

Protective effects of piceatannol on cardiovascular diseases

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ABSTRACT: Cardiovascular disease (CVD) is a significant global health concern, encompassing conditions such as atherosclerosis, arrhythmia, hypertension, hyperglycemia, and hyperlipidemia. In recent years, there has been extensive research focusing on the pharmacological effects of natural compounds as potential treatments for CVD. Piceatannol, a natural polyphenolic compound, has garnered attention in this regard. Being a structural analogue of resveratrol, piceatannol exhibits a variety of biological activities, including antioxidant and anti-inflammatory properties, stabilization of cell membrane potential, and inhibition of fat accumulation. We herein provide a comprehensive review on the potential therapeutic applications and molecular mechanisms of piceatannol in CVD.

Keywords: Piceatannol; polyphenolic compound; cardiovascular diseases protection; therapeutic potential

1. Introduction

Cardiovascular diseases (CVDs) are responsible for high mortality and disability rates worldwide, primarily including coronary heart disease, stroke, hypertension, heart failure, and other related disorders. Several major risk factors contribute to the development of CVDs, including hypertension, hyperlipidemia, diabetes, smoking, obesity, and physical inactivity (Dantas et al., 2012). The incidence and prevalence of CVDs have been continuously increasing due to factors such as economic and social development, as well as population aging. This trend poses a substantial burden on public

health and healthcare systems. In response, various strategies and policies have been developed to reduce the incidence of CVDs and prevent their occurrence. In clinical practice, pharmacological interventions play a critical role in the management and treatment of CVDs and their complications. Additionally, the consumption of functional foods or dietary supplements that can mitigate the risk of CVDs has gained widespread acceptance among the public (Wan et al., 2012). Piceatannol (3,4,3',5'-tetrahydroxy-trans-stilbene) is a natural polyphenolic compound and a hydroxylated

structural analogue of resveratrol. PIC can be found in various fruits and vegetables, such as grapes, blueberries, and passion fruit, allowing for dietary consumption (Wahdan et al., 2023).

Piceatannol is represented by the chemical formula $C_{14}H_{12}O_4$, and exists in both trans and cis isomeric forms, with the trans isomer being more stable (**Figure 1**).

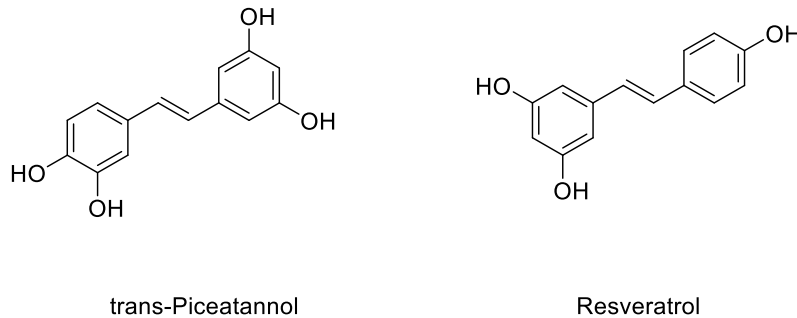


Figure 1. The chemical structures of piceatannol and resveratrol.

Pharmacological studies have primarily focused on the trans form of piceatannol. Although piceatannol as a non-polar compound is insoluble in water, it is soluble in organic solvents such as dimethyl sulfoxide and ethanol. The physical properties of piceatannol are summarized in **Table 1**. The commercial use of piceatannol mainly revolves around its role as selective spleen tyrosine kinase (Syk) inhibitor and silent information regulator 1 (SIRT1) activator. Numerous studies have investigated

the pharmacological properties of piceatannol. Due to its structural similarity to resveratrol, piceatannol is believed to exhibit pharmacological activities analogous to resveratrol. Both compounds share several cardioprotective effects, such as inhibiting the oxidation of low-density lipoprotein (LDL) cholesterol, inhibiting platelet aggregation, regulating cardiomyocyte function, and reducing myocardial tissue damage during ischemic events (Roupe et al., 2008; Roupe et al., 2006).

Table 1. Physical properties of piceatannol.

Piceatannol			
Molecular formula	$C_{14}H_{12}O_4$	Molecular weight	244.24 g/mol
Character	Off-white crystalline powder, sensitive to light	Solubility	Soluble in methanol, acetone, DMSO, benzene, toluene and other solvents; insoluble in petroleum ether
Density	$1.5 \pm 0.1 \text{ g/cm}^3$	Melting point	$223\text{--}227^\circ\text{C}$
Boiling point	$507.3 \pm 38.0 \text{ }^\circ\text{C}$ at 760 mmHg	Storage condition	$2\text{--}8^\circ\text{C}$, keep out of the light

Piceatannol has demonstrated significant preventive and therapeutic effects in certain CVDs. Advantages of piceatannol over resveratrol are its better bioavailability, more stable biological metabolism, and lower cytotoxicity. The promising findings

regarding the cardioprotective effects of piceatannol warrant further investigation to explore its potential therapeutic applications in these disease states.

2. Bioactivity and mechanism in the treatment and prevention of CVDs

CVDs involve a wide range of pathological processes, but from a basic point of view, most of them are driven by oxidative stress, inflammation, and metabolic disorders. Piceatannol has been found to have multiple beneficial activities that can target these underlying mechanisms of CVDs. Specifically, piceatannol can suppress inflammatory signaling pathways, reduce oxidative stress by modulating redox-sensitive pathways, stabilize cell membrane potential, enhance insulin sensitivity and glucose homeostasis, and regulate lipid metabolism. By acting on these fundamental pathways, piceatannol holds the potential to improve the development and progression of various CVD conditions. The comprehensive understanding of piceatannol's multifaceted mechanisms of action provides a rationale for its further exploration as a promising natural compound for the prevention and treatment of CVDs.

2.1. Protective effect on endothelial dysfunction

Endothelial dysfunction is featured by decreased vasodilators and increased vasoconstrictors, vascular smooth muscle cell abnormality, and excessive reactive oxygen species (ROS) production, and increased vascular tone; all contribute to the development and progression of various CVDs (Montezano et al., 2014; Touyz, 2004). Nitric oxide (NO) derived from endothelial nitric oxide synthase (eNOS) is considered as the most important endothelium-derived relaxing factors (EDRFs). Piceatannol upregulates eNOS mRNA and protein expression in human umbilical vein endothelial cells and its effect is more potent than resveratrol (Kinoshita et al., 2013).

2.2 Anti-inflammatory activity and anti-atherosclerosis effect

The pathogenesis of CVDs, such as atherosclerosis, coronary heart disease, myocardial infarction, stroke and heart failure, is inseparable from the key link of inflammation (Figure 2) (Marier et al., 2002; Yamamoto et al., 2016).

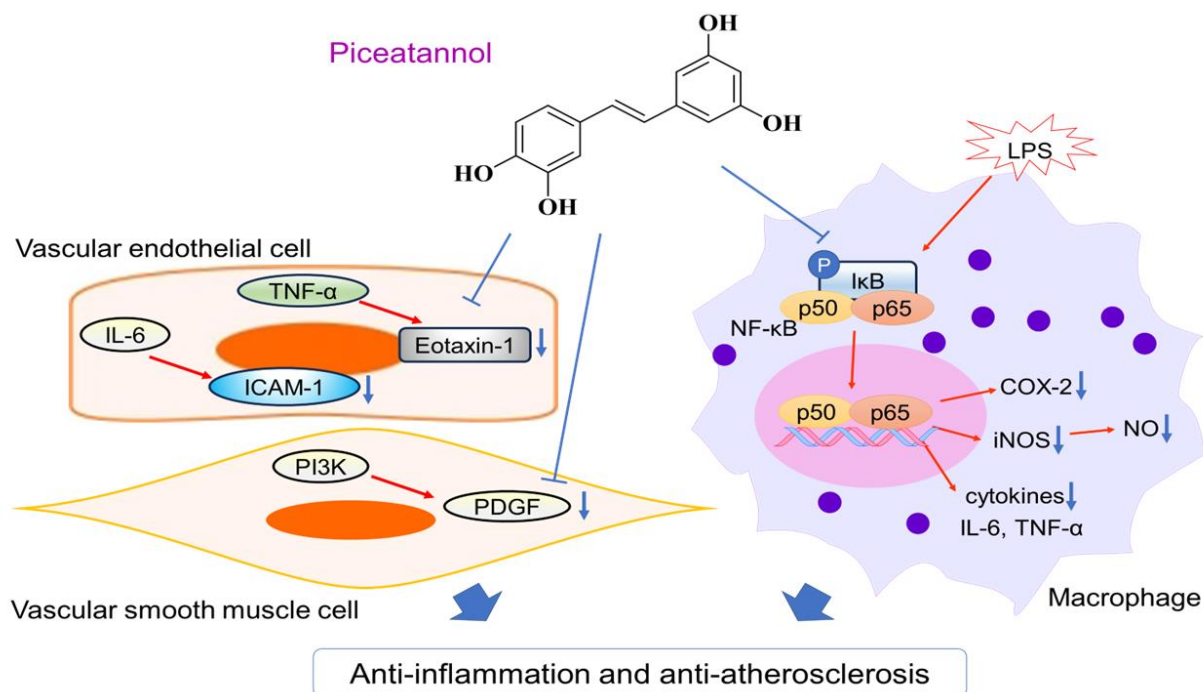


Figure 2. Anti-inflammatory and anti-atherosclerosis effects of piceatannol.

Piceatannol has a dose-dependent and significant anti-inflammatory effect in various cell models, reducing the overproduction of inflammatory mediators and cytokines, such as nitric oxide (NO), prostaglandin E2 (PGE2), tumor necrosis factor α (TNF- α), and interleukin-6 (IL-6). It also inhibits the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) at mRNA and protein levels (Tang et al., 2017). Moreover, piceatannol has been found to significantly decrease the expression of nuclear factor kappa B (NF- κ B) in lipopolysaccharide (LPS)-induced RAW264.7 macrophages (Rakib et al., 2023). These results highlight the strong anti-inflammatory effect of piceatannol, which provides an important basis for considering its potential application in the treatment of CVDs. However, further research involving animal studies and clinical validation is necessary to fully evaluate the efficacy and safety of piceatannol in the context of CVDs. Chronic inflammation is one of the key mechanisms in the development of atherosclerosis, starting from its early stages to the later stages involving plaque fragility and rupture. Human vascular endothelial cells are widely used as a cellular model to study the inflammatory mechanisms associated with atherosclerosis. Inflammatory factors such as interleukins (ILs) and TNF- α are involved in the damage of vascular endothelial cells, lipid deposition and smooth muscle cell proliferation. These inflammatory mediators can also induce the expression of chemokines, such as eotaxin-1, which further promotes the infiltration of inflammatory cells and aggravates the inflammatory response within the blood vessel wall. Studies have shown that piceatannol effectively inhibits the expression and release of IL-13 and TNF- α -induced eotaxin-1 mRNA in human pulmonary artery endothelial cells (Yang et al., 2011). As an important cytokine, the expression of eotaxin-1 is closely related to the progression of atherosclerosis (Farahi et al., 2007). By down-regulating the expression of eotaxin-1 and other chemokines, piceatannol

shows promise in attenuating the inflammatory processes involved in atherosclerosis.

IL-6 plays an important role in cardiovascular pathology, and its elevation leads to myocardial dysfunction, cardiomyocyte hypertrophy, loss of myocardial mass, and inhibition of cardiomyocyte apoptosis (Seta et al., 1996). By inhibiting the activation of signal transduction and 1/3 pathway of transcription, piceatannol inhibits the expression of IL-6 mRNA and protein induced by cardiomyotrophin-1 in human umbilical vein endothelial cells. Piceatannol also alleviates the release of intercellular adhesion molecule 1 (ICAM-1) in human aortic endothelial cells exposed to IL-6 and alleviates cell adhesion (Chen et al., 2012). These findings suggest that piceatannol has therapeutic potential in preventing atherosclerosis and slowing down its progression.

Apart from the inflammatory aspect, piceatannol inhibits abnormal migration and proliferation of vascular smooth muscle cells, which is strongly associated with atherosclerosis. Piceatannol directly binds with phosphoinositide 3-kinase (PI3K), suppressing PI3K activity; and thus, inhibits platelet-derived growth factor (PDGF)-BB-induced migration and proliferation of human aortic smooth muscle cells (Choi et al., 2010).

2.3 Antioxidant effect

Oxidative stress is one of the main pathogenesis of myocardial ischemia, so piceatannol may offer protection to cardiomyocytes by preventing cell damage and apoptosis through its antioxidant action. As a potential antioxidant, piceatannol has the ability to scavenge various free radicals, such as hydroxyl, superoxide, peroxy and lipid peroxy radicals; and its antioxidant effect is notably superior to that of resveratrol (Murias et al., 2005). Furthermore, piceatannol protects DNA in L1210, K562 and HL-60 leukemia cells from hydroxyl radical damage (Rhayem et al., 2008). Considerable research has been conducted on the

molecular biology of piceatannol's antioxidant effect. Studies have demonstrated that piceatannol effectively inhibits the increase of mitochondrial ROS levels induced by antimycin A. Importantly, its inhibitory effect on ROS induced by hydrogen peroxide surpasses that of

resveratrol and vitamin C. In addition, piceatannol can protect cells from mitochondrial ROS through SIRT1 and nuclear factor erythroid 2-related factor 2 (Nrf2)/ heme oxygenase-1 (HO-1)-dependent mechanisms (Figure 3) (Hosoda et al., 2021).

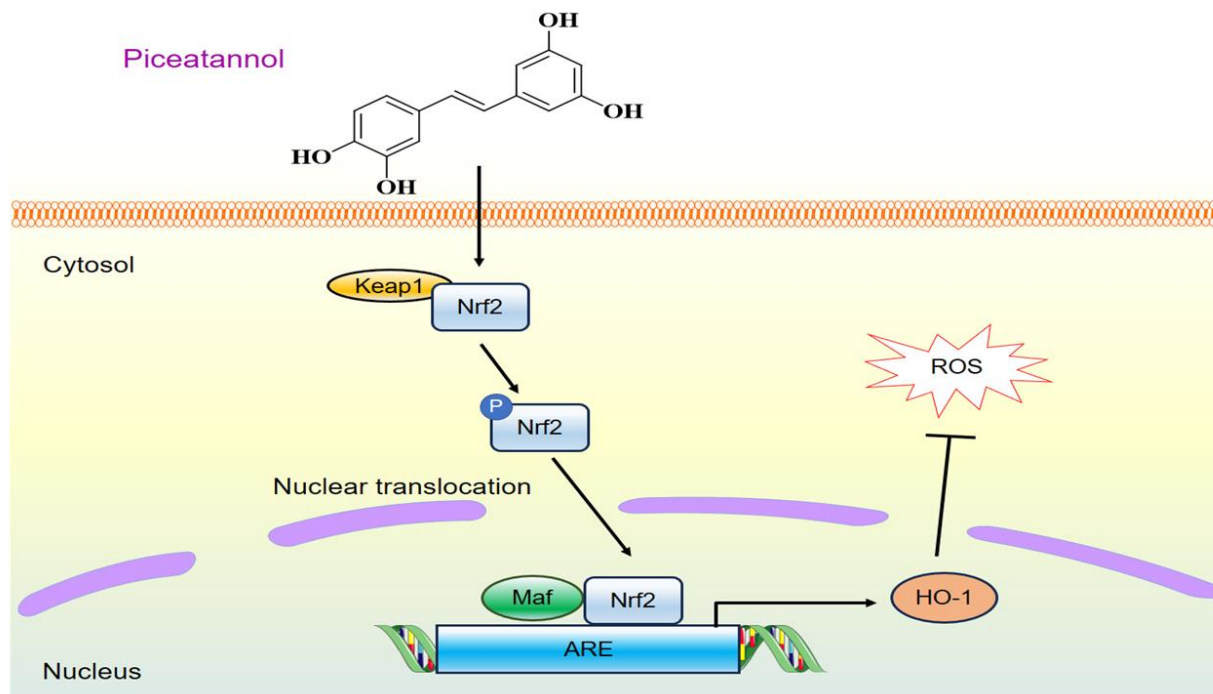


Figure 3. Piceatannol shows anti-oxidative effect through Nrf2/HO-1-dependent mechanism.

The antioxidant effect of piceatannol can be attributed to its ability to inhibit the accumulation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) aggregates. GAPDH is a key redox-sensitive protein, and prolonged exposure to oxidative stress may lead to the formation of intermolecular disulfide bonds, resulting in the accumulation of GAPDH aggregates and eventual cell death. Emerging evidence suggests that certain low-molecular-weight compounds can serve as effective inhibitors, preventing the translocation of GAPDH to the nucleus and impeding its aggregation and oligomerization. Piceatannol is a specific inhibitor that binds to GAPDH aggregates, hindering the formation of disulfide bonds and preventing GAPDH aggregation. By blocking the cysteine residues on GAPDH and

counteracting their oxidative modifications, piceatannol induces depolymerization and disrupts GAPDH aggregation (Gerszon et al., 2018).

2.4 Antiarrhythmic effect

Studies have shown that piceatannol has a cardiomyocyte protective effect, alleviating damage during myocardial ischemic events associated with arrhythmias. In a rat model of left main coronary artery occlusion, treatment with piceatannol significantly reduced the incidence of ventricular tachycardia and ventricular fibrillation (Hung et al., 2001). Notably, piceatannol treatment was effective in preventing death in rats subjected to coronary artery occlusion for 30 minutes or reperfusion after occlusion for 5 minutes (Hung et al., 2001). The

antiarrhythmic effect of piceatannol is significantly stronger than that of resveratrol in ischemia-reperfusion rat hearts. These findings indicate the cardiovascular protective role of piceatannol by safeguarding cardiomyocytes and inhibiting arrhythmia, implying its promising potential in the prevention and treatment of CVDs. However, further research is needed to fully understand the underlying mechanisms and explore the therapeutic implications of piceatannol in CVDs.

Other studies have provided insights into the mechanism of piceatannol's anti-arrhythmic action. Studies indicate that piceatannol's anti-arrhythmic action may be attributed to its ability to delay sodium ion current (I_{Na}) inactivation and prolong the duration of cardiomyocyte action potential, thereby extending the effective refractory period. At a concentration of 10 mmol/L, piceatannol can prolong the effective refractory period of cardiomyocytes through this mechanism and exert its antiarrhythmic effect in ischemia-reperfusion rats (Chen et al., 2009). Interestingly, heart failure is associated with down-regulated NaV1.5 protein expression and decreased peak I_{Na} density. Ischemia-reperfusion (I/R) injury further reduces peak I_{Na} density in the affected region, with a more pronounced effect in failing hearts compared to control hearts. The inhibitory effect of piceatannol on I_{Na} in failing cardiomyocytes is greater than that observed in control group. Thus, in heart failure with acute local I/R injury, the differential downregulation of I_{Na} may be contribute to the proarrhythmic effects of piceatannol. It is important to note that while piceatannol may offer benefits in ischemic heart disease through other mechanisms of action (such as inhibiting platelet aggregation, improving fibrinolysis, increasing high density lipoprotein (HDL) cholesterol, promoting NO release, etc.), the potential risk of arrhythmia associated with sodium channel inhibition should be carefully considered when evaluating its clinical use, especially in patients with heart failure due to alcohol abuse(Chang et al., 2018).

2.5 Hypoglycemic effect

Piceatannol can play a role in lowering blood glucose by affecting glucose metabolism and insulin signaling. Several studies have demonstrated the hypoglycemic properties of piceatannol in different animal models. In studies conducted on db/db mice and diet-induced obese C57BL/6 mice, piceatannol administration reduces fasting blood glucose levels (Minakawa et al., 2012; Uchida-Maruki et al., 2015). In addition, acute administration of piceatannol reduces serum glucose levels and improves glucose tolerance. Mechanistic studies have shed light on how piceatannol affects glucose handling. Piceatannol may enhance glucose uptake and utilization in cells by 5'AMP-activated protein kinase (AMPK) activation and glucose transporter 4 (GLUT4) translocation (Minakawa et al., 2012). The role of piceatannol in insulin secretion or insulin sensitivity is still a matter of debate and requires further investigation.

High glucose/lipid exposure results in the impairment of endothelial cell motility, adhesion and migration ability. Such glucolipototoxicity-induced vascular barrier injury can be alleviated by piceatannol through inhibition of NF- κ B signaling and oxidative stress (Wang et al., 2022).

2.6 Hypolipidemic effect

Hyperlipidemia is closely linked with numerous CVDs. Piceatannol plays a role in regulating blood lipids by inhibiting fat formation and accumulation. Previous study has demonstrated that piceatannol can block the accumulation of triglycerides in 3T3-L1 adipocytes by inhibiting insulin signaling in the early stage of adipocyte differentiation (Kwon et al., 2012). Furthermore, piceatannol administration exerts anti-obesity effect in DIO mice, decreasing body weight as well as serum total cholesterol, LDL cholesterol and HDL cholesterol (Tung

et al., 2016). However, controversial effects are observed in another animal model. Oral administration of piceatannol does not exhibit apparent anti-obesity effect in the obese Zucker rats (Hijona et al., 2016). These differential effects may be attributed to the differences in animal species and piceatannol treatment durations and dosages. Importantly, chronic intake of piceatannol-enriched passion fruit seed extract has been demonstrated to improve lipid profile, platelet aggregation, cardiac function, and aortic vasorelaxation in DIO rats (Ishihata et al., 2016).

2.7 Anti-hypertensive effect

Aging is one of the main risk factors of impaired endothelial function and hypertension. Piceatannol has been demonstrated to act as arginase inhibitor, effectively enhancing eNOS activity and NO generation as well as lowering blood pressure in aged mice (Nguyen and Ryo, 2017).

2.8 Anti-angiogenesis effect

Piceatannol exerts inhibitory effects on VEGF-induced angiogenesis both in vitro and in vivo. Piceatannol possibly binds with VEGF and thereby blocks VEGF-mediated Akt-eNOS signaling and ROS generation (Hu et al., 2020). This implies that piceatannol can protect against angiogenesis-related diseases and cancers like colon cancer. Since current review focuses on the cardiovascular effects of piceatannol, we do not discuss in detail about its anti-cancer effects.

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3 Future perspectives

As a natural product, piceatannol exhibits various biological activities and holds potential health benefits. Gaining a deeper understanding of its chemical properties, mechanisms of action, and potential applications in health and disease is crucial for exploring its pharmacological properties and developing relevant therapeutic strategies. Existing studies have shown that piceatannol plays a significant role in the prevention and treatment of CVDs, mainly based on evidence derived from animal experiments. While preclinical studies have provided valuable insights into the potential applications of piceatannol in the prevention and treatment of CVDs, future clinical studies further studies are necessary to verify its bioavailability, efficacy and safety. These investigations will serve as a foundation for subsequent clinical applications and transformations.

In comparison to resveratrol, piceatannol has shown higher bioavailability, more stable biological metabolic properties, and lower cytotoxicity, making it a promising candidate for biomedical applications. Currently, research on piceatannol mainly focuses on the pharmacological level, exploring its therapeutic and preventive effects on various diseases and investigating the underlying molecular biological mechanisms. Nevertheless, the journey from preclinical findings to actual clinical application and translation is a lengthy process. Future in-depth studies are expected to further elucidate the mechanisms of action of piceatannol in the prevention and treatment of CVDs, to facilitate its translation into clinical practice.

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