load in Hypertensive Patients: A Randomized Controlled Study. **Nutrients**, v. 8, n. 11, p. 727, 16 nov. 2016.

LARSON, A. et al. Acute, quercetin-induced reductions in blood pressure in hypertensive individuals are not secondary to lower plasma angiotensin-converting enzyme activity or endothelin-1: nitric oxide. **Nutrition Research**, v. 32, n. 8, p. 557–564, ago. 2012.

MARQUES, B. C. A. A. et al. Beneficial effects of acute trans-resveratrol supplementation in treated hypertensive patients with endothelial dysfunction. **Clinical and Experimental Hypertension**, v. 40, n. 3, p. 218–223, 3 abr. 2018.

MINZER, S.; ESTRUCH, R.; CASAS, R. Wine Intake in the Framework of a Mediterranean Diet and Chronic Non-Communicable Diseases: A Short Literature Review of the Last 5 Years. **Molecules**, v. 25, n. 21, p. 5045, 30 out. 2020.

OLIVEIRA, R. M. M. DE. Chá Verde na prevenção das doenças cardiovasculares. **Comun. ciênc. saúde**, p. 325–332, 2009.

PIRES, B. D. C. et al. CAMELLIA SINENSIS: BENEFÍCIOS NO AUXÍLIO AO TRATAMENTO DA OBESIDADE/CAMELLIA SINENSIS: BENEFITS IN AIDING THE TREATMENT OF OBESITY. **Brazilian Journal of Development**, v. 7, n. 2, p. 15411–15420, 2021.

REIS, R. C. et al. Compostos bioativos e atividade antioxidante de variedades melhoradas de mamão. **Ciência Rural**, v. 45, n. 11, p. 2076–2081, nov. 2015.

SAARENHOVI, M. et al. The effect of an apple polyphenol extract rich in epicatechin and flavan-3-ol oligomers on brachial artery flow-mediated vasodilatory function in volunteers with elevated blood pressure. **Nutrition Journal**, v. 16, n. 1, p. 73, dez. 2017.

SCHAAN, B. D. O papel da proteína quinase C no desenvolvimento das complicações vasculares do diabetes mellitus. **Arquivos Brasileiros de Endocrinologia & Metabologia**, v. 47, n. 6, p. 654–662, dez. 2003.

SENGER, A. E. V.; SCHWANKE, C. H. A.; GOTTLIEB, M. G. V. Chá verde (Camellia sinensis) e suas propriedades funcionais nas doenças crônicas não transmissíveis. **Sci. med**, p. 292–300, 2010.

SILVA, A. S.; ZANESCO, A. Exercício físico, receptores β-adrenérgicos e resposta vascular. **Jornal Vascular Brasileiro**, v. 9, n. 2, p. 47–56, jun. 2010.

SILVA-E-OLIVEIRA, J. et al. Low-dose resveratrol supplementation on heart rate variability in hypertensive volunteers: a controlled double-blind trial. **Medical Express**, v. 3, n. 6, 2016.

WONG, R. H. X. et al. Acute resveratrol supplementation improves flow-mediated dilatation in overweight/obese individuals with mildly elevated blood pressure. **Nutrition, Metabolism and Cardiovascular Diseases**, v. 21, n. 11, p. 851–856, nov. 2011.

YUGAR-TOLEDO, J. C. et al. Disfunção Endotelial e Hipertensão Arterial. v. 22, 2015.

ZHOU, B. et al. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. **The Lancet**, v. 389, n. 10064, p. 37–55, jan. 2017.