

Grape Polyphenols in the Improvement of Vascular Endothelial Dysfunction in Cardiovascular Diseases: Bioactive Components, Mechanisms and Clinical Evidence

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Abstract. Grape polyphenols are various bioactive substances that occur in many parts of grapes, such as the seed, skin, pulp and other grape-based products, including grape juice, grape powder, wine and seed extracts. Its main components are proanthocyanidins, anthocyanins, resveratrol, catechin, epicatechin, quercetin and others of the flavonoid group. Recently, it has been found that polyphenols in grapes can help maintain the elasticity of arterial walls and promote a healthier metabolism for the heart. The reason for this is that the substance has antioxidant and anti-inflammatory effects, increases the availability of nitric oxide, inhibits platelet aggregation, reduces oxidation of low-density lipoprotein, etc. Clinical studies of purple grape juice have shown some improvement in flow-mediated dilation and other indicators of endothelial function in people with coronary artery disease. Whole-grape consumption can also provide some good health effects due to the combined effects of fibre, organic acids and polyphenols in the food matrix. Grape polyphenols are generally expected to be beneficial for the health of people with heart disease in terms of prevention and treatment. However, there are differences in the origin of the grapes, processing methods, safety issues and a relatively short duration and small number of subjects of the current clinical trials; therefore, more large-scale, long-term experiments are needed.

Keywords: Grape polyphenols, Vascular endothelial dysfunction, Cardiovascular diseases

1. Introduction

Cardiovascular diseases (CVDs) rank among the primary triggers which drive weakened physical wellness and shortened lifespan across global human populations. Official reports issued by the World Health Organization (WHO) record large groups of individuals lose their lives to these circulatory ailments annually and such fatal cases make up a notable share of total worldwide mortalities [1]. Coronary artery illness, arterial plaque buildup and sustained high arterial pressure stand as progressive circulatory conditions which tie closely to impaired inner blood vessel cell function. Basic medical understanding points out that the endothelial cell layer which coats inner vessel walls forms a protective barrier that restricts unregulated blood cell movement and manages

circulatory speed while reacting to harmful harm brought by inflammatory reactions and oxygen-related metabolic strain [2].

Current scholarly investigations reveal that impaired endothelial performance tends to emerge ahead of symptomatic heart and vascular illnesses which mark the initial indicator for arterial plaque buildup and coronary vessel illness. Multiple hazards that raise the chance of heart and vascular troubles which include high blood pressure, excess body mass, glucose metabolic disorder, abnormal blood lipid levels, tobacco use and persistent tissue irritation will interfere with the operational state of endothelium units and cut down the volume of released nitric oxide (NO), a change which triggers narrowed blood vessels, stronger adhesion among blood platelet units and sustained bodily inflammatory responses across circulatory tissues [3].

Natural compounds known as plant polyphenols deliver oxidation-blocking, tissue-soothing and extra circulation-protective benefits which have drawn consistent academic notice over the past few years, and nutritional research platforms which explore health intervention tactics carry out moderate analytical work targeting these substances to support defensive and restorative care for circulatory system illnesses [4]. Grapes and grape-derived products are a good source of polyphenols in the diet and contain other bioactive substances, such as proanthocyanidins, anthocyanins, flavonoids and resveratrol. According to the above evidence, grape polyphenols are thought to be good for the heart and various diseases that occur in the heart, which can be achieved through several ways. Nutrient substances carry out physiological actions which lift the operational capacity belonging to endothelial tissue, which raise the synthetic output of nitric oxide molecules, which slow down oxidative degradation that affects low-density lipoprotein (LDL), and which block the clumping behavior that forms masses of blood platelet cells inside circulatory pathways (Figure 1) [5, 6].

The composition and biological activity of products derived from grapes also differ significantly among different varieties of grapes, cultivation environments and processing methods; thus, they may not have the same extent of cardiovascular protection. Red grape products generally have higher amounts of anthocyanins than white varieties and may therefore exhibit stronger antioxidant activity. In addition, the entire fruit of a grape may also provide a combined benefit through the synergistic effect of fibre, organic acids and polyphenols; thus, it can improve vascular health and regulate metabolism in the body. Therefore, when studying the health effects of grape polyphenols, one should consider the form and preparation methods of the food.

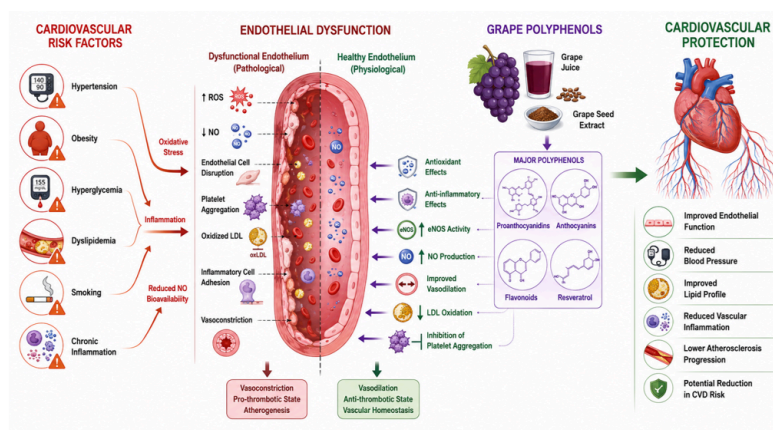


Figure 1. Polyphenols in grapes have antioxidant and anti-inflammatory effects, can reduce endothelial dysfunction, etc. (picture credit: original)

The aim of this paper is to introduce the origins and all kinds of biological activities of polyphenol compounds in grapes, as well as relevant clinical research results from humans that link them to changes in endothelial function and cardiovascular risks. The results will build up a theoretical framework which supports the creation of nourishment items with targeted physiological benefits, and accelerate standardized medical deployment which uses grape polyphenols to sustain stable wellness status inside the human circulatory system.

2. Relationship between vascular endothelial dysfunction and cardiovascular diseases

Vascular endothelial cells are the lining cells of the interior wall of blood vessels and regulate the status of the blood vessels. Generally speaking, the endothelium releases all kinds of substances that can either dilate or constrict blood vessels; among these, nitric oxide (NO), prostacyclin and endothelium-derived hyperpolarizing factor (EDHFs) are vasodilators, while endothelin-1 (ET-1) is a vasoconstrictor, and at the same time, other types of vasoconstrictors are also produced to regulate the balance of blood vessels [7]. Multiple bioactive molecules exist within circulatory tissues where nitric oxide (NO) acts as an essential mediator which governs the tension state of vascular pipelines, and this bioactive substance gets synthesized through endothelial nitric oxide synthase (eNOS) which resides inside vascular lining cells. This gaseous messenger widens the inner space of vascular channels, blocks the clumping reaction of blood platelet units, cuts down sticking interactions of white blood cells and slows pathological shifts which drive the progressive formation of atherosclerotic lesions across arterial walls, and this background makes diminished accessible NO content serve as a reliable marker which signals damaged functional performance of vascular endothelium tissue.

Long-term contact with harmful physiological triggers which threaten circulatory wellness including high blood pressure, elevated blood glucose, excess body mass, free radical oxidation pressure and persistent tissue irritation can weaken the working capacity that belongs to endothelium cells, cut down synthetic output of nitric oxide (NO), amplify radical oxidation pressure and lift the concentration of biochemical agents which trigger bodily inflammatory responses inside blood vessel systems. These changes are responsible for the start and development of atherosclerosis and heart disease. Endothelial dysfunction is usually an early change that occurs before the appearance of symptoms of cardiovascular disease. Therefore, promoting the health of the endothelium has begun to address problems in heart disease prevention and treatment. Recently, many people have paid more and more attention to the benefits of plant polyphenols, especially grape polyphenols, for improving endothelial function.

3. Major grape polyphenol constituents related to the improvement of endothelial function

Bioactive grape polyphenol compounds spread across outer peel layers, hard seed kernels and soft fleshy tissue of fresh grape fruits, alongside multiple processed goods which get refined from raw grape materials including squeezed grape liquid, dried grape fine powder, fermented grape alcoholic beverage and concentrated seed extraction mixtures. Hard grape seed kernels serve as a rich reservoir which holds abundant proanthocyanidin molecules and carry flavan-3-ol subtypes which cover catechin and epicatechin structures (Table 1) [6]. Proanthocyanidin molecules act as potent radical-neutralizing agents which research trials confirm can cut down reactive free radical particles, a trait which blocks oxidative breakdown of fatty lipid substances and may boost relaxed vascular wall states through activation pathways linked to endothelial NO-synthase (eNOS).

Grape skin has many anthocyanins, resveratrol and quercetin. Anthocyanins have also shown some antioxidant and anti-inflammatory effects and the regulation of blood vessels. Resveratrol has drawn considerable attention recently because it is expected to affect the signaling pathways of AMPK, Sirtuin 1 (SIRT1) and eNOS.

Purple grape juice is rich in many water-soluble polyphenols, such as anthocyanins, flavonoids and phenolic acids; thus, it has been frequently applied in human intervention studies [8]. Grape powder is more similar to the entire food matrix of the whole fruit and contains not only polyphenols but also dietary fibre and many other micronutrients that can work together to improve health.

Table 1. Sources of grape polyphenols, main polyphenolic components, and their connection to endothelial function

Grape source	Main polyphenolic components	Relationship with endothelial function
Grape seeds	Proanthocyanidins, catechin, epicatechin	Associated with antioxidant effects and improved vasodilation
Grape skins	Anthocyanins, resveratrol, quercetin	Associated with anti-inflammatory effects and nitric oxide regulation
Purple grape juice	Anthocyanins, flavonoids, phenolic acids	Commonly used in human intervention studies
Grape powder	Various complex polyphenols	More closely resembles the whole-fruit food matrix
Wine	Resveratrol, anthocyanins, flavonoids	Contains ethanol, with considerable safety concerns

4. Clinical evidence for the beneficial effects of grape polyphenols on vascular endothelial dysfunction

4.1. Purple grape juice improves flow-mediated dilation in patients with coronary artery disease: classical clinical evidence

Stein and his colleagues have carried out human intervention studies to show that purple grape juice may improve the vascular function of people with coronary artery disease (CAD). Of the 15 patients with CAD who were confirmed by angiography, two groups were formed, and about 4ml/kg of purple grape juice was given twice a day for 14 days to each group. High-resolution ultrasound was used to determine the extent of flow-mediated dilation of the brachial artery and at the same time determine how easily low-density lipoprotein (LDL) can be oxidised by copper in an LDL oxidation test.

At the start, the degree of functional endothelial-dependent vasodilation in the patients was $2.2 \pm 2.9\%$. FMD is now $6.4 \pm 4.7\%$ ($P=0.003$) after intervention. After fixing the other reasons mentioned above, it was still statistically significant. The lag time of the LDL oxidation assay also increased by 34.5% ($P=0.015$), and it was found that LDL particles had increased resistance to oxidative modification and were less prone to oxidation.

Damaged endothelial operation and oxidative transformation that affects low-density lipoprotein (LDL) share tight biological links which drive gradual worsening and initial formation of arterial plaque lesions alongside coronary cardiac disorders, and this biological connection supports reasonable speculation which states polyphenolic substances extracted from purple grape liquid deliver shielding influences for cardiac tissues inside living organisms. These natural bioactive compounds lift the measurable content of usable nitric oxide (NO), boost vessel widening reactions which rely on intact endothelial tissue, and cut down vulnerability toward oxidative damage that acts

on LDL lipid particles. This research holds limitations which include limited participant quantities and brief treatment cycles, a reality which demands larger randomized controlled testing programs that feature prolonged observation spans to validate all observed research outcomes reliably [9].

4.2. Promotion of nitric oxide release by grape polyphenols: an important mechanism for endothelial function improvement

Purple grape juice (PGJ) and some of its flavonoid compounds have been shown to inhibit platelet aggregation, increase the release of nitric oxide from platelets and reduce oxidative stress. An in vitro study has shown that incubation of platelets with diluted PGJ can reduce platelet aggregation, increase the production of platelet-derived NO, and decrease the generation of superoxide anions [10].

Later, a study by humans explored how to add PGJ to the diets of healthy people for the past 14 days, at a dose of $7 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$. According to the above results, platelet aggregation has decreased after the supplement. The amount of platelet-derived nitric oxide rose from $3.5 \pm 1.2 \text{ pmol}/10^8$ platelets to $6.0 \pm 1.5 \text{ pmol}/10^8$ platelets ($P < 0.01$) in the production stage. On the other hand, the amount of superoxide released by aggregated platelets can be measured with a lumiaggregometer under the influence of lucigenin; both were 29.5 ± 5.0 and 19.2 ± 3.1 arbitrary units ($P < 0.05$), respectively.

Therefore, it can be concluded that PGJ may improve the bioavailability of NO in the following ways: strengthen the antioxidant defense mechanism to reduce degradation of NO by reactive oxygen species and directly modify platelet function through certain flavonoid compounds.

Nitric oxide helps to keep the blood vessels in good condition. NO can also relax the smooth muscle of the blood vessel and cause vasodilation; thus, it reduces platelet adhesion, aggregation and thrombosis. Therefore, sufficient bioavailability of NO is required to keep the endothelium healthy and form an anticoagulant state in the blood.

Freedman and others have found that by increasing the release of platelet-derived NO, decreasing superoxide production and inhibiting platelet aggregation, purple grape juice can promote the good health of the cardiovascular system without causing harm to it. Distinct flavonoid segmented mixtures which get isolated from liquid squeezed out of purple grape fruits display capacities which cut down superoxide generation inside platelet cells, yet the functional influences which these mixtures exert on full blood clumping, platelet cell gathering and nitric oxide (NO) discharge present obvious differences across test samples. Analysis which relies on all recorded experimental findings confirms that circulatory protective advantages linked to grape polyphenol substances do not stem from one isolated chemical component, and such positive outcomes originate from synergistic influences which multiple flavonoid molecules bring alongside their radical-neutralizing traits. Logical deduction which draws from these analytical facts states that boosted NO outflow, raised accessible NO levels and balanced platelet cellular activity deliver strengthened shielding impacts which grape polyphenols provide for blood vessel lining tissue and lower potential hazards which relate to thrombotic mass formation within circulatory channels [10].

5. Conclusion

Grape polyphenols are useful bioactive compounds found in grapes and grape products. Proanthocyanidins, anthocyanins, flavan-3-ols, flavonols and resveratrol are the main components. Current academic investigative works deliver proof which confirms grape polyphenolic substances supply protective support for cardiac tissue and assist in elevating the operational capacity belonging

to endothelial layers, lift synthetic yields of nitric oxide (NO), ease pressure triggered by free radical oxidation and adjust immune inflammatory responses inside bodily tissues.

Clinical analysis which focuses on human participant intervention trials reveals that liquid pressed from purple grape fruit and additional edible supplies which carry abundant grape polyphenol content raise flow-mediated dilation (FMD) values and slow chemical oxidation alterations that act upon low-density lipoprotein (LDL) lipid particles within blood circulation. Similar effects have also been observed in people with coronary artery disease and healthy people, indicating that this intervention may promote the blood vessels of all people and is not only for those at risk of cardiovascular disease.

Grape polyphenols are generally considered to have some good nutritional effects that help protect the heart and blood vessels. In addition, the heart and blood vessels will also be healthier in all regards due to grape polyphenols. As natural bioflavonoids, grape polyphenols are abundant in many daily food and drink items and have thus become popular subjects of long-term dietary research. Compared with pharmacological therapy, the new direction for treating cardiovascular disease risks will be nutritional intervention by increasing the intake of polyphenol-rich foods, especially in the early stages of the disease when vascular dysfunction can still be reversed; at the same time, many studies have also been conducted on personalised nutrition for heart health. Different people are affected by different ages, lifestyles, diets, changes in gut microbes and metabolic abilities, and thus will absorb and use grape polyphenols differently. Therefore, the effect of grape polyphenol intervention will vary among different people. Understanding how different people are affected enables the adjustment of food recommendations for everyone in the future to better suit their needs. From the perspective of public health, increasing the consumption of polyphenols and other beneficial substances in fruit-based foods can promote healthy eating and better health. With the development of research, grape polyphenols may be one of the contents recommended in nutritional guidance to reduce the risk of heart disease and maintain good vascular health for all people.

The samples, intervention times, products used and outcomes measured in the existing studies are all different. Therefore, high-quality clinical trials have not determined an optimal dose or how long it should be taken safely. In the future, more research will be conducted on how various polyphenol constituents in grapes work together, what changes occur at the molecular level under such conditions, and thus more scientific basis for applying grape polyphenols to protect the cardiovascular system will be provided.

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