Cardiovascular Protective Effects of Polyphenols Contained in Passion Fruit Seeds Namely Piceatannol and Scirpusin B: A Review

Yutaka MATSUMOTO[*1] and Yumi KATANO[*2]

[*1]*Faculty of Nursing, Tokai University School of Medicine*
[*2]*Division of Theoretical Nursing and Pathophysiology, Yamagata University School of Medicine*

(Received May 7, 2021; Accepted August 6, 2021)

Cardiovascular disease is a global health problem. According to the World Health Organization, ischemic heart disease was the leading cause of death globally in 2019, followed by stroke. The French paradox, which has been known since the early 1990s, describes the lower incidence of ischemic heart disease in French people despite the consumption of a diet rich in saturated fatty acids. This phenomenon has been attributed to the high intake of red wine, which is rich in polyphenols, namely, resveratrol and piceatannol. It is becoming clear that scirpusin B, a dimer of piceatannol, has anti-atherosclerotic properties such as vasodilation, antioxidant effects, and suppression of postprandial hyperglycemia; nonetheless, the effects of scirpusin B on the cardiovascular system have not been fully elucidated. This review aimed to describe the cardiovascular effects of piceatannol and scirpusin B on aortic and coronary artery dilation and cardiac function and to outline the cardiovascular effects of prostacyclin and nitric oxide, as these substances are involved in the vasodilatory effects exerted by these polyphenols.

Key words: polyphenol, piceatannol, scirpusin B, ischemic heart disease, passion fruit

INTRODUCTION

Global Increase in Cardiovascular Disease (CVD) and the French Paradox

In recent years, atherosclerosis caused by the increasing prevalence of dyslipidemia and diabetes has become a major issue in public health and preventive medicine. Vascular risk factors such as smoking, diabetes, hypertension, and dyslipidemia increase the risk of atherosclerosis and a wide range of complications including ischemic heart disease, cerebrovascular disease, atherosclerosis obliterans, and dementia [1–3]. Ischemic heart disease and cerebrovascular disease have been the major leading causes of death in Japan over the past 20 years. Heart disease replaced cerebrovascular disease as the second most common cause of death in Japan in 1985; the mortality rate from heart disease has continued to increase since then. Currently, heart disease accounts for approximately 15% of all deaths in Japan (Table 1). By contrast, according to the World Health Organization [4], ischemic heart disease was the leading cause of death worldwide in 2019 (approximately 8.9 million), which accounted for 16% of the total deaths. Since 2000, ischemic heart disease has been the largest contributor to the increase in deaths. Stroke is the second leading cause of death (approximately six million), followed by lower respiratory tract infections (approximately three million). Atherosclerosis, which is a risk factor for ischemic heart disease and stroke, continues to be a major health challenge worldwide.

In France, the incidence of ischemic heart disease is low despite a diet rich in saturated fatty acids, as opposed to other developed countries with a similar diet; this phenomenon was reported in 1992 and was termed the “French paradox” [5]. This epidemiological paradox has been linked to the high consumption of red wine; the latter has been associated with a lower incidence of myocardial infarction in France by approximately 40% compared with that in other European countries [5]. The French paradox has been attributed to the inhibitory effect of polyphenolic antioxidants, such as resveratrol, which are present in red wine, on cardiovascular events [6]. While oxidative stress, which causes dysfunction of vascular endothelial cells, is associated with the development of atherosclerosis and CVD [7], polyphenols exhibit various anti-atherosclerotic effects such as the inhibition of platelet aggregation [8], improvement in endothelial function [9], and inhibition of low-density lipoprotein oxidation. This topic remains debatable 30 years after the French paradox was first reported; nonetheless, considerable evidence-based data support the idea that trace components of wine can exert a powerful cardioprotective effect [10]. This review aimed to focus on the polyphenols that can be extracted from passion fruit seeds namely, piceatannol and scirpusin B, and outline the cardioprotective effects of these compounds and the mechanisms through which they exert those effects.

Yutaka MATSUMOTO, Faculty of Nursing, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan
Tel: +81-463-90-2046 E-mail: matu@tsc.u-tokai.ac.jp

Table 1 Annual change in the number of deaths due to various causes in Japan (Ministry of Health, Labor, and Welfare website: modified from the 2004, 2009, 2014, and 2019 Annual Vital Statistics).

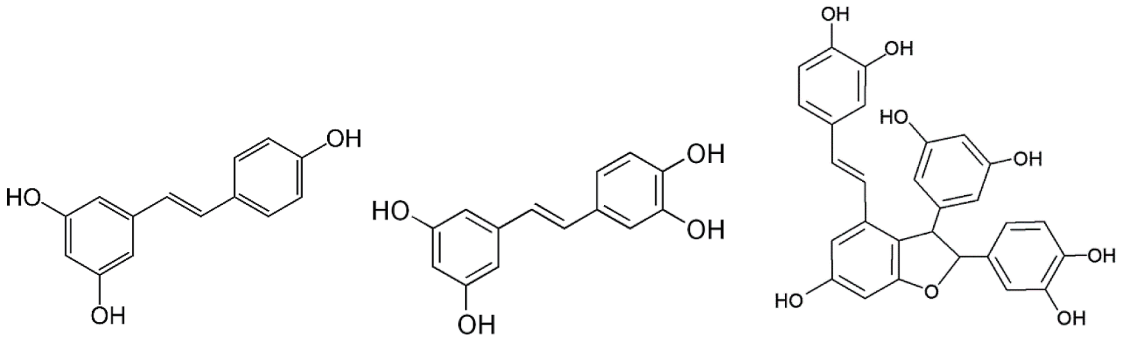
	2004		2009		2014		2019	
Rank	Cause of death	N	Cause of death	N	Cause of death	N	Cause of death	N
1	Malignant neoplasms	320,358	Malignant neoplasms	343,954	Malignant neoplasms	367,943	Malignant neoplasms	376,392
2	Heart diseases	159,625	Heart diseases	180,602	Heart diseases	196,760	Heart diseases	207,628
3	Cerebrovascular diseases	129,055	Cerebrovascular diseases	122,274	Pneumonia	119,566	Senility	121,868
4	Pneumonia	95,534	Pneumonia	111,922	Cerebrovascular diseases	114,118	Cerebrovascular diseases	106,506

The French Paradox Reveals the Cardiovascular Benefits of Polyphenols

In general, polyphenols are recognized as important antioxidants that are found in many plants. Resveratrol, which is thought to play an important role in the French paradox, is a polyphenol that is found in grapes and red wine [11]. Resveratrol is a phytoalexin that is produced by seed plants in response to external stimuli such as a fungal infection or an injury. Phytoalexins are secondary metabolites with antimicrobial activity that accumulate at the site of infection, are generally undetectable in the plant body before infection, and are rapidly synthesized when the plant is attacked by microorganisms. Resveratrol is found in red wine, grapes, mulberries, passion fruits [12], and peanuts [13]. Biological activities of resveratrol against CVD include anti-inflammation [10, 14], suppression of the *ICAM-1* gene expression [15], antioxidation [16, 17], inhibition of vascular smooth muscle cell proliferation [18, 19], enhancement of endothelial nitric oxide synthase (eNOS) activity [20, 21], inhibition of platelet aggregation [22], suppression of postprandial hyperglycemia [23], and promotion of vasodilation [20, 24].

Piceatannol (3,4,3',5'-tetrahydroxy-*trans*-stilbene), which is an analog of resveratrol (3,4,5-trihydroxy-*trans*-stilbene) (Fig. 1), has been reported to have the following effects: antioxidation [25, 26], anti-inflammation [14, 27–29], inhibition of smooth muscle cell proliferation [30], anti-arrhythmia [31], anticancer [32, 33], anti-melanin generation [12, 25], stimulation of collagen synthesis [12], inhibition of α-amylase activity in mouse plasma [34], enhanced expression of eNOS as manifested by increased levels of eNOS mRNA and protein [35], suppression of postprandial hyperglycemia [23], increased fat oxidation [36], inhibition of androgen synthesis and androgen receptor activation [37], and alleviation of endoplasmic reticulum stress [38]. In addition, piceatannol has been reported to have beneficial effects on many pathological conditions including behavioral disorders and brain injury in an aging mouse model [39], *Streptococcus suis* infection [40], cytomegalovirus infection [41], ischemic heart disease [42], arrhythmias, neurodegenerative diseases, diabetes [43–45], liver fibrosis [46], benign prostatic hypertrophy [38], obesity [47], obesity-related early-stage nephropathy [48], angiogenesis-related disease [49], and dry skin [50]. However, in many cases, the anti-inflammatory and antioxidative effects of piceatannol are involved in the underlying mechanisms. Thus, both resveratrol and piceatannol exert inhibitory effects on atherosclerosis; however, piceatannol has been reported to be more effective in improving the vascular endothelial dysfunction caused by oxidative stress [51].

As shown in Table 2, piceatannol is abundantly present in passion fruit seeds [12]. In addition to piceatannol, scirpusin B is another polyphenol that is abundant in passion fruit seeds [52]. Resveratrol, piceatannol, and scirpusin B are all stilbene derivatives. As shown in Fig. 1, scirpusin B is a dimer of piceatannol and has been shown to exert various biological actions such as vasodilation [52], superoxide anion removal [53], inhibition of postprandial hyperglycemia [34], inhibition of α-amylase activity [34], protection of neurons from neurotoxins [54], anti-amyloid-β aggre-



(a) Resveratrol (b) Piceatannol (c) Scirpusin B

Fig. 1 Chemical structure of stilbene derivatives.
Stilbene derivatives are a type of polyphenol found in plants. When plants are attacked by microorganisms, stilbene derivatives are rapidly produced and act as antimicrobial active substances. Piceatannol is a more active resveratrol analog due to the presence of additional hydroxyl group at 3' position, and scirpusin B is a dimer of piceatannol.

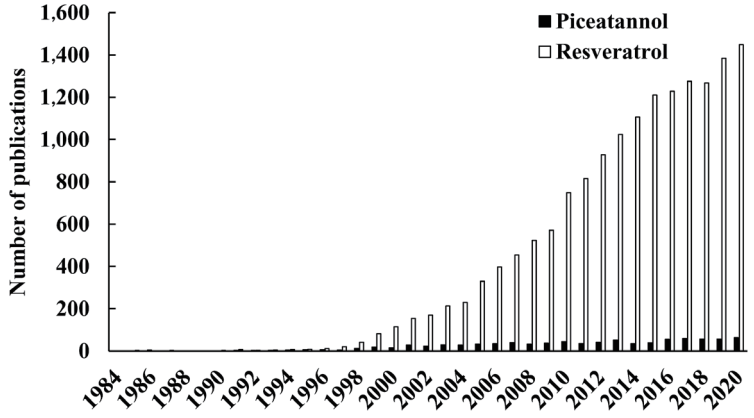


Fig. 2 Annual trend of the number of publications regarding resveratrol, piceatannol, and scirpusin B in PubMed.
The figure shows the number of hits when the three stilbene derivatives were searched on PubMed using the words "resveratrol," "piceatannol," and "scirpusin B." The number of published papers on resveratrol increased rapidly from around 1998, while the number of papers on piceatannol has remained constant at 50–60 in recent years. The number of published papers on scirpusin B is very low (0–2 papers per year) that it cannot be identified on the graph, and data labels are not shown. The total number of publications on scirpusin B per year includes one article per year in 2005, 2006, 2011, 2013, 2017, 2019, and 2020 and two articles in 2016.

gation effect [54], and anti-human immunodeficiency virus activity [55]. Furthermore, scirpusin B has been reported to have stronger antioxidative effect and stronger nitric oxide (NO)-mediated vasodilation than piceatannol [52]. These findings suggest that piceatannol and scirpusin B (a dimer of piceatannol), which are both analogs of resveratrol, may be useful in the prevention of cardiovascular events.

The Number of Publications Related to Resveratrol, Piceatannol, and Scirpusin B in PubMed

Figure 2 shows the results of a PubMed search performed using the keywords "resveratrol," "piceatannol," and "scirpusin B" to examine the trends in the research on stilbene derivatives. The annual number of papers published on resveratrol began to increase rapidly around 1998, and at present, nearly 1,400 papers are published annually. While the number of publications regarding piceatannol started to increase around the same time as that on resveratrol, the current annual number of publications has remained 50–60 (Fig. 2). The number of papers published on scirpusin B is even lower, with 0–2 papers per year and only nine papers over 15 years from 2005 to 2020. Thus, although resveratrol is well documented in the literature, the cardiovascular effects of piceatannol and scirpusin B have remained largely unexplored.

CARDIOVASCULAR EFFECTS OF PICEATANNOL AND SCIRPUSIN B

The information provided in this section is mainly based on the data obtained from our laboratory, as a limited number of studies have been performed on the

topic.

Effects of Piceatannol and Scirpusin B on the Aorta

When intact rat thoracic aortic endothelial specimens were suspended in an organ bath and cumulative doses (1–30 μM) of piceatannol and scirpusin B were administered, weak vasoconstrictor effects at low concentrations (1–10 μM) and strong vasodilator effects at higher concentrations (30 μM) were observed with both drugs [52]. Scirpusin B exerted a weaker vasoconstrictor effect than piceatannol at low concentrations and a stronger vasodilator effect at high concentrations. The administration of the NOS inhibitor, N^G-nitro-L-arginine methyl ester hydrochloride (L-NAME), significantly attenuated the vasodilatory effect. Therefore, dilation of the aorta by piceatannol and scirpusin B is thought to be mediated by NO.

Effects of Piceatannol and Scirpusin B on the Coronary Arteries

The Langendorff technique of heart perfusion was used to measure the direct effects of piceatannol and scirpusin B on the heart. The Langendorff technique is a classic experimental technique in which a cannula is inserted into the aorta of the removed heart, and the heart is perfused through the coronary arteries. The advantage of this technique is its ability to evaluate the direct effects of drugs on the heart while excluding the effects of bioactive substances derived from the autonomic nervous system and other organs. Therefore, it allows for a multifaceted evaluation of cardiac function [56]. The experiments showed that a single dose of piceatannol (100 μM) did not significantly increase the perfusion of the heart through rat coronary arteries; however, a continuous infusion of piceatannol (final concentration 30 μM) into rat coronary arteries increased the coronary perfusion to approximately 120% after 10 min, compared with 100% before the infusion [57]. When the coronary perfusion rate was 10 mL/min, the final concentration of 0.1 mL of a solution of 100 μM of the drug administered over 10 s was approximately 5.64 μM. With the continuous infusion of piceatannol, a significant increase in coronary perfusion began 1 min after the start of the infusion [57]. Based on the above, two possible reasons have been formulated to account for the fact that a single dose of piceatannol did not increase the coronary perfusion: (1) a single dose with a concentration of 100 μM might have diluted the drug to a concentration below that at which it could exert its effect in the perfusion circuit, and (2) it might have taken some time (in the order of several tens of seconds) for piceatannol to exert its dilating effect on the coronary arteries.

By contrast, a single dose of scirpusin B (100 μM) injected into the rat coronary arteries increased coronary perfusion to approximately 108% compared with a pre-dose perfusion of 100% [58]. In addition, the dilating effect of scirpusin B on the coronary arteries was dependent on the concentration; with the administration of single doses of ≥ 30 μM, the coronary arteries were significantly dilated. To investigate the mechanism underlying dilation of the coronary arteries with a single dose of scirpusin B, L-NAME was used as an NOS inhibitor and diclofenac as a cyclooxygenase (COX) inhibitor. As a result, the dilating effect of scirpusin B on the coronary arteries in the L-NAME pretreatment group and the diclofenac pretreatment group was significantly weakened compared with the scirpusin B monotherapy group. These findings suggest that the vasodilatory effect of scirpusin B may be mediated by the release of NO and prostacyclin (PGI_2). At present, few studies have reported the direct effects of scirpusin B and piceatannol on the heart using Langendorff's technique of heart perfusion. Therefore, further studies are needed on this topic.

Effects of Piceatannol and Scirpusin B on Cardiac Function

Piceatannol and scirpusin B do not exert an effect on heart rate (HR), left ventricular pressure, and its first derivative (dP/dt) [58]. Continuous administration of piceatannol and single-dose administration of scirpusin B increased the coronary perfusion without increasing the myocardial oxygen demand. The heart requires a large amount of oxygen, and the oxygen uptake rate in the coronary circulation is extremely high (approximately 75%) compared with the oxygen uptake rate in other organs (approximately 25%). The normal partial pressure of oxygen (PaO_2) in humans is 80–100 mmHg, whereas the PaO_2 in the coronary sinuses, which collect blood from the coronary circulation, is approximately 20 mmHg. Therefore, it is difficult to further increase the oxygen uptake rate of the myocardium during the increased oxygen demand associated with elevated heart rate during exercise, and hence the myocardial oxygen demand and supply are balanced by the dilation of the coronary arteries to increase the coronary perfusion.

In ischemic heart disease, the oxygen supply to the myocardium does not meet the oxygen demand. The fact that piceatannol and scirpusin B dilate the coronary arteries without increasing oxygen consumption suggests that these drugs may have a protective effect against ischemic heart disease. Table 3 describes the direct effects of piceatannol and scirpusin B on the cardiovascular system and their various protective effects against atherosclerosis. Since the aorta and coronary arteries are considered to have different properties as blood vessels, Table 3 describes the effects of piceatannol and scirpusin B on the aorta and coronary arteries separately. A study reported a difference in the development of atherosclerosis between the coronary arteries and the aorta [59]. Moreover, NO plays a major role in the regulation of vascular tonus of relatively large vessels, and PGI_2 has been reported to exert its effects somewhat uniformly on both large vessels and microvessels [60–62].

Cardioprotective Effects of Piceatannol and Scirpusin B

Thrombolytic therapy for cardiac disease can cause reperfusion arrhythmias, transient mechanical dysfunction, and cell death when oxygenated blood flows into the ischemic region [63, 64]. Overproduction of reactive oxygen species (ROS) [65] and overload or redistribution of intracellular calcium [66] have been proposed as mechanisms by which these tissue injuries occur. The preinfusion of piceatannol dramatically reduced the incidence and duration of reperfusion-in-

duced arrhythmias (ventricular tachycardia and ventricular fibrillation) and reduced the cardiac infarct size from 44.4 ± 4.1% to 19.1 ± 2.4% in the rat hearts after ischemia/reperfusion [42].

In the piceatannol group, there was a significant improvement in left ventricular pressure, but no effects on heart rate, coronary flow, and the first derivative of left ventricular pressure [57]. Resveratrol is also an antioxidant present in red wine [16, 17], and it has been reported that preinfusion of resveratrol can effectively prevent reperfusion-induced arrhythmias and mortality [63]. Similar studies have not been conducted on the effects of scirpusin B, and future studies are needed. Moreover, the concept that ROS plays a role in the pathogenesis of myocardial ischemia and myocardial infarction has been proposed, and antioxidants such as polyphenols present in foods may be beneficial in the prevention of these diseases [67, 68].

ROLE OF NO AND PGI_2 IN THE CARDIOVASCULAR SYSTEM

Endothelial cells secrete various vasoactive substances including PGI_2, NO, endothelium-derived hyperpolarizing factor, protein C, protein S, tissue plasminogen activator, thromboxane, and endothelin; these substances contribute to the maintenance of the physiological state of the circulatory system through the regulation of vascular tonus and their antithrombotic effects [2, 61, 69–71]. In addition, *in vivo* experiments have demonstrated that atrial natriuretic peptide plays an important role in the regulation of coronary flow [72]. Endothelial dysfunction is characterized by the decreased production of vasodilators such as PGI_2 and NO. Therefore, endothelial dysfunction is associated with cardiovascular events [73].

The effects of PGI_2 and NO on the cardiovascular system are summarized in Table 4. PGI_2 is known to mobilize vascular endothelial progenitor cells from the bone marrow to the bloodstream and to the site of ischemic injury. The non-cardiovascular effects of NO include synaptic transmission in the brain [74], dilation of gastrointestinal smooth muscle [75], sterilization when produced by macrophages and neutrophils [76, 77], neural plasticity (learning and memory) [74], and cell apoptosis [78, 79]. Although further investigation is needed, the vasodilatory effects of piceatannol and scirpusin B are thought to be mediated by PGI_2 and NO, as mentioned above. A comparison of the effects of piceatannol and scirpusin B (Table 3) with those of PGI_2 and NO on the cardiovascular system (Table 4) led to the conclusion that the anti-atherosclerotic effects including vasodilation, anti-inflammation, and inhibition of smooth muscle cell proliferation were consistent between the two substances. This finding supports the fact that piceatannol and scirpusin B exert their effects via PGI_2 and NO. Furthermore, piceatannol and scirpusin B have been reported to have antioxidative effects [52]. Since a relationship exists between oxidative stress and development of atherosclerosis [80–82], these polyphenols with antioxidative effects where suggested to have anti-atherosclerotic effects. Hence, piceatannol and scirpusin B may inhibit cardiovascular events such as ischemic heart disease in the presence of preserved endothelial cell function.

The administration of NOS inhibitors to animals

Table 2 Major cardiovascular effects of piceatannol and scirpusin B.

	Large vessel dilation	Coronary artery dilation	Other effects that affect the cardiovascular system (The table also includes the indirect effects of inhibiting arteriosclerosis)
Piceatannol	Yes [52]	Yes (Continuous dose) [57]	Antioxidative effect [25, 26, 52]
		No (Single dose) [58]	Anti-arrhythmic action [31]
			Improvement of ischemia-reperfusion injury [57]
			Inhibition of smooth muscle cell proliferation [30]
Scirpusin B	Yes [52]	Yes [58]	Antioxidative effect [52]
			Free radical scavenging action [52, 53]
			Inhibition of postprandial hyperglycemia [34]

MMP-9, matrix metalloproteinase-9; eNOS, endothelial nitric oxide synthase.

Anti-inflammatory effects [14, 27, 28, 52]
Inhibitory effect on MMP-9 expression
Enhanced expression level of eNOS mRNA and protein [35]

Table 3 Effects of prostacyclin (PGI_2) and nitric oxide (NO) on the cardiovascular system [61, 74, 89].

	Effects on the cardiovascular system	
PGI_2	Vasodilation	Inhibition of platelet aggregation
	NO production from vascular endothelial cells	Inhibition of pro-inflammatory cytokine production
	Inhibition of leukocyte adhesion	Inhibition of neutrophil migration
	Inhibition of smooth muscle cell migration and proliferation	Inhibition of PDGF production
	Protection of vascular endothelium	Myocardial protection against ischemic injury
	Promotion of cholesterol esterase activity	Inhibition of superoxide anion production
NO	Vasodilation	Inhibition of platelet aggregation
	Increased production of PGI_2 from vascular endothelial cells	Inhibition of pro-inflammatory cytokine production
	Inhibition of leukocyte adhesion	Inhibition of LDL oxidation
	Inhibition of blood coagulation	Inhibition of angiotensin II action
	Involved in vascular reconstruction and angiogenesis	

PDGF, platelet-derived growth factor; LDL, low density lipoprotein.

and humans causes vasoconstriction and a marked increase in blood pressure [83]. This implies that the sustained release of NO is essential in the maintenance of normal blood pressure. In the Langendorff-perfused heart, continuous administration of an NOS inhibitor (L-NAME) caused a sustained decrease in coronary perfusion. This could be attributed to the inhibition of NO production by L-NAME, which results in a reduction in the vascular smooth muscle relaxation of the coronary arteries. By contrast, continuous administration of a COX inhibitor (diclofenac) in Langendorff-perfused hearts did not reduce coronary perfusion. This finding may appear contradictory since COX inhibitors suppress the production of PGI_2; however, experiments performed on PGI_2 receptor (IP receptor) knockout mice might enable us to understand the reasons behind such a finding. A study reported that IP-deficient mice develop normally and show no change in bleeding time or blood pressure [84]. This suggests that the effects of PGI_2 on platelets and vascular smooth muscle are not exerted under normal conditions; instead, PGI_2 is involved in the regulation of platelet function and local organ blood flow during various pathological conditions [84]. Regarding the regulation of vascular tonus, NO acts on large vessels, and PGI_2 acts on vessels of both large and small caliber [60]. Furthermore, the crosstalk between NO and PGI_2 [85] and the actions of other bioactive substances are intricately intertwined to maintain blood circulation *in vivo*.

CONTENT OF PICEATANNOL AND SCIRPUSIN B IN FOODS AND BEVERAGES

The human body can obtain piceatannol through two routes: the metabolism of resveratrol by CYP1A2 to piceatannol and the ingestion of piceatannol from food [87–90]. In addition to both red wine and grapes, passion fruit (*Passiflora edulis*), highbush blueberry, deerberry, and peanuts are known to contain piceatannol [89–91]. The amount of piceatannol in passion fruit is approximately 50 times higher than that in grapes [12, 92], and approximately 88% of the total polyphenols (by weight) in passion fruit are found in its seeds [12]. The most important sources of piceatannol in the human diet are grapes and wine [90]. Piceatannol is produced by the action of bacterial β-glucosidase during grape ripening and during the fermentation process [93].

Resveratrol in grapes is reported to be 3.18 μg/g, while piceatannol in grapes is about a quarter of that, 0.78 μg/g [94]. Alternately, the concentration of *trans*-resveratrol in wine ranges from 0.63–3.39 mg/L, *cis*-resveratrol from 0.48–4.93 mg/L, and *trans*-piceatannol is 0.54–5.22 mg/L [90]. There is limited information on the piceatannol content in foods; the search results are summarized in Table 4. At present, there are few studies scirpusin B (Fig. 2), and the scirpusin B content in foods and the oral pharmacokinetic profiles are unknown.

CLINICAL STUDIES THAT EXAMINED RELATIONSHIP BETWEEN INTAKE OF PICEATANNOL AND SCIRPUSIN B AND INCIDENCE OF CVD

Currently, the oral dosage of piceatannol and scirpusin B necessary to prevent the development of CVD is unknown. The vasodilatory effects of piceatannol and scirpusin B are shown in Table 2, but the coronary artery dilatation observed in Langendorff perfused hearts was transient. Therefore, the anti-atherosclerotic effect of these polyphenols may be more important than its vasodilator effect in terms of prevention of CVD by oral intake. Presently, there are very few studies on scirpusin B, and no clinical studies have been reported. On the other hand, two clinical studies of piceatannol have been reported. In the first report, oral administration (20 mg/day for 8 weeks) of piceatannol, which was purified from passion fruit seed extract (purity 81.4%) improved insulin sensitivity and blood pressure in overweight men [97]. In the second report, the effects of oral administration of passion fruit seed extract (5 mg/day of piceatannol for 8 weeks) on dry skin showed improvements after 4 weeks, with the effects maintained at 8 weeks [50].

The effective dose of piceatannol for humans can be deduced from a previously reported research paper on resveratrol. Many clinical studies conducted on resveratrol in overweight and obese individuals have reported an improvement in risk factors for CVD such as systolic blood pressure, total cholesterol, and fasting glucose when the dose of resveratrol was 300 mg or more per day [98, 99]. On the other hand, the antioxidant effects and bioavailability of piceatannol have been reported to be superior to resveratrol [100]. The estimated oral bioavailability of resveratrol in humans has been reported to be less than 1.0% [101]. Besides, the bioavailability of piceatannol in humans is unknown, but animal studies have shown that piceatannol has much more effective oral bioavailability of more than 1% [49, 102]. As reference data, in a study where piceatannol was orally administered to rats at 200 ml/kg, the maximal plasma concentration and

Table 4 Piceatannol content of selected beverages, juices, and fruits, based on published papers.

Sample	Ref.	Concentration	
Black tea 1	[95]	14 ± 1	[μg/g]
Black tea 2	[95]	53 ± 6	[μg/g]
Red tea 1	[95]	34 ± 2	[μg/g]
Red tea 2	[95]	40 ± 3	[μg/g]
Green tea 1	[95]	53 ± 3	[μg/g]
Green tea 2	[95]	14 ± 2	[μg/g]
Breakfast tea	[95]	36 ± 3	[μg/g]
Ceylon tea	[95]	49 ± 4	[μg/g]
Lime blossom	[95]	68 ± 2	[μg/g]
Camomile	[95]	11 ± 0.2	[μg/g]
Black tea drink	[95]	48 ± 1	[ng/mL]
Peach flavor tea drink	[95]	23 ± 2	[ng/mL]
Apple juice	[95]	15 ± 3	[ng/mL]
Peach/grape juice	[95]	36 ± 5	[ng/mL]
Peach juice	[95]	14 ± 4	[ng/mL]
Apple	[95]	ND	[ng/g]
Pear	[95]	ND	[ng/g]
Grape	[92]	520	[ng/g]
Red grape	[95]	376 ± 16	[ng/g]
White grape	[95]	43 ± 5	[ng/g]
Deerberry	[91]	195	[ng/g dry sample]
Deerberry	[91]	138	[ng/g dry sample]
Highbush blueberry	[91]	186	[ng/g dry sample]
Highbush blueberry	[91]	422	[ng/g dry sample]
White wine 1	[96]	37 ± 1	[ng/mL]
White wine 2	[96]	96 ± 18	[ng/mL]
White wine 3	[96]	32 ± 3	[ng/mL]
White wine 4	[96]	ND	[ng/mL]
White wine 5	[96]	ND	[ng/mL]
White wine 6	[96]	37 ± 6	[ng/mL]
Red wine 1	[96]	595 ± 92	[ng/mL]
Red wine 2	[96]	ND	[ng/mL]
Red wine 3	[96]	111 ± 8	[ng/mL]
Red wine 4	[96]	ND	[ng/mL]
Red wine 5	[96]	388 ± 17	[ng/mL]
Red wine 6	[96]	166 ± 6	[ng/mL]
Red wine 7	[96]	271 ± 26	[ng/mL]
Red wine 8	[96]	215 ± 21	[ng/mL]
Red wine 9	[96]	378 ± 36	[ng/mL]
Passion fruits seed	[12]	4,800 *	[μg/g dry sample]

ND: not detected

* It translates to 2,200 μg/g in raw passion fruit seed.

mean residence time of piceatannol after oral administration were 2.34 ± 2.04 μM and 117 ± 53 min, respectively; however, its bioavailability (F = 6.99% ± 2.97) was low [103]. The potential mechanism by which piceatannol exerts its superior antioxidant activity compared to resveratrol and its anti-apoptotic effects is via the nuclear factor erythroid 2-related factor 2/heme oxygenase-1 in addition to the sirtuin 1-dependent pathway [100]. Several reports have shown the superior efficacy of piceatannol as compared to resveratrol in inhibiting COX-2 activity, NF-κB activity, and cytokine production (TNF-α, IL-1β) [14].

In summary, oral intake of piceatannol in the order of 100 mg/day may reduce the risk factors for CVD. However, as shown in Table 4, it is difficult to obtain such high quantities of piceatannol from a single source of food. If we assume that the piceatannol content in red wine is 300 ng/mL (Table 4), drinking 400 mL would provide 120 mg of piceatannol, but in the long term, ethanol will pose adverse health risks. Foods also contain other polyphenols, such as resveratrol, and a practical approach for optimal polyphenol intake is needed to prevent the development of CVD. Since passion fruit seeds are rich in piceatannol, it would be possible to extract piceatannol from the seeds and use it as a supplement. It has been pointed out that the low water solubility and bioavailability of piceatannol may limit its use in the pharmaceutical and food industries [104], and further research is needed for its application in dietary supplements.

CONCLUSION

In the 19th century, William Osler, who described the Osler's node, stated, "A man is as old as his arteries." In the 21st century, the fact that ischemic heart disease and cerebrovascular disease are the leading causes of death in many countries supports the statement made by Dr. Osler. Based on our findings, a modern interpretation of the statement would be,

"A man is as old as his vascular endothelium." The vascular endothelium is not simply the lining of blood vessels, but it also plays an important role in blood circulation through the production of biologically active substances with anti-thrombotic and vasodilatory properties, such as NO and PGI_2. The plasma levels of NO are considered a major indicator of endothelial function.

This review focused on the polyphenols that can be extracted from passion fruit seeds namely, piceatannol and scirpusin B. Unfortunately, the number of published papers on scirpusin B is very low (Fig. 2), therefore the cardioprotective effects of scirpusin B is not fully elucidated. On the other hand, piceatannol has anti-inflammatory and antioxidative effects and has been reported to have potential beneficial effects on many pathological conditions such as cancer, ischemic heart disease, arrhythmia, neurodegenerative diseases, diabetes, liver fibrosis, benign prostatic hypertrophy, and obesity-related early-stage nephropathy. Since most of the experimental results were obtained in cells and rodents, further research is needed for validation in humans. Nonetheless, since passion fruit seeds are rich in piceatannol (Table 4), it is worthwhile to utilize the piceatannol present in passion fruit seeds instead of discarding those seeds. Furthermore, it has been reported that modifications such as prenylation and methylation are useful for increasing the bioavailability of piceatannol [89], and further research in this direction is needed. An efficient method for extracting piceatannol and scirpusin B from passion fruit seeds has been described [105], and it is hoped that an efficient and low-cost extraction method will be widely available in the future.

Increasing the intake of polyphenols as an isolated measure to completely suppress atherosclerosis is challenging due to population aging and changing dietary and lifestyle habits. However, previous studies [3, 70] have shown that regular exercise and a healthy diet can inhibit the development of atherosclerosis to a considerable extent. We hope that further research on polyphenols such as piceatannol and scirpusin B, which are expected to be studied in detail, will lead to a healthier population with a longer life expectancy.

AUTHOR CONTRIBUTIONS

Conceptualization, Y.M.; writing - original draft preparation, Y.M.; writing - review and editing, Y.K. All authors have read and agreed to the published version of the manuscript.

FUNDING

This research received no external funding. This study was conducted using research funds distributed by the authors' affiliations.

ACKNOWLEDGMENTS

The authors thank late Professor Akira Ishihata (Division of Theoretical Nursing and Pathophysiology, Yamagata University School of Medicine) for encouragement during the early days of the study; Shoko Sano (Health Care Division, Morinaga & Co., Ltd.) for past collaborative research on piceatannol and scirpusin B. The authors wish to thank the anonymous reviewers for their helpful comments.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1) Gottesman RF, Albert MS, Alonso A, Coker LH, Coresh J, Davis SM, *et al*. Associations between midlife vascular risk factors and 25-year incident dementia in the atherosclerosis risk in communities (ARIC) cohort. JAMA Neurol. 2017; 74(10): 1246–54.
2) Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: Epidemiology, pathophysiology, and management. JAMA. 2002; 287(19): 2570–81.
3) Lusis AJ. Atherosclerosis. Nature. 2000; 407(6801): 233–41.
4) WHO. The top 10 causes of death. 2020 https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death (accessed March 8, 2021).
5) Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. Lancet. 1992; 339(8808): 1523–6.
6) Das DK, Sato M, Ray PS, Maulik G, Engelman RM, Bertelli AA, *et al*. Cardioprotection of red wine: Role of polyphenolic antioxidants. Drugs Exp Clin Res. 1999; 25(2–3): 115–20.
7) Ross R. The pathogenesis of atherosclerosis: A perspective for the 1990s. Nature. 1993; 362(6423): 801–9.
8) Serafini M, Maiani G, Ferro-Luzzi A. Alcohol-free red wine enhances plasma antioxidant capacity in humans. J Nutr. 1998; 128(6): 1003–7.
9) Duarte J, Perez-Palencia R, Vargas F, Ocete MA, Perez-Vizcaino F, Zarzuelo A, *et al*. Antihypertensive effects of the flavonoid quercetin in spontaneously hypertensive rats. Br J Pharmacol. 2001; 133(1): 117–24.
10) Fragopoulou E, Antonopoulou S. The French paradox three decades later: Role of inflammation and thrombosis. Clin Chim Acta. 2020; 510: 160–9.
11) Sala G, Minutolo F, Macchia M, Sacchi N, Ghidoni R. Resveratrol structure and ceramide-associated growth inhibition in prostate cancer cells. Drugs Exp Clin Res. 2003; 29(5–6): 263–9.
12) Matsui Y, Sugiyama K, Kamei M, Takahashi T, Suzuki T, Katagata Y, *et al*. Extract of passion fruit (*Passiflora edulis*) seed containing high amounts of piceatannol inhibits melanogenesis and promotes collagen synthesis. J Agric Food Chem. 2010; 58(20): 11112–8.
13) Sanders TH, McMichael RW, Jr., Hendrix KW. Occurrence of resveratrol in edible peanuts. J Agric Food Chem. 2000; 48(4): 1243–6.
14) Dvorakova M, Landa P. Anti-inflammatory activity of natural stilbenoids: A review. Pharmacol Res. 2017; 124: 126–45.
15) Wung BS, Hsu MC, Wu CC, Hsieh CW. Resveratrol suppresses IL-6-induced ICAM-1 gene expression in endothelial cells: Effects on the inhibition of STAT3 phosphorylation. Life Sci. 2005; 78(4): 389–97.
16) Frankel EN, Waterhouse AL, Kinsella JE. Inhibition of human LDL oxidation by resveratrol. Lancet. 1993; 341(8852): 1103–4.
17) Brito P, Almeida LM, Dinis TC. The interaction of resveratrol with ferrylmyoglobin and peroxynitrite; protection against LDL oxidation. Free Radic Res. 2002; 36(6): 621–31.
18) Haider UG, Sorescu D, Griendling KK, Vollmar AM, Dirsch VM. Resveratrol increases serine15-phosphorylated but transcriptionally impaired p53 and induces a reversible DNA replication block in serum-activated vascular smooth muscle cells. Mol Pharmacol. 2003; 63(4): 925–32.
19) Mnjoyan ZH, Fujise K. Profound negative regulatory effects by resveratrol on vascular smooth muscle cells: A role of p53-$p21^{WAF1/CIP1}$ pathway. Biochem Biophys Res Commun. 2003; 311(2): 546–52.
20) Wallerath T, Deckert G, Ternes T, Anderson H, Li H, Witte K, *et al*. Resveratrol, a polyphenolic phytoalexin present in red wine, enhances expression and activity of endothelial nitric oxide synthase. Circulation. 2002; 106(13): 1652–8.
21) Klinge CM, Blankenship KA, Risinger KE, Bhatnagar S, Noisin EL, Sumanasekera WK, *et al*. Resveratrol and estradiol rapidly

activate MAPK signaling through estrogen receptors alpha and beta in endothelial cells. J Biol Chem. 2005; 280(9): 7460–8.
22) Pace-Asciak CR, Hahn S, Diamandis EP, Soleas G, Goldberg DM. The red wine phenolics *trans*-resveratrol and quercetin block human platelet aggregation and eicosanoid synthesis: Implications for protection against coronary heart disease. Clin Chim Acta. 1995; 235(2): 207–19.
23) Zhang AJ, Rimando AM, Mizuno CS, Mathews ST. α-Glucosidase inhibitory effect of resveratrol and piceatannol. J Nutr Biochem. 2017; 47: 86–93.
24) Chen CK, Pace-Asciak CR. Vasorelaxing activity of resveratrol and quercetin in isolated rat aorta. Gen Pharmacol. 1996; 27(2): 363–6.
25) Yokozawa T, Kim YJ. Piceatannol inhibits melanogenesis by its antioxidative actions. Biol Pharm Bull. 2007; 30(11): 2007–11.
26) Wung BS, Hsu MC, Wu CC, Hsieh CW. Piceatannol upregulates endothelial heme oxygenase-1 expression via novel protein kinase C and tyrosine kinase pathways. Pharmacol Res. 2006; 53(2): 113–22.
27) Montanher AB, Zucolotto SM, Schenkel EP, Frode TS. Evidence of anti-inflammatory effects of *Passiflora edulis* in an inflammation model. J Ethnopharmacol. 2007; 109(2): 281–8.
28) Matsuda H, Kageura T, Morikawa T, Toguchida I, Harima S, Yoshikawa M. Effects of stilbene constituents from rhubarb on nitric oxide production in lipopolysaccharide-activated macrophages. Bioorg Med Chem Lett. 2000; 10(4): 323–7.
29) Su L, David M. Distinct mechanisms of STAT phosphorylation via the interferon-α/β receptor. Selective inhibition of STAT3 and STAT5 by piceatannol. J Biol Chem. 2000; 275(17): 12661–6.
30) Lee B, Lee EJ, Kim DI, Park SK, Kim WJ, Moon SK. Inhibition of proliferation and migration by piceatannol in vascular smooth muscle cells. Toxicol In Vitro. 2009; 23(7): 1284–91.
31) Chen WP, Hung LM, Hsueh CH, Lai LP, Su MJ. Piceatannol, a derivative of resveratrol, moderately slows INa inactivation and exerts antiarrhythmic action in ischaemia-reperfused rat hearts. Br J Pharmacol. 2009; 157(3): 381–91.
32) Wieder T, Prokop A, Bagci B, Essmann F, Bernicke D, Schulze-Osthoff K, *et al*. Piceatannol, a hydroxylated analog of the chemopreventive agent resveratrol, is a potent inducer of apoptosis in the lymphoma cell line BJAB and in primary, leukemic lymphoblasts. Leukemia. 2001; 15(11): 1735–42.
33) Djoko B, Chiou RY, Shee JJ, Liu YW. Characterization of immunological activities of peanut stilbenoids, arachidin-1, piceatannol, and resveratrol on lipopolysaccharide-induced inflammation of RAW 264.7 macrophages. J Agric Food Chem. 2007; 55(6): 2376–83.
34) Kobayashi K, Ishihara T, Khono E, Miyase T, Yoshizaki F. Constituents of stem bark of *Callistemon rigidus* showing inhibitory effects on mouse alpha-amylase activity. Biol Pharm Bull. 2006; 29(6): 1275–7.
35) Kinoshita Y, Kawakami S, Yanae K, Sano S, Uchida H, Inagaki H, *et al*. Effect of long-term piceatannol treatment on eNOS levels in cultured endothelial cells. Biochem Biophys Res Commun. 2013; 430(3): 1164–8.
36) Tsukamoto-Sen S, Kawakami S, Maruki-Uchida H, Ito R, Matsui N, Komiya Y, *et al*. Effect of antioxidant supplementation on skeletal muscle and metabolic profile in aging mice. Food Funct. 2021; 12(2): 825–33.
37) Lundqvist J, Tringali C, Oskarsson A. Resveratrol, piceatannol and analogs inhibit activation of both wild-type and T877A mutant androgen receptor. J Steroid Biochem Mol Biol. 2017; 174: 161–8.
38) Kil JS, Jeong SO, Chung HT, Pae HO. Piceatannol attenuates homocysteine-induced endoplasmic reticulum stress and endothelial cell damage via heme oxygenase-1 expression. Amino Acids. 2017; 49(4): 735–45.
39) Zhang Y, Zhang LH, Chen X, Zhang N, Li G. Piceatannol attenuates behavioral disorder and neurological deficits in aging mice via activating the Nrf2 pathway. Food Funct. 2018; 9(1): 371–8.
40) Wang G, Gao Y, Wu X, Gao X, Zhang M, Liu H, *et al*. Inhibitory effect of piceatannol on *Streptococcus suis* infection both *in vitro* and *in vivo*. Front Microbiol. 2020; 11: 593588.
41) Wang SY, Zhang J, Xu XG, Su HL, Xing WM, Zhang ZS, *et al*. Inhibitory effects of piceatannol on human cytomegalovirus (hCMV) *in vitro*. J Microbiol. 2020; 58(8): 716–23.
42) Hung LM, Chen JK, Lee RS, Liang HC, Su MJ. Beneficial effects of astringinin, a resveratrol analogue, on the ischemia and reperfusion damage in rat heart. Free Radic Biol Med. 2001; 30(8): 877–83.
43) Xu X, Zhao M, Han Q, Wang H, Zhang H, Wang Y. Effects of piceatannol on the structure and activities of bovine serum albumin: A multi-spectral and molecular modeling studies. Spectrochim Acta A Mol Biomol Spectrosc. 2020; 228: 117706.
44) Oritani Y, Okitsu T, Nishimura E, Sai M, Ito T, Takeuchi S. Enhanced glucose tolerance by intravascularly administered piceatannol in freely moving healthy rats. Biochem Biophys Res Commun. 2016; 470(3): 753–8.
45) Uchida-Maruki H, Inagaki H, Ito R, Kurita I, Sai M, Ito T. Piceatannol lowers the blood glucose level in diabetic mice. Biol Pharm Bull. 2015; 38(4): 629–33.
46) Abd-Elgawad H, Abu-Elsaad N, El-Karef A, Ibrahim T. Piceatannol increases the expression of hepatocyte growth factor and IL-10 thereby protecting hepatocytes in thioacetamide-induced liver fibrosis. Can J Physiol Pharmacol. 2016; 94(7): 779–87.
47) Tung YC, Lin YH, Chen HJ, Chou SC, Cheng AC, Kalyanam N, *et al*. Piceatannol exerts anti-obesity effects in C57BL/6 mice through modulating adipogenic proteins and gut microbiota. Molecules. 2016; 21(11): 1419.
48) Llarena M, Andrade F, Hasnaoui M, Portillo MP, Perez-Matute P, Arbones-Mainar JM, *et al*. Potential renoprotective effects of piceatannol in ameliorating the early-stage nephropathy associated with obesity in obese Zucker rats. J Physiol Biochem. 2016; 72(3): 555–66.
49) Hu WH, Dai DK, Zheng BZ, Duan R, Dong TT, Qin QW, *et al*. Piceatannol, a natural analog of resveratrol, exerts anti-angiogenic efficiencies by blockage of vascular endothelial growth factor binding to its receptor. Molecules. 2020; 25(17): 3769.
50) Maruki-Uchida H, Morita M, Yonei Y, Sai M. Effect of passion fruit seed extract rich in piceatannol on the skin of women: A randomized, placebo-controlled, double-blind trial. J Nutr Sci Vitaminol. 2018; 64(1): 75–80.
51) Frombaum M, Therond P, Djelidi R, Beaudeux JL, Bonnefont-Rousselot D, Borderie D. Piceatannol is more effective than resveratrol in restoring endothelial cell dimethylarginine dimethylaminohydrolase expression and activity after high-glucose oxidative stress. Free Radic Res. 2011; 45(3): 293–302.
52) Sano S, Sugiyama K, Ito T, Katano Y, Ishihata A. Identification of the strong vasorelaxing substance scirpusin B, a dimer of piceatannol, from passion fruit (*Passiflora edulis*) seeds. J Agric Food Chem. 2011; 59(11): 6209–13.
53) Xiang T, Uno T, Ogino F, Ai C, Duo J, Sankawa U. Antioxidant constituents of *Caragana tibetica*. Chem Pharm Bull. 2005; 53(9): 1204–6.
54) Sim Y, Choi JG, Gu PS, Ryu B, Kim JH, Kang I, *et al*. Identification of neuroactive constituents of the ethyl acetate fraction from cyperi rhizoma using bioactivity-guided fractionation. Biomol Ther. 2016; 24(4): 438–45.
55) Yang GX, Zhou JT, Li YZ, Hu CQ. Anti-HIV bioactive stilbene dimers of *Caragana rosea*. Planta Med. 2005; 71(6): 569–71.
56) Olejnickova V, Novakova M, Provaznik I. Isolated heart models: Cardiovascular system studies and technological advances. Med Biol Eng Comput. 2015; 53(7): 669–78.
57) Nasu F, Sintaro O, Matsumoto Y, Kurita I, Uchida Y, Ito T, *et al*. Cardioprotective effect of piceatannol against ischemia-reperfusion injury (in Japanese). J Jpn Mibyou Assoc. 2013; 19(2): 102–6.
58) Matsumoto Y, Gotoh N, Sano S, Sugiyama K, Ito T, Abe Y, *et al*. Effects of scirpusin B, a polyphenol in passion fruit seeds, on the coronary circulation of the isolated perfused rat heart. Int J Med Res Health Sci. 2014; 3(3): 547.
59) Oya H. The study on the development of atherosclerotic lesions in the WHHL rabbits -The comparison of the coronary and aortic atherosclerosis- (in Japanese). Hiroshima J Med Sci. 2000; 48(2): 139–51.
60) Shimokawa H, Yasutake H, Fujii K, Owada MK, Nakaike R,

Fukumoto Y, *et al*. The importance of the hyperpolarizing mechanism increases as the vessel size decreases in endothelium-dependent relaxations in rat mesenteric circulation. J Cardiovasc Pharmacol. 1996; 28(5): 703–11.
61) Nava E, Llorens S. The paracrine control of vascular motion. A historical perspective. Pharmacol Res. 2016; 113(Pt A): 125–45.
62) Hwa JJ, Ghibaudi L, Williams P, Chatterjee M. Comparison of acetylcholine-dependent relaxation in large and small arteries of rat mesenteric vascular bed. Am J Physiol. 1994; 266(3 Pt 2): H952–8.
63) Hung LM, Chen JK, Huang SS, Lee RS, Su MJ. Cardioprotective effect of resveratrol, a natural antioxidant derived from grapes. Cardiovasc Res. 2000; 47(3): 549–55.
64) Robicsek F, Schaper J. Reperfusion injury: Fact or myth? J Card Surg. 1997; 12(3): 133–7.
65) Zweier JL. Measurement of superoxide-derived free radicals in the reperfused heart. Evidence for a free radical mechanism of reperfusion injury. J Biol Chem. 1988; 263(3): 1353–7.
66) Brooks WW, Conrad CH, Morgan JP. Reperfusion induced arrhythmias following ischaemia in intact rat heart: Role of intracellular calcium. Cardiovasc Res. 1995; 29(4): 536–42.
67) Sato M, Maulik G, Ray PS, Bagchi D, Das DK. Cardioprotective effects of grape seed proanthocyanidin against ischemic reperfusion injury. J Mol Cell Cardiol. 1999; 31(6): 1289–97.
68) Campo GM, Squadrito F, Campo S, Altavilla D, Quartarone C, Ceccarelli S, *et al*. Beneficial effect of raxofelast, an hydrophilic vitamin E analogue, in the rat heart after ischemia and reperfusion injury. J Mol Cell Cardiol. 1998; 30(8): 1493–503.
69) Golshiri K, Ataei Ataabadi E, Portilla Fernandez EC, Jan Danser AH, Roks AJM. The importance of the nitric oxide-cGMP pathway in age-related cardiovascular disease: Focus on phosphodiesterase-1 and soluble guanylate cyclase. Basic Clin Pharmacol Toxicol. 2020; 127(2): 67–80.
70) Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: A marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol. 2003; 23(2): 168–75.
71) Schiffrin EL. The endothelium and control of blood vessel function in health and disease. Clin Invest Med. 1994; 17(6): 602–20.
72) Liu Q, Nakae I, Tsutamoto T, Takaoka A, Kinoshita M. *In vivo* vasodilatory action of atrial natriuretic peptides in canine coronary circulation. Jpn Circ J. 1996; 60(5): 300–10.
73) Lerman A, Zeiher AM. Endothelial function: Cardiac events. Circulation. 2005; 111(3): 363–8.
74) Picón-Pagès P, Garcia-Buendia J, Muñoz FJ. Functions and dysfunctions of nitric oxide in brain. Biochim Biophys Acta Mol Basis Dis. 2019; 1865(8): 1949–67.
75) Dijkstra G, van Goor H, Jansen PL, Moshage H. Targeting nitric oxide in the gastrointestinal tract. Curr Opin Investig Drugs. 2004; 5(5): 529–36.
76) Coleman JW. Nitric oxide in immunity and inflammation. Int Immunopharmacol. 2001; 1(8): 1397–406.
77) Weiss G, Schaible UE. Macrophage defense mechanisms against intracellular bacteria. Immunol Rev. 2015; 264(1): 182–203.
78) Li CQ, Wogan GN. Nitric oxide as a modulator of apoptosis. Cancer Lett. 2005; 226(1): 1–15.
79) Brune B, von Knethen A, Sandau KB. Nitric oxide (NO): An effector of apoptosis. Cell Death Differ. 1999; 6(10): 969–75.
80) Poznyak AV, Grechko AV, Orekhova VA, Chegodaev YS, Wu WK, Orekhov AN. Oxidative stress and antioxidants in atherosclerosis development and treatment. Biology. 2020; 9(3): 60.
81) Racis M, Stanislawska-Sachadyn A, Sobiczewski W, Wirtwein M, Krzeminski M, Krawczynska N, *et al*. Association of genes related to oxidative stress with the extent of coronary atherosclerosis. Life. 2020; 10(9): 210.
82) Toualbi LA, Adnane M, Abderrezak K, Ballouti W, Arab M, Toualbi C, *et al*. Oxidative stress accelerates the carotid atherosclerosis process in patients with chronic kidney disease. Arch Med Sci Atheroscler Dis. 2020; 5: e245–54.
83) Aluko EO, Nna VU, Fasanmade AA. Angiotensin converting enzyme inhibitor potentiates the hypoglycaemfic effect of N^G-nitro-L-arginine methyl ester (L-NAME) in rats. Arch Physiol Biochem. 2020: 1–9.
84) Murata T, Ushikubi F, Matsuoka T, Hirata M, Yamasaki A, Sugimoto Y, *et al*. Altered pain perception and inflammatory response in mice lacking prostacyclin receptor. Nature. 1997; 388(6643): 678–82.
85) Niwano K, Arai M, Tomaru K, Uchiyama T, Ohyama Y, Kurabayashi M. Transcriptional stimulation of the eNOS gene by the stable prostacyclin analogue beraprost is mediated through cAMP-responsive element in vascular endothelial cells: Close link between PGI_2 signal and NO pathways. Circ Res. 2003; 93(6): 523–30.
86) Ando A, Yang A, Mori K, Yamada H, Yamada E, Takahashi K, *et al*. Nitric oxide is proangiogenic in the retina and choroid. J Cell Physiol. 2002; 191(1): 116–24.
87) Potter GA, Patterson LH, Wanogho E, Perry PJ, Butler PC, Ijaz T, *et al*. The cancer preventative agent resveratrol is converted to the anticancer agent piceatannol by the cytochrome P450 enzyme CYP1B1. Br J Cancer. 2002; 86(5): 774–8.
88) Piver B, Fer M, Vitrac X, Merillon JM, Dreano Y, Berthou F, *et al*. Involvement of cytochrome P450 1A2 in the biotransformation of trans-resveratrol in human liver microsomes. Biochem Pharmacol. 2004; 68(4): 773–82.
89) Kershaw J, Kim KH. The Therapeutic potential of piceatannol, a natural stilbene, in metabolic diseases: A review. J Med Food. 2017; 20(5): 427–38.
90) Piotrowska H, Kucinska M, Murias M. Biological activity of piceatannol: Leaving the shadow of resveratrol. Mutat Res. 2012; 750(1): 60–82.
91) Rimando AM, Kalt W, Magee JB, Dewey J, Ballington JR. Resveratrol, pterostilbene, and piceatannol in vaccinium berries. J Agric Food Chem. 2004; 52(15): 4713–9.
92) Bavaresco L, Fregoni M, Trevisan M, Mattivi F, Vrhovsek U, Falchetti R. The occurrence of the stilbene piceatannol in grapes. Vitis. 2002; 41(3): 133–6.
93) Tang YL, Chan SW. A review of the pharmacological effects of piceatannol on cardiovascular diseases. Phytother Res. 2014; 28(11): 1581–8.
94) Cantos E, Espin JC, Fernandez MJ, Oliva J, Tomas-Barberan FA. Postharvest UV-C-irradiated grapes as a potential source for producing stilbene-enriched red wines. J Agric Food Chem. 2003; 51(5): 1208–14.
95) Viñas P, Martínez-Castillo N, Campillo N, Hernández-Córdoba M. Directly suspended droplet microextraction with in injection-port derivatization coupled to gas chromatography-mass spectrometry for the analysis of polyphenols in herbal infusions, fruits and functional foods. J Chromatogr A. 2011; 1218(5): 639–46.
96) Rodriguez-Cabo T, Rodriguez I, Lopez P, Ramil M, Cela R. Investigation of liquid chromatography quadrupole time-of-flight mass spectrometry performance for identification and determination of hydroxylated stilbene antioxidants in wine. J Chromatogr A. 2014; 1337: 162–70.
97) Kitada M, Ogura Y, Maruki-Uchida H, Sai M, Suzuki T, Kanasaki K, *et al*. The effect of piceatannol from passion fruit (Passiflora edulis) seeds on metabolic health in humans. Nutrients. 2017; 9(10).
98) Cebova M, Pechanova O. Protective effects of polyphenols against ischemia/reperfusion injury. Molecules. 2020; 25(15): 3469.
99) Huang H, Chen G, Liao D, Zhu Y, Pu R, Xue X. The effects of resveratrol intervention on risk markers of cardiovascular health in overweight and obese subjects: A pooled analysis of randomized controlled trials. Obes Rev. 2016; 17(12): 1329–40.
100) Hosoda R, Hamada H, Uesugi D, Iwahara N, Nojima I, Horio Y, *et al*. Different antioxidative and antiapoptotic effects of piceatannol and resveratrol. J Pharmacol Exp Ther. 2021; 376(3): 385–96.
101) Walle T. Bioavailability of resveratrol. Ann N Y Acad Sci. 2011; 1215: 9–15.
102) Kukreja A, Wadhwa N, Tiwari A. Therapeutic role of resveratrol and piceatannol in disease prevention. J Blood Disord Transfus. 2014; 05(09).
103) Dai Y, Lim JX, Yeo SCM, Xiang X, Tan KS, Fu JH, *et al*. Biotransformation of piceatannol, a dietary resveratrol derivative: Promises to human health. Mol Nutr Food Res. 2020; 64(2): e1900905.

104) Messiad H, Amira-Guebailia H, Houache O. Reversed phase high performance liquid chromatography used for the physico-chemical and thermodynamic characterization of piceatannol/β-cyclodextrin complex. J Chromatogr B Analyt Technol Biomed Life Sci. 2013; 926: 21–7.

105) Vigano J, Aguiar AC, Moraes DR, Jara JLP, Eberlin MN, Cazarin CBB, *et al*. Sequential high pressure extractions applied to recover piceatannol and scirpusin B from passion fruit bagasse. Food Res Int. 2016; 85: 51–8.