

# The Role of Polyphenols, with Particular Emphasis on Resveratrol, in the Prevention of Selected Cardiovascular Diseases – A Review of the Current Literature

Jakub Dudek<sup>1,A,B,C,D,E,F</sup>

ORCID: 0009-0001-7111-887X

Grzegorz Sochań<sup>3,B,C,D,E,F</sup>

ORCID: 0009-0002-7634-2253

Dominika Wodziak<sup>5,B,C,D,E,F</sup>

ORCID: 0009-0001-2880-4217

Kinga Bodziony<sup>7,B,C,D,E,F</sup>

ORCID: 0009-0007-4363-7692

Wiktor Górecka<sup>2,A,B,C,D,E,F</sup>

ORCID: 0009-0000-7591-8340

Kinga Filip<sup>4,B,C,D,E,F</sup>

ORCID: 0009-0008-3731-1087

Anna Pszonka<sup>6,B,C,D,E,F</sup>

ORCID: 0000-0002-9525-5908

Aleksandra Komoń<sup>8,B,C,D,E,F</sup>

ORCID: 0009-0002-8355-3147

<sup>1</sup> Lower Silesian Specialist Hospital – Centre for Emergency Medicine, Wrocław, Poland; <sup>2</sup> University Centre of Dentistry, Wrocław, Poland; <sup>3</sup> Jagiellonian University Medical College, Kraków, Poland; <sup>4</sup> 5th Military Clinical Hospital with Polyclinic, Kraków, Poland; <sup>5</sup> Ministry of the Interior and Administration Hospital in Opole, Opole; <sup>6</sup> Regional Center of Health, Lubin, Poland; <sup>7</sup> Lower Silesian Oncology, Pulmonology and Hematology Center, Wrocław, Poland; <sup>8</sup> Mazowiecki Hospital Sp. z o.o., Radom, Poland

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## ABSTRACT

*The Role of Polyphenols, with Particular Emphasis on Resveratrol, in the Prevention of Selected Cardiovascular Diseases – A Review of the Current Literature*

Dudek J.<sup>1</sup>, Górecka W.<sup>2</sup>, Sochań G.<sup>3</sup>, Filip K.<sup>4</sup>, Wodziak D.<sup>5</sup>, Pszonka A.<sup>6</sup>, Bodziony K.<sup>7</sup>, Komoń A.<sup>8</sup>

<sup>1</sup> Lower Silesian Specialist Hospital – Centre for Emergency Medicine, Wrocław, Poland; <sup>2</sup> University Centre of Dentistry, Wrocław, Poland; <sup>3</sup> Jagiellonian University Medical College, Kraków, Poland; <sup>4</sup> 5th Military Clinical Hospital with Polyclinic, Kraków, Poland; <sup>5</sup> Ministry of the Interior and Administration Hospital in Opole, Opole, Poland; <sup>6</sup> Regional Center of Health, Lubin, Poland; <sup>7</sup> Lower Silesian Oncology, Pulmonology and Hematology Center, Wrocław, Poland; <sup>8</sup> Mazowiecki Hospital sp. z o.o., Radom, Poland

**Introduction and aim of the study.** Cardiovascular disease (CVD) represents a significant global health concern. The potential benefits of molecules that have a positive impact on the cardiovascular system are still being investigated. The objective of this study is to conduct a comprehensive review of the existing literature and to evaluate the effect of polyphenols on a range of selected cardiovascular diseases.

## STRESZCZENIE

*Rola polifenoli, ze szczególnym uwzględnieniem resweratrolu, w profilaktyce wybranych chorób układu sercowo-naczyniowego – przegląd aktualnego piśmiennictwa*

Dudek J.<sup>1</sup>, Górecka W.<sup>2</sup>, Sochań G.<sup>3</sup>, Filip K.<sup>4</sup>, Wodziak D.<sup>5</sup>, Pszonka A.<sup>6</sup>, Bodziony K.<sup>7</sup>, Komoń A.<sup>8</sup>

<sup>1</sup> Dolnośląski Szpital Specjalistyczny im. T. Marciniaka – Centrum Medycyny Ratunkowej, Wrocław; <sup>2</sup> Uniwersyteckie Centrum Stomatologiczne, Wrocław; <sup>3</sup> Uniwersytet Jagielloński – Collegium Medicum, Kraków; <sup>4</sup> 5. Wojskowy Szpital Kliniczny z Polikliniką SPZOZ im. gen. bryg. prof. Mariana Garlickiego w Krakowie, Kraków; <sup>5</sup> Samodzielny Publiczny Zakład Opieki Zdrowotnej MSWiA w Opolu, Opole; <sup>6</sup> Regionalne Centrum Zdrowia, Lubin; <sup>7</sup> Dolnośląskie Centrum Onkologii, Pulmonologii i Hematologii, Wrocław; <sup>8</sup> Mazowiecki Szpital Specjalistyczny Sp. z o.o., Radom

**Wprowadzenie i cel pracy.** Choroby układu krążenia (CVD) są współcześnie jednym z głównych problemów zdrowotnych na całym świecie. Wciąż badane są cząsteczki mające pozytywny wpływ na układ sercowo-naczyniowy. Celem niniejszej pracy jest przegląd piśmiennictwa i ocena wpływu polifenoli na wybrane choroby układu sercowo-naczyniowego.

**Review methods.** Relevant information was collected through a systematic search of PubMed and Google Scholar. The following search terms were used: “polyphenols,” “resveratrol,” “atherosclerosis,” “stroke,” “heart failure,” “hypertension,” “coronary artery disease,” “obesity.” The scientific articles subjected to analysis included meta-analyses and randomized clinical trials, presented in both Polish and English. A total of 44 scientific articles were analyzed, of which 41 were published after 2016.

**Current knowledge.** Polyphenols are present in a multitude of commonly consumed and readily available products, including nuts, olive oil, fruits and vegetables, wine, and tea. The anti-inflammatory properties of polyphenols underscore their significance in the management of cardiovascular diseases. In recent years, particular attention has been paid to the impact of resveratrol on cardiovascular diseases.

**Conclusions.** The cited studies have demonstrated that polyphenols, including resveratrol, may have a significant impact on reducing the incidence of selected cardiovascular diseases, decreasing mortality, and alleviating disease progression. However, further research in this area is undoubtedly necessary.

**Keywords:** polyphenols, resveratrol, atherosclerosis, heart failure, obesity

**Metody przeglądu.** Istotne informacje zostały zestawione poprzez systematyczny przegląd baz PubMed i Google Scholar. Zastosowano kombinację słów kluczowych: „polifenole”, „resweratrol”, „miażdżyca”, „udar mózgu”, „niewydolność serca”, „nadciśnienie tętnicze”, „choroba niedokrwienności serca” i „otyłość”. Wśród analizowanych artykułów naukowych znalazły się metaanalizy oraz randomizowane badania kliniczne w języku polskim i angielskim. Analizą objęto 44 artykułów naukowych, z czego 41 zostało opublikowanych po 2016 roku.

**Opis stanu wiedzy.** Polifenole obecne są w wielu powszechnie dostępnych i spożywanych produktach, takich jak orzechy, oliwa z oliwek, owoce i warzywa, wino, herbata. Przeciwzapalnie właściwości polifenoli sprawiają, że coraz częściej podkreśla się ich znaczenie w terapii chorób sercowo-naczyniowych. W ostatnich latach szczególnie dużą uwagę poświęca się wpływowi resweratrolu na choroby układu sercowo-naczyniowego.

**Wnioski.** Przytoczone badania pokazały, że polifenole, w tym resweratrol, mogą mieć istotny wpływ na zmniejszenie zapadalności na wybrane choroby sercowo-naczyniowe, spadek śmiertelności z ich powodu, a także łagodzenie przebiegu tych chorób. Niewątpliwie konieczne jest jednak przeprowadzenie większej liczby badań w tym zakresie.

**Słowa kluczowe:** polifenole, resweratrol, miażdżyca, niewydolność serca, otyłość

## Introduction and aim of the study

Cardiovascular diseases (CVDs) represent a significant global health concern [1]. Data published by Statistics Poland (GUS) indicate that mortality due to cardiovascular system dysfunction is the leading cause of death in Poland [2]. It is a priority for the scientific community to identify novel factors that may prevent the development of cardiovascular diseases. One area of ongoing research is the impact of polyphenols on the human body.

The aim of this paper is to provide a comprehensive review of the existing literature on resveratrol and other polyphenols, with a particular focus on their effects on a range of diseases, including hypertension, heart failure, obesity, coronary artery disease, and stroke.

## Review methods

A review of the literature was conducted using scientific articles from online databases in both Polish and English. The articles included meta-analyses and randomized clinical trials. The PubMed and Google Scholar databases were reviewed. The following keywords were used in combination to search the literature: “polyphenols,” “resveratrol,” “atherosclerosis,” “stroke,” “heart failure,” “hypertension,” “coronary artery disease,” “obesity,” and “inflammation.” A total of 44 scientific articles were analyzed, of which 41 were published after 2016.

## Current knowledge

Current scientific evidence demonstrates that polyphenols—specifically resveratrol, quercetin, and caffeic and coumaric acids—are widely distributed across a diverse range of dietary sources. These compounds are particularly abundant in fruits (including apples, grapes, citrus fruits, and berries), vegetables such as onions, and various legumes such as soy. Furthermore, significant concentrations are found in daily staples and stimulants, notably tea, wine, green coffee beans, cocoa, nuts, and olive oil, as well as in botanical sources such as hibiscus flowers. The role of polyphenols in the prevention of chronic diseases characterized by inflammation is a topic of considerable emphasis in the literature. These compounds represent a vital component of the oxidative-reductive system, endowing them with distinctive anti-inflammatory properties that distinguish them from other therapeutic modalities for cardiovascular diseases. In recent years, polyphenols have been shown to play a significant role in the prevention of cardiovascular disease. The beneficial effects of these compounds have been observed in patients with heart failure, coronary artery disease, stroke, and obesity. At present, one of the most extensively researched polyphenols is resveratrol.

## Polyphenols – mechanism of action

During the process of cellular respiration, reactive oxygen species (ROS) are produced. These are

molecules that contain oxygen atoms with unpaired electrons, for example, the superoxide anion and hydroxyl radical, or peroxide bonds, such as hydrogen peroxide [3]. Reactive oxygen species (ROS) perform a number of physiological functions within the body, including signal transmission, cell differentiation, apoptosis, immune system regulation, and metabolic control. However, an excess of ROS can result in the activation of pathological processes [3,4].

ROS primarily exert destructive effects by deactivating or modifying enzymes, which disrupts cellular metabolism and signal transduction. This pathomechanism contributes to the development of chronic diseases through increased inflammatory response, enhanced cell mobility, uncontrolled cell proliferation, apoptosis, and induction of epithelial-mesenchymal transition [3].

In order to maintain equilibrium between oxidative and antioxidative processes, the body requires substances capable of neutralizing the effects of ROS. These include tocopherols, ascorbates, urates, thiol compounds, carotenoids, retinoids, and polyphenols such as resveratrol, quercetin, caffeic acids, and coumaric acids. These compounds, in conjunction with enzymatic systems such as glutathione peroxidase, constitute an effective oxidative-reductive system that helps prevent oxidative stress [3,5]. Polyphenols are plant metabolites found in fruits and vegetables that, when consumed, have been shown to reduce levels of pro-inflammatory cytokines, including IL-6, IL-1 $\beta$ , TNF- $\alpha$ , interferon- $\gamma$ , IL-2, and nitric oxide. Furthermore, evidence indicates that these compounds reduce inflammation by inhibiting nuclear factor  $\kappa$ B, regulating mitogen-activated protein kinase, modulating inducible nitric oxide synthase, and inhibiting cyclooxygenase-2 and lipoxygenase [6,7,8].

## Resveratrol

Resveratrol (3,5,4-trihydroxystilbene) is a natural phytoalexin occurring in a variety of plant species, including grapes, nuts, and red wine [9]. A substantial body of scientific evidence has demonstrated the beneficial effects of resveratrol on cardiovascular diseases, including coronary artery disease, heart failure, and stroke. It is hypothesized that the protective action of resveratrol on the cardiovascular system is related to its ability to reduce oxidative stress and inflammation, as well as to decrease the intensity of fibrinogenesis in the heart muscle. Research has demonstrated that resveratrol is 20 times more effective than vitamin C and 50 times more effective than vitamin E in preventing lipid peroxidation [10].

Additionally, resveratrol has been demonstrated to enhance the activity of heme oxygenase in neural stem cells within the brain's neurogenic zones [8,11].

The promotion of faster proliferation and increased survival of brain stem cells has been confirmed to result from high activity of heme oxygenase (HO-1). Furthermore, elevated heme oxygenase activity enhances the resilience of neuronal cells to oxidative stress that occurs following the restoration of circulation in damaged brain regions, where there is increased post-reperfusion production of reactive oxygen species.

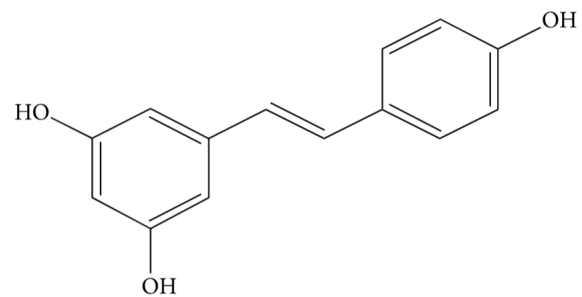


Figure 1. Chemical structure of resveratrol [9]

It is crucial to acknowledge that the plasma concentration of resveratrol is dependent upon the dosage and duration of supplementation. For instance following oral administration of a 5 g dose, plasma concentration of resveratrol was approximately 500 ng/mL, whereas a 25 mg dose resulted in a concentration of only 5 ng/mL. Notably, in a 29-day study in which participants were administered resveratrol at a dose of 5 g, plasma concentrations reached as high as 900 ng/mL. Furthermore, the hypothesis that resveratrol interacts safely with the body remains unchallenged. Raj et al. highlight that even very high doses of resveratrol (5 g) are considered safe, with only minor to moderate gastrointestinal issues reported [8].

Importantly, although high doses of resveratrol (1–5 g) are considered safe, the consumption of resveratrol-rich foods in typical dietary amounts does not provide sufficient intake of this polyphenol. In their study, Weiskirchen et al. presented an illustrative diagram demonstrating the substantial amounts of various products—such as peanuts, red wine, white wine, rosé wine, beer, dark chocolate, milk chocolate, tomatoes, red grapes, white grapes, apples, and tea—that would need to be consumed to achieve the recommended daily intake of resveratrol [12].

Table 1. Average resveratrol concentrations in products [12]

Food product	Average resveratrol concentration	Estimated amount required to achieve a daily intake of 1g of resveratrol
peanuts	0.03–0.14 µg/g	7143–33333 kg
red wine	0.361–1.972 mg/l	505–2762 L
white wine	0–1.089 mg/l	2564–17544 L
rose wine	0.29 mg/l	3448 L
beer	1.34–77.0 µg/l	12987–746269 L
dark chocolate	350 µg/kg	2857 kg
milk chocolate	100 µg/kg	10000 kg
tomato, skin	19 µg/g	52.6 kg
red grapes	92–1604 µg/kg	795 kg
white grapes	59–1759 µg/kg	2584 kg
apple	400 µg/kg	2500 kg
Itadori tea	68 µg/100 ml	1471 L

From the above table, it is evident that although red wine contains relatively higher amounts of resveratrol compared to other polyphenol-rich products, these levels are far from sufficient to meet daily intake recommendations without additional supplementation [12]. It should be emphasized that achieving the recommended dose of resveratrol would require the consumption of several hundred liters of wine per day, which is toxic due to its ethanol content. According to the study by LaHood et al., blood alcohol concentrations (BAC) between 0.05% and 0.1% already exert adverse physiological effects, while BAC values exceeding 0.4% may induce respiratory depression, coma, or even death [13]. The ingestion of such large volumes of wine far exceeds the detoxification capacity of the human body and is therefore inherently toxic. In practice, high resveratrol intake can only be realistically achieved through supplementation with resveratrol-enriched preparations rather than through wine consumption.

### The effect of polyphenols on blood pressure

The influence of polyphenols on blood pressure is a well-documented phenomenon. According to the SCORE-2 scale, blood pressure is a risk factor for cardiovascular disease, particularly in relation to cardiac workload. It is noteworthy that even prehypertension, defined as a systolic blood pressure (SBP) of 120–139 mmHg and/or a diastolic blood pressure (DBP) of 80–89 mmHg, is associated with an elevated risk of cardiovascular diseases, including stroke, coronary artery disease, myocardial infarction, and fatal cardiovascular events [14].

The most recent guidelines on hypertension place considerable emphasis on the importance of preven-

tion, including the role of an appropriate diet. The probability of being diagnosed with hypertension is 8% lower in individuals who consume increased amounts of anthocyanins (polyphenols) compared to those with a diet low in polyphenols [11]. Scientific reports indicate that desirable dietary components rich in polyphenols include apples, onions (which contain quercetin and rutin), green tea (rich in polyphenols such as epigallocatechin gallate, gallic acid, gallic acid, gallic acid, catechin, epigallocatechin, epicatechin, and epicatechin gallate), small berries and stone fruits such as blackberries, green coffee beans, hibiscus flowers, and dark chocolate. It is hypothesized that both chlorogenic acid, which is present in green coffee beans, and polyphenols found in hibiscus flowers may act as specific inhibitors of angiotensin-converting enzyme (ACE), thereby blocking the conversion of angiotensin I to angiotensin II. This results in a reduction in the contraction of vascular smooth muscle and a subsequent lowering of blood pressure. A reduction in systolic blood pressure from 134.8 mmHg to 112.7 mmHg was observed over a one-month period in a study in which participants consumed approximately one cup of hibiscus tea daily [11].

Furthermore, wine produced through the fermentation of grape seeds and skins contains procyanidins, which exert an effect on endothelium-dependent vasodilation by reducing the secretion of endothelin-1, a vasoconstrictor peptide [5]. Other sources indicate that polyphenols present in grapes stimulate the production of nitric oxide (NO), which causes vasodilation [11].

Resveratrol may also prove effective as an antiplatelet agent by inhibiting monocyte adhesion to the vessel wall, promoting vasodilation, and inhibiting smooth muscle cell proliferation in blood vessels via endothelial nitric oxide synthase [8].

A meta-analysis conducted by Liu et al. included six studies with 247 patients and demonstrated that resveratrol intake does not significantly lower systolic blood pressure (SBP) and diastolic blood pressure (DBP). The study showed that higher doses of resveratrol ( $\geq 150$  mg/day) were associated with a reduction in SBP by 11.9 mmHg, whereas lower doses did not exhibit a comparable effect. The meta-analysis concluded that high-dose resveratrol significantly reduces systolic blood pressure (SBP) but has no effect on diastolic blood pressure (DBP) [15].

In a further meta-analysis conducted by Fogacci et al., no significant effect of resveratrol on the reduction of SBP, DBP, mean arterial pressure (MAP), or pulse pressure was observed. Nevertheless, a significant reduction in systolic blood pressure was reported in subjects administered high-dose resveratrol ( $\geq 300$  mg/day). Notably, no analogous correlation was identified between resveratrol and a reduction in mean arterial pressure (MAP) or pulse pressure. The results of this meta-analysis indicate that resveratrol may confer health benefits when administered in high doses, particularly in patients with diabetes [16].

Another meta-analysis demonstrated that the consumption of polyphenols extracted from dark grape fruits at a dose of approximately 730 mg per day resulted in a significant reduction in systolic blood pres-

sure within a single month. However, no impact on diastolic blood pressure was found [11].

## The effect of polyphenols on heart failure

Heart failure (HF) is a syndrome of symptoms caused by functional dysfunction of the heart muscle. A failing heart is unable to maintain adequate organ perfusion due to the inability of the ventricles to fill with blood (diastolic dysfunction) or insufficient contractile force (systolic dysfunction). Current understanding of the classification of heart failure (HF) is based on left ventricular ejection fraction (LVEF). Regrettably, despite the implementation of highly sophisticated therapeutic strategies, the treatment of heart failure continues to present a significant challenge [8].

One of the most well-established causes of heart failure is cardiac fibrosis. This condition manifests as an adaptive response of the cardiac muscle to stressful stimuli. Myocardial fibrosis can be caused by a number of pathological factors, including hypertension, myocardial infarction, and arrhythmias. Myocardial fibrosis results in significant functional impairment of the heart muscle, characterized by increased stiffness and, consequently, systolic and diastolic dysfunction, as well as reduced coronary reserve [17].

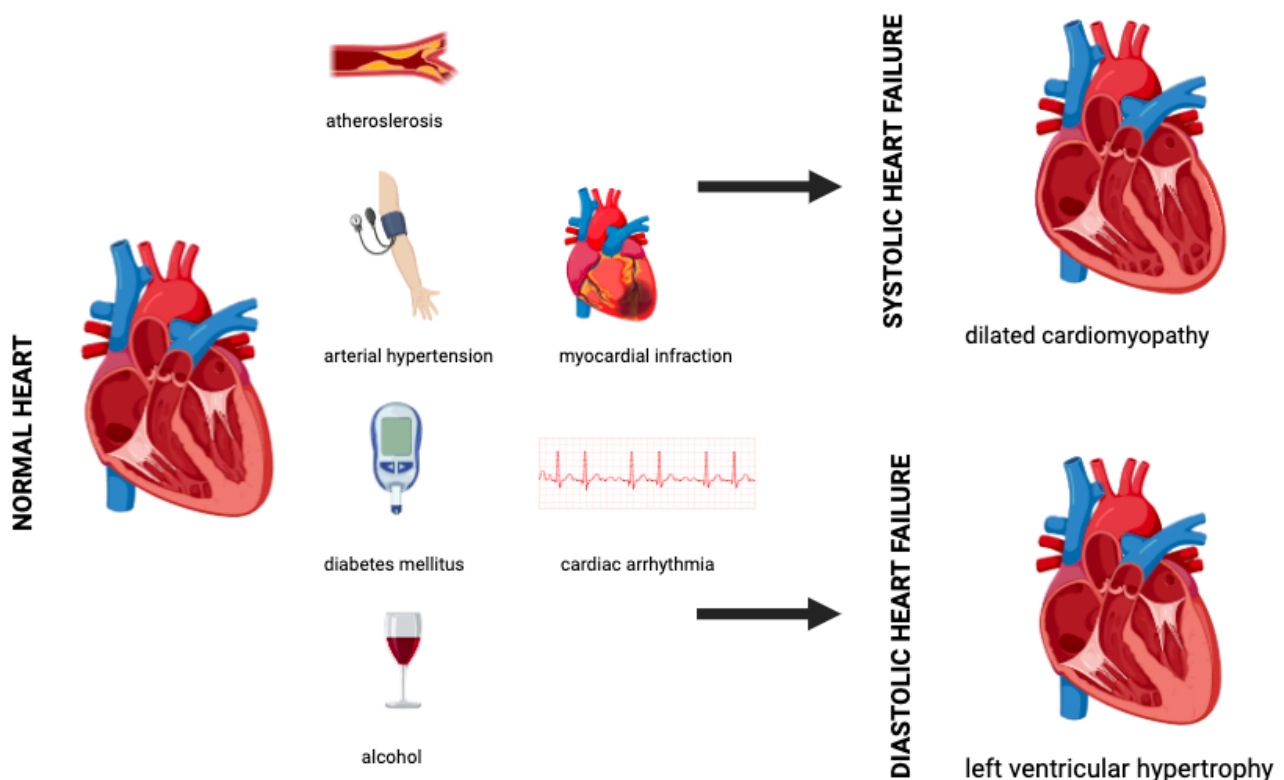


Figure 2. Pathophysiology of heart failure

Source: BioRender illustration; <http://app.biorender.com/illustrations/68aefbe3fe10c7ceadfc4fbf> (accessed 02.04.2024).

In a study by Yu et al., the mechanisms of action of resveratrol were elucidated, demonstrating its ability to protect the heart muscle from fibrosis induced by atherosclerosis, viral myocarditis, alcohol, and diabetes [17].

It was demonstrated that resveratrol can induce matrix metalloproteinase-2 (MMP-2), a pivotal enzyme in the degradation and synthesis of new collagen fibers. Resveratrol has been shown to inhibit the fibrotic process in the heart by disrupting the equilibrium between MMP-2 and tissue inhibitor of metalloproteinases-2 (TIMP-2) expression. This occurs via a mechanism involving the reduction of MMP-2 expression and the elevation of TIMP-2 expression [17].

Another beneficial effect of resveratrol has been observed in the protection of cardiac muscle from fibrosis resulting from chronic alcohol consumption. It is well documented that chronic alcohol consumption can result in the development of cardiomyopathy and subsequent heart failure. This process leads to enlargement of the heart, impaired function, and, in some cases, atrial fibrillation, which is associated with an increased risk of embolism and stroke [18]. MMP-2 and MMP-9 are involved in both the degradation and synthesis of collagen fibers. It has been observed that excessive alcohol intake is associated with increased expression of MMP-2, which may contribute to myocardial damage. In their study, Yu et al. proposed a potential mechanism by which resveratrol protects the heart muscle, namely by inhibiting the overexpression of gelatinases MMP-2 and MMP-9 [17,19].

Wu et al. investigated the fibrinolytic action of resveratrol in diabetic cardiomyopathy. Myocardial fibrosis is a key component of diabetic cardiomyopathy, contributing to cardiac dysfunction and, ultimately, heart failure. Resveratrol, an antioxidant, has been shown to impede myocardial fibrosis by curbing the generation of excessive reactive oxygen species (ROS) and obstructing the ERK/TGF- $\beta$ /periostin pathway. The authors underscored the potential of resveratrol to reverse fibrosis in diabetic cardiomyopathy [20].

SIRT1 is a nicotinamide adenine dinucleotide (NAD<sup>+</sup>)-dependent histone and protein deacetylase encoded by the SIRT1 gene in humans. Notably, the SIRT1 gene is also referred to as the longevity gene, as it has been shown to enhance insulin sensitivity and prolong the lifespan of mice by approximately 20% [5]. SIRT1 plays a regulatory role in cellular responses, including responses to oxidative stress and energy starvation. The SIRT1 gene is expressed in cardiomyocytes. Resveratrol functions as an activator of SIRT1. In 2022, Kuno et al. investigated the effect of SIRT1 activation on doxorubicin-induced cardiotoxicity in mice. The authors demonstrated, via echocardiographic studies, that resveratrol had a beneficial effect

on ejection fraction (EF) in mice subjected to doxorubicin-induced cardiotoxicity [21].

The administration of resveratrol led to a reduction in the levels of atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), which inhibited the progression of hypertrophic changes in cardiomyocytes. The beneficial impact of resveratrol was nullified by the introduction of a SIRT1 inhibitor, thereby indicating a potential interaction between the two [22].

## **The effect of polyphenols on ischemic heart disease (IHD)**

Ischemic heart disease (IHD) is the leading cause of mortality globally [1]. It is well established that acute myocardial ischemia is primarily caused by erosion of atherosclerotic lesions and subsequent rupture of the thin fibrous cap of pre-existing atherosclerotic plaques in the coronary arteries. This event results in the release of thrombogenic substances and platelet activation, which contribute to the restriction or complete occlusion of blood flow to myocardial cells. Despite modification of modifiable cardiovascular risk factors, such as smoking, hyperlipidemia, hypertension, and diabetes, as well as the implementation of primary and secondary prevention therapies aimed at preventing cardiovascular events, the need for new treatments to improve patient prognosis remains. It is noteworthy that current therapeutic approaches do not prioritize the reduction of oxidative stress and the alleviation of inflammation, both of which are implicated in the pathogenesis of atherosclerosis. Resveratrol, however, has been shown to reduce non-HDL cholesterol levels, inhibit lipid peroxidation, reduce inflammation, prevent platelet aggregation, and enhance endothelial function. These mechanisms indicate that resveratrol may have a beneficial role in the treatment of IHD [8,23].

The conventional treatment for chronic ischemic heart disease is coronary angioplasty, a technique used to address narrowing and occlusion of coronary arteries, which has been the preferred method in recent years. This procedure is frequently performed in conjunction with drug-eluting stents [8].

In a study conducted by Kamman et al., the use of resveratrol-coated balloon catheters during angioplasty on coronary and peripheral vessels in a group of sixteen pigs resulted in a notable reduction in the number of microvessels and macrophages present in the adventitia. Additionally, there was a noticeable improvement in endothelialization of the lumens of peripheral vessels, which directly indicated a reduction in post-angioplasty inflammation. Nevertheless, no analogous effect was observed in the coronary arteries [24].

Tolva et al. administered a resveratrol solution (140  $\mu\text{g/mL}$ ) via a catheter directly into the common iliac

artery of adult male New Zealand White rabbits following traumatic angioplasty. The results demonstrated that resveratrol reduced the risk of restenosis by inhibiting intimal proliferation following traumatic angioplasty [4].

Kazemirad et al. investigated the cardioprotective effects of resveratrol in a group of isolated rat hearts subjected to 30 minutes of myocardial ischemia and 120 minutes of reperfusion. The administration of resveratrol (10  $\mu$ M perfusion solution) resulted in a significant improvement of myocardial function following ischemia and reperfusion, as evidenced by a reduction in laboratory markers such as CK-MB, LDH, and troponin I in the resveratrol-treated group [8,25].

Similar studies have been conducted in patients with stable coronary artery disease. The administration of resveratrol (20 mg/day) for a period of three months, or a combination of resveratrol (20 mg/day) and calcium fructoborate (112 mg/day), resulted in a reduction in high-sensitivity C-reactive protein (hs-CRP) and N-terminal prohormone BNP. Furthermore, the clinical status of these patients notably improved, with a reduction in the frequency of angina attacks and a decrease in weekly nitroglycerin consumption [8].

In a study conducted by Chekalina, the effects of resveratrol treatment were evaluated in a cohort of 85 patients diagnosed with stable ischemic heart disease. The patients were divided into two groups: a control group ( $n = 55$ ) receiving standard treatment for stable IHD (beta-blockers, statins, aspirin) and a study group, in which resveratrol (100 mg/day) was added to standard therapy. The efficacy of the treatment was evaluated through echocardiographic examination. Following a two-month period, a significant improvement in left ventricular systolic function was observed in both cohorts. It is noteworthy that the results observed in the study group were significantly more favorable than those seen in the control group. The left ventricular ejection fraction (LVEF) improved by 9.7% in the study group and by 3.2% in the control group [26].

### **The Impact of Polyphenols on Peripheral Artery Disease (PAD)**

Promising findings have emerged regarding the potential effects of polyphenols in peripheral artery disease (PAD). Keremat et al. conducted a review of studies investigating antioxidant therapy in patients with PAD, demonstrating both the efficacy of antioxidants and the superiority of natural antioxidants over synthetic compounds in the management of PAD [27]. In an experimental study, Fan et al. showed that oral administration of resveratrol improved hindlimb ischemia in mice [28]. Conversely, McDermott et al. evaluated the effects of nicotinamide riboside (NR), with and without resveratrol, compared with placebo on the six-minute

walk test in patients with PAD. Their findings revealed that NR significantly improved walking distance (by 31 meters), whereas the addition of resveratrol conferred no additional benefit (improvement of 26.9 meters), indicating that resveratrol did not enhance the therapeutic effect of NR in PAD [29].

### **The impact of polyphenols on obesity**

As early as the 1990s, the pro-inflammatory effects of adipose tissue were identified. It has been shown that adipose tissue secretes, among other factors, tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), which plays a role in the development of insulin resistance. In subsequent years, additional pro-inflammatory molecules secreted by adipose tissue were identified, including interleukins, CRP, and PAI-1. This led to the conclusion that obesity is a disease associated with chronic inflammation [30]. Polyphenols, in particular resveratrol, epigallocatechin gallate (EGCG), and quercetin, have demonstrated a wide range of beneficial effects in the treatment and prevention of diseases associated with chronic inflammation [31].

Resveratrol has been shown to reduce levels of insulin, glucose, and IGF-1 in the blood, thereby increasing insulin sensitivity and raising HDL cholesterol levels. Furthermore, resveratrol has been shown to reduce fat accumulation in both adipocytes and liver cancer cells [23].

In a study conducted by Dal-Pan et al., lemur mice (*Microcebus murinus*) were fed a diet enriched with resveratrol for a period of five weeks. The findings demonstrated that animals in the resveratrol cohort exhibited weight gain that was one-fifth of that observed in the control group, which did not receive resveratrol. Furthermore, the experimental group exhibited a 29% increase in resting metabolic rate, which was attributed to elevated energy expenditure, reduced appetite, and increased physical activity. Additionally, the study observed elevated levels of pancreatic polypeptide and glucose-dependent insulinotropic peptide (GIP) in plasma, which may prove crucial in the treatment and prevention of obesity [5,32].

Epigallocatechin gallate (EGCG), a polyphenol compound found in green tea, has been shown to inhibit the differentiation of preadipocytes, reduce adipocyte proliferation, inhibit lipogenesis, induce adipocyte apoptosis, and promote lipolysis and  $\beta$ -oxidation of fatty acids [31].

Fang Li et al. demonstrated that EGCG reduced obesity and epididymal white adipose tissue mass in mice, partly by activating AMP-activated protein kinase (AMPK) [33].

Another polyphenol with beneficial effects on obesity and chronic inflammation is quercetin [34]. In

a study conducted by Forney et al. on rodents with obesity and diet-induced insulin resistance, treatment with quercetin for 9 weeks led to a reduction in adipocyte hypertrophy and hyperplasia, inhibition of lipid accumulation in the liver through the induction of genes related to  $\beta$ -oxidation, and a reduction in inflammation in subcutaneous adipose tissue [34,35].

In a six-week study by Arias et al., the impact of quercetin, resveratrol, and a combination of both polyphenols on body weight and fat distribution was investigated in rats fed an obesity-promoting diet. Histological analysis demonstrated that supplementation with both resveratrol and quercetin resulted in remodeling of unilocular adipocytes (white adipose tissue) into multilocular adipocytes (brown adipose tissue) and an increase in the level of thermogenin in brown adipose tissue [36].

It is also important to consider the effects of maternal obesity on offspring health. Maternal obesity is a significant risk factor for the subsequent development of obesity in offspring, largely due to elevated cytokine production and the prevalence of placental inflammation [31]. In a study by Fortunato et al., the potential of polyphenols to mitigate the inheritance of obesity in offspring from obese mothers was investigated. It was demonstrated that provision of a diet rich in soy isoflavones to pregnant rats conferred a protective effect on the cardiovascular system of the offspring by stimulating the expression of antioxidant-sensitive genes [31]. Similarly, Liu et al. described the impact of resveratrol supplementation during the perinatal period on the incidence of obesity in offspring. It was demonstrated that resveratrol supplementation during pregnancy led to a reduction in offspring obesity due to an increase in lipolysis [37].

At present, there is a growing body of evidence indicating that resveratrol exerts beneficial effects on obesity during pregnancy in non-human primates. Nevertheless, further research is required to ascertain the safety of resveratrol use during pregnancy [31].

## The impact of polyphenols on stroke

Stroke is a significant social problem, ranking as one of the leading causes of long-term disability and the second leading cause of death worldwide [5]. Approximately 17 million individuals experience a stroke annually, with a fatality occurring approximately every six seconds. Furthermore, one in six individuals will experience a stroke at some point in their lifetime [38]. In accordance with the established definition, a stroke is a pathological condition precipitated by leakage of blood or a reduction in blood flow to a specific region of the central nervous system (CNS). The principal categories of stroke are ischemic stroke (80–85%),

hemorrhagic stroke (10–15%), subarachnoid hemorrhage (5–10%), and venous stroke (0.5–1%) [39,40].

Treatment of ischemic stroke can be divided into two distinct approaches: causal and symptomatic. In reperfusion therapy, thrombolysis with alteplase (recommended within 4.5 hours) and thrombectomy (recommended within 6 hours) are the primary interventions. The total dose of recombinant tissue plasminogen activator (rt-PA) is 0.9 mg per kilogram of body weight, with a maximum dose of 90 mg. A bolus of 10% of the calculated dose is administered, with the remaining 90% delivered as a continuous intravenous infusion over 60 minutes. Symptomatic treatment encompasses fluid therapy, blood pressure management, glycemic control, and rehabilitation [38].

In recent years, there has been a growing emphasis on the use of primary prevention methods for stroke, with polyphenols emerging as a potentially beneficial factor. As evidenced by scientific reports, consumption of polyphenol-rich products, including soy, tea, cocoa beans, citrus fruits, grapes, and their derivatives, has been linked to a reduced risk of stroke [11]. It has been demonstrated that consumption of approximately four cups of black tea per day is associated with a 21% reduction in the risk of major cardiovascular events, which can be attributed to the presence of theaflavins and thearubigins. Similarly, soy-derived compounds such as daidzein and genistein, which belong to the polyphenol group, have been shown to reduce the risk of ischemic stroke when consumed at doses ranging from 100 mg to 1 g per day. The antioxidants present in cocoa seeds, including catechins and epicatechins, have also been demonstrated to contribute to the maintenance of endothelial function in the cerebral vasculature. Furthermore, it has been demonstrated that individuals who consume elevated quantities of dark grapes, chocolate, and red wine, which are rich in resveratrol, exhibit higher levels of resveratrol in their blood and are 55% less likely to experience severe complications following a stroke compared to those with lower levels of resveratrol [11].

In a study by Chen et al., the impact of resveratrol was examined following standard treatment with rt-PA on the prognosis of stroke patients. The findings indicated that resveratrol, by reducing MMP-2 and MMP-9 levels, improved treatment outcomes on the National Institutes of Health Stroke Scale (NIHSS) in patients who received both standard therapy and a placebo [41].

Preclinical studies in rats have demonstrated that resveratrol exhibits neuroprotective properties in the context of ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage [42,43]. A study conducted by Bonsack et al. showed that treatment with resveratrol in rodents following a hemorrhagic stroke significantly alleviated acute neurological deficits,

neurodegeneration, and brain swelling compared with the control group. Furthermore, the study found a reduction in the expression of the pro-inflammatory cytokine IL-1 $\beta$  and improved resolution of hematomas following resveratrol administration [44].

## Conclusions

The studies cited in this review demonstrate that a diet rich in polyphenols, including resveratrol, may have

a significant impact on reducing the incidence of certain cardiovascular diseases, lowering mortality rates associated with these conditions, and alleviating their progression. The table below summarizes the effects of polyphenols on cardiovascular disease. Nevertheless, further research is undoubtedly required to gain a more comprehensive understanding of these effects and to establish more definitive conclusions regarding the potential benefits of polyphenols in cardiovascular health.

Table 2. Summary of the effects of polyphenols on cardiovascular diseases

Cardiovascular diseases	Impact of polyphenols
blood pressure	<ul style="list-style-type: none"> <li>– reduction in systolic blood pressure;</li> <li>– reduction in or no effect on diastolic blood pressure</li> </ul>
heart failure	<ul style="list-style-type: none"> <li>– inhibition of myocardial fibrosis;</li> <li>– improvement of myocardial ejection fraction</li> </ul>
ischemic heart disease	<ul style="list-style-type: none"> <li>– reduction of inflammation in the coronary vessels =&gt; reduction of the risk of atherosclerotic plaque rupture;</li> <li>– reduction of angina symptoms and reducing the amount of nitroglycerin taken</li> </ul>
peripheral arterial disease	<ul style="list-style-type: none"> <li>– improvement in limb ischemia in mice in preclinical studies;</li> <li>– no clear positive effects in clinical studies</li> </ul>
stroke	<ul style="list-style-type: none"> <li>– reduction of the risk of stroke;</li> <li>– improvement of treatment outcomes after stroke;</li> <li>– neuroprotective effects</li> </ul>
obesity	<ul style="list-style-type: none"> <li>– decreased adipocyte proliferation and hypertrophy,</li> <li>– reduced obesity-induced inflammation,</li> <li>– increased metabolism,</li> <li>– reduced appetite,</li> <li>– reduced obesity in offspring (maternal supplementation)</li> </ul>

Table 3. Dietary sources of selected polyphenols and their cardiovascular effects

Dietary source	Polyphenol	Cardiovascular effect
grapes, wine, nuts, blackberries	resveratrol	reduction of: ischemic heart disease, heart failure, peripheral artery disease risk, and blood pressure; obesity management, prevention of stroke
apple, tomato, tea	quercetin	obesity management, reduction of blood pressure, reduction of ischemic heart disease risk
tea	epigallocatechin gallate	reduction of blood pressure, prevention of stroke, obesity management
olive oil, dark chocolate, tomato	caffeic acids	prevention of stroke, obesity management
soy, wine, tomato	coumaric acids	reduction of blood pressure, reduction of ischemic heart disease risk

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The authors declare no conflict of interest.

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**Correspondence address:**

Jakub Dudek  
e-mail: [jakub.dudi@gmail.com](mailto:jakub.dudi@gmail.com)  
tel. 503 009 005  
ul. Adriana Głębockiego 13  
42-209 Częstochowa

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