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REVIEW

The Therapeutic Potential of Piceatannol, a Natural Stilbene, in Metabolic Diseases: A Review

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ABSTRACT Metabolic disease comprises a set of risk factors highly associated with obesity and insulin resistance and is a consequence of central adiposity, hyperglycemia, and dyslipidemia. Furthermore, obesity increases the risk of the development of metabolic disease due to ectopic fat deposition, low-grade inflammation, and systemic energy disorders caused by dysregulated adipose tissue function. Piceatannol is a naturally occurring polyphenolic stilbene found in various fruits and vegetables and has been reported to exhibit anticancer and anti-inflammatory properties. In addition, recently reported beneficial effects of piceatannol on hypercholesterolemia, atherosclerosis, and angiogenesis underscore its therapeutic potential in cardiovascular disease. However, investigation of its role in metabolic disease is still in its infancy. This review intensively summarizes *in vitro* and *in vivo* studies supporting the potential therapeutic effects of piceatannol in metabolic disease, including inhibition of adipogenesis and lipid metabolism in adipocytes, and regulation of hyperlipidemia, hyperglycemia, insulin resistance, and fatty acid-induced inflammation and oxidative stress.

KEYWORDS: • ***adipocytes*** • ***adipose tissue*** • ***bioavailability*** • ***insulin resistance*** • ***obesity*** • ***resveratrol***

INTRODUCTION

METABOLIC SYNDROME affects approximately one in every four adults across the globe and as many as 34% of people in the United States.[1,2] Insulin resistance, adiposity, dyslipidemia, hypertension, inflammation, and hyperglycemia characterize the syndrome, resulting in increased risk for a number of chronic diseases, including cardiovascular disease (CVD), stroke, type 2 diabetes (T2D), and all-cause mortality.[3] In this review, diagnostic criteria for metabolic syndrome will simply be referred to as metabolic disorders as they can occur individually without clinical diagnosis of the condition.

Phytochemicals, plant secondary metabolites produced in response to environmental stress, are putative therapeutic agents in the treatment of metabolic disorders. Resveratrol is a well-studied phytochemical in the treatment of metabolic disorders. This polyphenol has been shown to reverse the adverse effects of a high-calorie diet, protect against diet-induced obesity, and improve overall health in rodents.[4,5] Although a meta-analysis of randomized clinical trials revealed that resveratrol lowered fasting insulin, glucose, and insulin resistance, a conclusive physiologically relevant benefit has not been demonstrated in healthy populations.[6,7] Limited oral bioavailability is suspected to be one of the main barriers to resveratrol's potency in human studies: resveratrol is extensively metabolized and has an estimated oral bioavailability of less than 1.0%.[8] Therefore, identification of more stable resveratrol metabolites and synthetic derivatives with improved bioavailability is emerging as an alternative option to treat metabolic disorders. Piceatannol is identical in structure to resveratrol, with the exception of an additional hydroxyl group at the 3′-carbon (Table 1). Of note, piceatannol has been shown to be more metabolically stable than resveratrol.[9] Although reviews of piceatannol's role in cancer, CVD, and other chronic diseases have been conducted, the literature regarding its effect in metabolic disorders is limited.[10–13] This review will focus on the biological role of piceatannol in metabolic disorders. We conclude that although *in vivo* and human studies of piceatannol are currently insufficient to recommend its clinical use, the effect of piceatannol in modulating energy metabolism and inflammation merits further investigation of its use in the treatment and prevention of metabolic disease.

SOURCES OF PICEATANNOL

Dietary sources

Piceatannol is naturally present in a variety of foods typically consumed in the human diet. For example, both red grapes and white grapes contain piceatannol at concentrations of 374 and 43 ng/g, respectively.[14] In addition, passion fruit contains a high amount of piceatannol in its seed,

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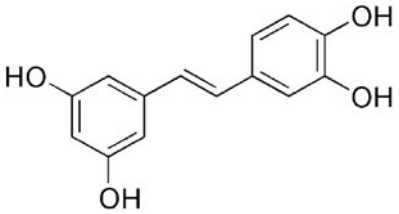
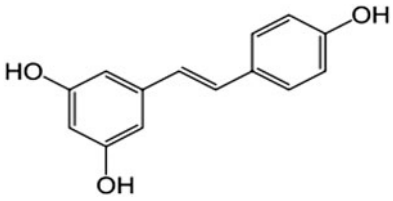
Table 1. Structure and Physical Properties of Piceatannol and Resveratrol

	Piceatannol	*Resveratrol*
Molecular weight	244.24	228.24
Solubility	10 g/L in DMSO, 10 g/L in ethanol, 0.5 g/L in water	≥16 g/L in DMSO, 50 g/L in ethanol, 0.03 g/L in water
Structure		

detected at a dry weight concentration of 4.8 mg/g.[15] Vaccinium berries (blueberries) also contain piceatannol at a dry concentration of 138–422 ng/g.[16] As with most secondary plant metabolites, piceatannol is produced in response to stress. UV irradiation, for example, has been shown to increase piceatannol in both peanut callusses and grapes.[17,18] Additionally, wine made with UV-irradiated grapes contains 1.5 times as much piceatannol (311 μg/L) as wine made form untreated grapes.[18] Fungal stress also increases piceatannol in peanut calluses to levels as high as 6.93 μg/g.[19] For further details regarding natural sources of piceatannol, the reader is directed to the extensive review by Piotrowska *et al.*[10]

Piceatannol as a resveratrol metabolite

In addition to natural sources, piceatannol is also a metabolite of the well-studied resveratrol. *In vitro*, piceatannol is formed by CYP450 metabolism of resveratrol, as seen in human lymphoblasts, liver microsomes, and other models.[10,20,21] Furthermore, piceatannol has been detected as a resveratrol metabolite *in vivo*: 5 min following resveratrol administration (75 mg/kg), piceatannol was found in the plasma (5.26 μmol), skin (2.4 nmol/g), and liver (11.5 nmol/g) of athymic mice.[22] In addition, after 5 weeks of resveratrol administration in mice, piceatannol was found as a product of phase 1 metabolism in the small intestine.[23]

METABOLISM AND BIOAVAILABILITY OF PICEATANNOL

An understanding of piceatannol's metabolism and bioavailability is necessary to determine physiologically relevant doses and to translate findings from model systems to human applications. Bioactive compounds such as piceatannol must be present in sufficient concentration, stable for an adequate exposure time, and in an active form at the site of putative action to exert their effects.

Piceatannol metabolites

In vivo, piceatannol is metabolized to glucuronidated, methylated, and sulfated metabolites and to unique compounds, as outlined in Table 2. Following intravenous (IV) administration, glucuronidated compounds appeared to be the main piceatannol metabolites. In addition, piceatannol was metabolized by the liver and highly distributed in tissues, as indicated by a high hepatic clearance rate and volume distribution, respectively.[24,25] Oral administration of piceatannol provides

Table 2. Piceatannol Metabolism *In Vitro* and *In Vivo*

Model	*Route*	*Detected metabolites*	*Ref.*
Sprague-Dawley rats	Oral	Piceatannol-diglucuronide, piceatannol monoglucuronide, *O*-methyl piceatannol monoglucuronide,*O*-methyl piceatannol monosulfate, isorhapontigenin, rhapontigenin	9
Sprague-Dawley rats	Oral	Glucuronidated piceatannol, *O*-methylated piceatannol, isorhapontigenin	33
Sprague-Dawley rats	IV	Glucurondiated metabolites	24
Sprague-Dawley rats	IV	Glucurondiated metabolites	25
Rat liver microsomes with uridine diphosphate–glucuronosyltransferase	*In vitro*	Glucurondiated metabolites	25
Human liver cytosol	*In vitro*	Piceatannol disulfate, piceatannol monosulfate (two peaks)	77
Recombinant sulfotransferase isoforms	*In vitro*		
Human liver microsomes	*In vitro*	Piceatannol monoglucuronides (three peaks)	78
Recombinant UDP-glucuronosyltransferase isoforms	*In vitro*		

IV, intravenous.

additional understanding of piceatannol metabolism, as described in the study by Setoguchi *et al*. using Sprague-Dawley rats. As with the Roupe studies, this group also identified a monoglucuronide as the main piceatannol metabolite. Unlike the other study, novel compounds such as the antiarteriosclerotic and anticancer compound isorhapontigenin, were also detected. Rhapontigenin was also detected in plasma and urine, as were glucuronidated, methylated, and sulfated piceatannol metabolites: piceatannol diglucuronide, piceatannol monoglucuronide, *O*-methyl piceatannol monoglucuronide, and *O*-methyl piceatannolmonosulfate.[9] *In vitro*, piceatannol is transformed to sulfated and glucuronidated metabolites, as previously reviewed.[10]

Of note, piceatannol was not detected as a metabolite of resveratrol *in vivo*, in the study by Setoguchi *et al.* which differs from previous studies.[9,22,23] In contrast to piceatannol, where *O*-methyl piceatannol conjugates were identified, only conjugates of the resveratrol parent compound were detected. This observation supports the hypothesis that piceatannol's catechol group enables unique metabolism by catechol-*O*-methyltransferase, which catalyzes methylation of meta-OH functional groups, specifically. Therefore, it is suggested that piceatannol undergoes more complex metabolism than resveratrol, which could affect its properties such as toxicity.[9,26,27]

Bioavailability, pharmacokinetics, and stability of piceatannol

In addition to understanding the metabolism of bioactive compounds, greater knowledge of phytochemical bioavailability and pharmacokinetics can inform clinical recommendations (Table 3). Following an IV injection of piceatannol (10 mg/kg body weight) in Sprague-Dawley rats, plasma area under curve (AUC) reached 8.48 μg h/mL with a plasma elimination half-life of 4.23 h. Because piceatannol was detected in urine 84 h postdose and displayed a urinary elimination half-life of 19.88 h, the authors hypothesized that actual half-life may be much higher.[24,25] Following oral administration, others have found a maximum piceatannol concentration of 8.1 μM at the highest tested dose of 360 μmol/kg. Of note, piceatannol was undetected in plasma after 24 h for any dose in this study.[9]

Phytochemical stability is a product of both metabolism and pharmacokinetics and provides a useful measure of bioactive potential. Piceatannol, as an intact polyphenol, exhibited stability 2.1–2.6 times higher than resveratrol. Although total polyphenol concentration (intact and metabolites) of resveratrol was higher than that of piceatannol, piceatannol showed greater metabolic stability as calculated as the ratio of intact stilbene to total stilbene (3.7–4.3-fold higher than resveratrol) and as a percentage of intact parent compound in relation to total detected polyphenol (16.3% compared with 5.5% for resveratrol).[9] As further support of piceatannol's superior metabolic stability, serum from piceatannol-treated, but not resveratrol-treated, rats maintained the ability to suppress hepatoma cell proliferation, even though both parent polyphenols showed antiproliferative properties.[28] Differences in

TABLE 3. *IN VIVO* BIOAVAILABILITY OF PICEATANNOL

Model	*Route*	*Dose (μmol/kg)*	*Modification*	*AUC (0–8 h) (μmol h/L)*	C_{max} *(μM)*	T_{max} *(min)*	$t_{1/2}$ *plasma (h)*	$t_{1/2}$ *urine (h)*	*Cl (L/h kg)*	*Vd (L/kg)*	*Ref.*
Sprague-Dawley rats	Oral	90	—	4.3±0.3	3.3	15	—	—	—	—	9
		180	—	12.3±1.8	7.5	15	—	—	—	—	
		360	—	20.6±2.2	8.1	15	—	—	—	—	
Sprague-Dawley rats	Oral	180	—	9.1±1.0	2.5	30	—	—	—	—	33
		180	90 μmol/kg α-cyclodextrin	10.1±0.6	5.3	15	—	—	—	—	
		180	180 μmol/kg α-cyclodextrin	9.0±0.7	4.8	30	—	—	—	—	
		180	540 μmol/kg α-cyclodextrin	8.6±0.9	5.8	15	—	—	—	—	
Sprague-Dawley rats	IV	40.94	—	34.72±10.15	—	—	4.23±1.25	19.88±5.66	2.13±0.92	10.76±2.88	24
Sprague-Dawley rats	Oral	40.94	Methylated piceatannol	9.819±2.91 (12 h)	2.91±0.89	45, 60, or 120	—	—	—	—	31
	IV	16.38	Analog in 0.3 M 2-hydroxypropyl-β-cyclodextrin	7.75±0.984 (12 h)	—	—	5.21±0.33	—	1.986±0.234	3.396±5.07	

AUC, area under curve.

metabolite action and degradation kinetics could partially explain the disparate biological effects of piceatannol and resveratrol treatment. In addition, hepatoma cells treated with rat serum samples collected 2 h postpiceatannol administration showed a greater antiproliferative effect than serum samples collected at 1 h; considering piceatannol's maximum serum concentration (C_{max}) of 15 min, this finding could imply that piceatannol metabolites are responsible for some of the anticancer properties.[9,28] These observations highlight the need for more studies investigating the biological effects of piceatannol metabolites.

To have clinical relevance, piceatannol must be present at a biologically relevant concentration in humans. Although no human studies of piceatannol pharmacokinetics have been conducted to our knowledge, studies of resveratrol may provide an approximation. After repeated doses of resveratrol (as high as 150 mg) for 2 weeks, a C_{max} of 63.8 ng/mL (0.28 μM) and an AUC of 78.9 ng h/mL (0.35 μmol h/L) were observed.[29] Even if intact piceatannol was present at a concentration 2.6 times higher than resveratrol, as suggested by the Setoguchi study, the maximum concentration of piceatannol would still be <1.0 μmol, which falls short of the concentration found in majority of *in vitro* studies. Therefore, there is a need to investigate methods to increase piceatannol exposure, as discussed in the following section.

Strategies to increase piceatannol bioavailability

As piceatannol is metabolized relatively quickly, improving its stability could increase potency. Modification of piceatannol is one strategy to improve its bioavailability. Brents *et al.* found that the prenylated form of piceatannol (*trans*-arachidin-1 [tA1]) exhibited slower glucuronidation. Of note, prenylated piceatannol (tA1) showed higher affinity for cannabinoid receptors; therefore, prenylated piceatannol may demonstrate higher biological activity than its parent compound in certain pathways.[30] Additionally, methylated piceatannol (*trans*-3,5,3′,4′-tetramethoxystilbene) demonstrated enhanced oral bioavailability, further demonstrating the potential of piceatannol modification to enhance absorption.[31] Delivery method can also enhance piceatannol bioavailability. Messiad *et al.* demonstrated that β-cyclodextrin dose-dependently increased piceatannol solubility.[32] Furthermore, Inagaki *et al.* found that delivering piceatannol with α-cyclodextrin more than doubled its solubility *in vitro.* In Sprague-Dawley rats, the use of α-cyclodextrin increased the C_{max} of piceatannol from 2.5 to 5.8 μmol; however, this change was not statistically significant. Interestingly, the use of α-cyclodextrin also increased the AUC and C_{max} of *O*-methyl conjugates and recovery of total stilbenes from the small intestine.[33]

Taken together, these findings suggest that therapeutic concentrations of piceatannol may be achievable *in vivo*. Although several researchers have evaluated piceatannol levels in blood and serum, data revealing piceatannol concentration in specific tissues are lacking. Future research focusing on piceatannol content in target tissues will provide critical information to understand the potential mode of action. Furthermore, investigations of piceatannol pharmacokinetics in humans are needed.

THE ROLE OF PICEATANNOL IN METABOLIC DISORDERS

As delineated in the Introduction section, metabolic syndrome is characterized by adiposity, insulin resistance, hyperglycemia, and inflammation.[3] Therefore, the following sections will highlight piceatannol's putative role in addressing each of these risk factors. Table 4 summarizes metabolic targets of piceatannol, whereas a summary of *in vivo* studies of piceatannol in metabolic disorders is shown in Table 5.

Adipogenesis

Obesity is characterized by excess adipose tissue and is a risk factor for a number of metabolic diseases, including T2D and CVD.[34] Visceral adiposity, in particular, is correlated with insulin resistance. Indeed, weight reduction is a primary strategy to counter metabolic syndrome.[3] An increase in adipocyte size (hypertrophy) and number (hyperplasia) both contribute to increased fat mass. In obese individuals, more adipocytes are added annually than in lean individuals. Although the number of adipocytes is set primarily in childhood and adolescence, 10% of adipocytes turnover annually.[35] Thus, preventing adipogenesis, especially during developmental stages, may be a strategy to combat obesity.

Our group demonstrated that piceatannol inhibited adipogenesis in 3T3-L1 adipocytes. Piceatannol dose-dependently inhibited differentiation and intracellular lipid accumulation in cultured murine 3T3-L1 adipocytes, as shown by both Oil red O staining and by coherent anti-Stokes Raman scattering microscopy, independent of cellular toxicity. The effect of piceatannol on the differentiation process was further confirmed by lower protein and gene expression of key adipogenic markers, such as peroxisome proliferator-activated receptor γ (PPARγ) and CCAAT/enhancer-binding protein β (C/EBPβ). Furthermore, piceatannol inhibited adipogenesis by targeting mitotic clonal expansion during the early phase of adipocyte differentiation. In addition, piceatannol blocked insulin signaling during differentiation, as seen by inhibited phosphorylation of protein kinase B (Akt), insulin receptor substrate-1 (IRS-1), insulin receptor (IR), ERK (a serine/threonine kinase involved in adipogenesis), and lower phosphatidylinositol 3-kinase (PI3K) and IR kinase activities. Further studies revealed a direct binding of piceatannol to IR in a dose-dependent and ATP-noncompetitive manner. It is possible that piceatannol binds to both IR on the cell surface and to intracellular PI3K, although more research is needed to fully elucidate its effect on insulin signaling.[36]

In addition to targeting mitotic clonal expansion and impairing insulin signaling, piceatannol may affect adipogenesis through other mechanisms. Huang *et al.* found that piceatannol treatment induced C/EBP homologous protein (CHOP)

Table 4. Metabolic Targets of Piceatannol

Model	*Target and effect*	*Putative role*	*Ref.*
Murine adipocytes (3T3-L1)	Inhibited adipogenesis, blocked mitotic clonal expansion, inhibited insulin signaling due to noncompetitive binding to insulin receptor, lowered lipid accumulation during late stages of differentiation	Antiadipogenic	36
Human liposarcoma preadipocytes (LiSa-2)	Induced CHOP expression, inhibited adipocyte differentiation as demonstrated by lack of lipid accumulation	Antiadipogenic	37
Human liposarcoma adipocytes (LiSa-2)	Induced CHOP expression, reduced VEGF production	Antiadipogenic	37
Mouse (C57BL/6) WAT	Lowered PPARγ and FAS protein expression, increased AMPKα, PPARα, and CPT1-α protein expression and ACC phosphorylation	Antiadipogenic, antilipogenic	45
Mouse (C57BL/6) liver	Lowered PPARγ, C/EBPα, and FAS protein expression, increased AMPKα and ACC phosphorylation,	Antiadipogenic, antilipogenic	45
Murine adipocytes (3T3-L1)	Lowered TG accumulation, lipid droplet accumulation	Antilipogenic	41
Murine adipocytes (3T3-L1)	Lowered TG accumulation	Antilipogenic	44
HUVECs	Inhibited ATP synthesis	Antilipogenic	42
Rat brain mitochondrial fractions	Inhibited F0F1-ATPase	Antilipogenic	79
Recombinant, full-length human holocarboxylase synthase	Inhibited holocarboxylase synthase	Antilipogenic	80
Rat myoblasts (L6)	Increased glucose uptake, increased AMPK phosphorylation and GLUT4 translocation	Glucose handling improvement	46
Yeast α-glucosidase	Inhibited α-glucosidase activity	Glucose handling improvement	81
Murine subcutaneous adipocytes	Impaired insulin-stimulated lipogenesis, inhibited basal and stimulated glycerol and FFA release	Antilipolytic	43
Primary human osteoarthritic osteoblasts	Inhibited alkaline phosphatase activity, carboxy-terminal propeptide of collagen type 1 production, lowered TGF-β1 expression	Leptin signaling	48
Human adipose tissue	Lowered H_2O_2 production, inhibited tyramine- and benzylamine-induced H_2O_2 production, inhibited [14C]-tyramine oxidation	Antioxidant	43
Rat liver microsomes	Increased oxygen consumption	Antioxidant	27
WAT explants from obese Zucker rats	Lowered amine-induced hydrogen peroxide generation	Antioxidant	44
HUVECs	Increased expression and activity of HO-1 through Nrf2; decreased IL-6, TNF-α, ROS formation, p-65 phosphorylation, NF-κB activation in palmitic acid-induced inflammation; restored IRS-1 phosphorylation, eNOS phosphorylation in palmitic acid-induced inflammation through HO-1	Anti-inflammatory	53
Bone marrow-derived macrophages	Restored HO-1 mRNA and protein expression after RANKL inhibition, decreased miR-183	Anti-inflammatory	59
Human mammary epithelial cells (MCF10A)	Upregulated HO-1 mRNA and protein expression, decreased Keap1 levels, increased Nrf2 translocation, increased Akt activation	Anti-inflammatory	61
Rat liver	Increased HO-1 expression and Akt activation, reduced trauma-induced IL-6, ICAM-1, CINC-1, and CINC-3 levels	Anti-inflammatory	62
Murine neuronal cells (HT22)	Reduced glutamate-induced toxicity and ROS production, increased HO-1 expression and activity, induced Nrf2 activation	Anti-inflammatory, antioxidant	63
Murine macrophages (RAW264.7)	Decreased LPS-induced TNF-α and IL-1β levels, induced HO-1 expression	Anti-inflammatory	58
Bovine aortic endothelial cells	Increased HO-1 protein and mRNA expression	Anti-inflammatory	60
Murine macrophages (RAW264.7)	Decreased LPS-induced NO release and iNOS expression; prevented LPS-induced degradation of κBα, p65 translocation, STAT3 phosphorylation and translocation; increased HO-1 protein and mRNA expression	Anti-inflammatory	65

(*continued*)

Table 4. (Continued)

Model	*Target and effect*	*Putative role*	*Ref.*
Human lymphoma (RAMOS) cells	Inhibited STAT3 and STAT5 phosphorylation	Anti-inflammatory	67
Human lymphocytes (Jurkat T cells)	Inhibited Jak1 and IFNAR1 tyrosine phosphorylation	Anti-inflammatory	67
human prostate cancer (DU145) cells	Inhibited STAT3 phosphorylation, IL-6 secretion	Anti-inflammatory	66
Human astrocytoma (U373) cells	Inhibited LPS-induced IRF3 activation, ISG induction, and TNF-α, ICAM-1, and MCP-1 upregulation	Anti-inflammatory	74
Murine macrophages (RAW264.7)	Inhibited LPS-induced IL-6 upregulation	Anti-inflammatory	74
Swiss mice	Prevented LPS-induced septic shock and liver and spleen damage	Anti-inflammatory	74
HUVECs	Inhibited CT-1-induced IL-6 mRNA and protein expression	Anti-inflammatory	70
Murine microglia (BV2) cells	Inhibited LPS-induced NO release, PGE2 release, iNOS expression, COX-2 mRNA and protein expression, NF-κB activity, p65 translocation, IL-1β levels, IL-6 levels, and TNF-α levels,	Anti-inflammatory	71
Peripheral blood mononuclear cell	Lowered OK-432-stimulated (penicillin-killed Streptococcus pyogenes) IL-6 and TNF-α secretion and mRNA expression	Anti-inflammatory	69
Human peripheral blood mononuclear leukocytes	Inhibited PGE2 levels, Lowered LPS and IFN-γ-stimulated TNF-α, IL-8 levels, and COX-2, TNF-α, IL-8, IL-6, IL-1α mRNA expression	Anti-inflammatory	72
Human monocytes (mono Mac 6)	Inhibited LPS-stimulated IL-6 levels	Anti-inflammatory	68
Human bronchial epithelial cells	Inhibited TNF-α-induced ICAM-1 expression and IL-6 release	Anti-inflammatory	73
Human myeloid cells (KBM-5)	Lowered TNF-α, PMA, LPS, okadic acid, ceramide, and H_2O_2-induced NF-κB activation; inhibited TNF-α-induced IκBα phosphorylation, IKK activation, and p65 phosphorylation and translocation	Anti-inflammatory	82
Human lymphocytes (Jurkat T cells)	Lowered TNF-α-induced NF-κB activation	Anti-inflammatory	82
Epithelial cells (MCF-7, HeLa)	Lowered TNF-α-induced NF-κB activation	Anti-inflammatory	82
Human monocytic (THP-1) cells	Upregulated SIRT1 mRNA and protein expression	SIRT activation	83
HeLa cells	Stimulated SIRT1 activity	SIRT activation	84
Human hepatoma (HepG2) cells	Increased SIRT1 expression, decreased c-Myc, β-catenin, and PHD2 expression	SIRT activation	85

AMPK, 5′ AMP-activated protein kinase; eNOS, endothelial nitric oxide synthase; FFAs, free fatty acids; GLUT4, glucose transporter 4; HO-1, heme oxygenase-1; HUVEC, human umbilical vein endothelial cell; IL, interleukin; IRS-1, insulin receptor substrate-1; MCP-1, monocyte chemotactic protein-1; NF-κB, nuclear factor-κB; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription factor-3; TG, triglyceride; TNF-α, tumor necrosis factor-alpha; WAT, white adipose tissue.

expression in both undifferentiated and differentiated LiSa-2 adipocytes; of note, CHOP expression delays C/EBPβ activity.[37] Additionally, the immune receptor mediator spleen tyrosine kinase (Syk), a well-established piceatannol target, plays a key role in the early stages of adipocyte differentiation: overexpression of Syk promotes adipogenesis.[38,39] It should be noted that for both of these putative pathways, more evidence is needed to establish piceatannol's mechanistic involvement.

Lipid synthesis and accumulation

Piceatannol also affects lipid synthesis and storage, as demonstrated in several *in vitro* models. Our group found that piceatannol lowered lipid accumulation when added during later stages (days 4–6) of adipocyte differentiation, suggesting a possible inhibitory role of piceatannol in lipogenesis.[36] Additionally, inhibition of H^+-ATP synthase, a piceatannol target that is highly expressed during adipocyte differentiation, blocked triglyceride (TG) accumulation in 3T3-L1 adipocytes.[40–42] However, more evidence is needed to directly link piceatannol-induced H^+-ATP synthase inhibition as the mechanism responsible for decreased lipid droplet accumulation, as causal evidence has not been investigated.[40] Piceatannol also lowered TG content in 3T3-L1 adipocytes and insulin-stimulated lipogenesis in isolated mouse adipocytes.[43,44] Although piceatannol shows several potential antiobesity mechanisms *in vitro*, caution should be

Table 5. *In vivo* Studies of Piceatannol in Metabolic Disorders

Model	*Dose and route*	*BW*	*Food intake*	*Glucose*	*Lipids*	*Insulin*	*Fat mass*	*Other*	*Ref.*
Male C57BL/6 mice, HFD-induced obesity (60% fat), 12 weeks old	1, 3, 10, and 30 mg/kg piceatannol, daily oral, 5 weeks	NSD	NSD	Lower serum glucose	—	—	NSD	NSD in leptin	47
Male *db/db* mice, 11 weeks old	50 mg/kg, single oral dose	—	—	Lower serum glucose after 1 h. NSD after 2–4 h	—	—	—	—	47
Male Zucker rats, 7 weeks old	15 or 45 mg/kg, daily oral, 6 weeks	NSD	NSD	NSD in serum glucose	Lower NEFA. NSD in TG. Lower serum LDL. NSD in cholesterol, HDL	NSD in serum insulin	NSD	Lower serum leptin. Lowered serum lactate. NSD in urea, adiponectin, or LPS. NSD in gut microbiota phyla	44
Male *db/db* mice, 6 weeks old	50 mg/kg, daily oral, 3 weeks	NSD	NSD	Lower blood glucose after 2 and 3 weeks	—	—	—	—	46
Male *db/db* mice, 11 weeks old	50 mg/kg, single oral dose	—	—	Lower fasting blood glucose levels 1, 3, and 5 h postadministration. Lower blood glucose AUC during a GTT	—	—	—	—	46
Male Sprague-Dawley rats, 11 weeks old, chow diet	10, 50, and 100 mg/kg, single intravascular dose	—	—	Lower blood glucose 150 and 180 min postadministration with 100 mg/kg dose only. Lowered blood glucose AUC during a GTT	—	Higher insulinogenic index. NSD in overall insulin secretion	—	NSD in blood glucose concentrations, plasma insulin concentrations, or glucose infusion rate during euglycemic clamp	49
Male C57BL/6 mice, HFD-induced obesity (45% fat), 6 weeks old	0.1% or 0.25% piceatannol mixed into diet, 18 weeks	Lower body weight	NSD	Lower glucose	Lower total cholesterol, LDL, HDL, and LDL/HDL ratio. Lowered serum TG	—	Lowered % body fat, retroperitoneal WAT, and perigonadal fat. Decreased adipocyte size	Lowered PPARγ, C/EBPα, and FAS. Increased ACC phosphorylation, PPARα, and CPT1. Increased Firmicutes-to-Bacteroidetes ratio. Increased Lactobacillus	45

ACC, acetyl coa carboxylase; FAS, fatty-acid synthase; GTT, glucose tolerance test; HDL, high-density lipoprotein; HFD, high-fat diet; LDL, low-density lipoprotein; NEFA, non-esterified fatty acids; NSD, no significant difference.

taken to interpret these findings in the context of whole-body metabolism as only limited evidence of the role of piceatannol in obesity in animals and humans is available.

In vivo *effects of piceatannol in metabolic disorders*

Although piceatannol has demonstrated antiadipogenic and antilipogenic effects *in vitro*, only one study has shown a significant impact on body weight, while the remainder of *in vivo* studies showed no significant differences.[45] Indeed, orally administered piceatannol in *db/db* obese mice, obese Zucker rats, or diet-induced obese C57BL/6 mice was ineffective for preventing weight gain, inducing weight loss, or altering adipose mass or food intake in mice.[44,46,47] However, a recent study employing a milder obesity model and increased dosage and duration (0.25% in the diet [$\sim$370 mg/kg body weight] for 18 weeks) demonstrated a preventative effect of piceatannol in high-fat diet-induced obesity.[45] The same group demonstrated decreased white adipose tissue (WAT) and adipocyte size and no difference in food intake.[45] Route of administration, a treatment or prevention model, and dose must all be considered when evaluating piceatannol's role in body weight and adiposity.

Despite limited evidence of an effect on body weight, piceatannol influenced other obesity-related parameters. Decreased low-density lipoprotein (LDL) was observed in both obese Zucker rats and DIO mice.[44,45] While no difference in cholesterol or high-density lipoprotein (HDL) was observed in the study by Hijona *et al*., Tung *et al*. noted decreased cholesterol and LDL:HDL ratio in piceatannol-treated mice.[44,45] Piceatannol also decreased serum-free fatty acids (FFAs) and TGs.[44,45] Taken together, these data support a role of piceatannol in altering lipid handling. However, although lowered serum lactate levels were observed, piceatannol failed to alter hepatic TG content, degree of steatosis, or markers of hepatic health (glutamate-pyruvate transaminase and glutamic oxaloacetic transaminase), suggesting that piceatannol was unable to prevent hepatic steatosis.[44] Piceatannol has also been shown to lower circulating leptin.[44] Although more evidence is required, a few hypotheses may explain piceatannol's impact on this key adipokine: piceatannol could lower leptin indirectly as a result of decreasing adipose mass or directly by inhibiting signal transducer and activator of transcription factor-3 (STAT3), a downstream leptin target.[48]

Hyperglycemia and insulin resistance

Several studies have demonstrated piceatannol's glucose-lowering properties, thus suggesting a role in glucose handling and insulin signaling.[45–47,49] Daily administration of piceatannol lowered fasting glucose levels in both *db/db* mice and diet-induced obese C57BL/6 mice without affecting body weight or food intake.[46,47] Furthermore, acute piceatannol administration lowered serum glucose levels and improved glucose tolerance in various rodent models.[46,47,49] Collectively, these data demonstrate that both chronic and acute piceatannol treatments influence glucose handling in obese and healthy rodents. However, the supraphysiological doses used in many of these studies must be considered when translating the evidence. Furthermore, the glucose-lowering effect of piceatannol has not been observed in all studies.[44,50] Clearly, more research is needed to ascertain the mechanism of piceatannol involvement in hyperglycemia.

Although influencing insulin secretion or sensitivity is one possible explanation of piceatannol's glucose-lowering properties, current literature suggests that other mechanisms may have a more significant role. Oritani *et al*. observed that an acute high dose (100 mg/kg body weight) of piceatannol lowered fasting glucose concentration independent of insulin secretion in healthy Sprague-Dawley rats. Furthermore, a subsequent euglycemic clamp study showed no difference in glucose infusion rates, implying that piceatannol did not significantly affect insulin sensitivity.[49] Others have also found no difference in serum insulin levels.[44] Furthermore, piceatannol stimulated glucose uptake in the absence of insulin in cultured myotubes.[46] However, piceatannol significantly increased the insulinogenic index in healthy rats during a glucose tolerance test despite no significant difference in plasma insulin level.[49] Timing and physiological relevance of any observed differences must all be taken into consideration when determining piceatannol action in insulin secretion. Indeed, it is possible that piceatannol may lower hyperglycemia through insulin-independent mechanisms.

Piceatannol may affect glucose handling by increasing glucose disposal. Minakawa *et al*. found that piceatannol dose-dependently promoted glucose uptake in cultured myotubes through activation of 5′ AMP-activated protein kinase (AMPK) and glucose transporter 4 (GLUT4) translocation.[46] Of note, AMPK activators may be a useful strategy to treat T2D as AMPK is a known stimulator of GLUT4 translocation and skeletal muscle accounts for a large majority of glucose disposal.[51,52] *In vivo* studies examining piceatannol's effect on AMPK-mediated skeletal muscle glucose uptake are needed to test this hypothesis.

Collectively, the observations that piceatannol lowered fasting glucose *in vivo*, activated AMPK in myotubes, and minimally impacted insulin secretion *in vivo* suggest a beneficial role of piceatannol in glucose handling.[44,46,49] Piceatannol's role in insulin signaling may be tissue dependent as it blocked insulin signaling in adipocytes and improved it in endothelial cells under inflammatory stress.[36,53] Further investigation of piceatannol's tissue-specific effects in insulin signaling and glucose uptake will provide greater understanding of its role in hyperglycemia. Clearly, as metabolic perturbations are the consequence of systemic interdependence, studies examining the whole-body effect of piceatannol are needed.

Oxidative stress and inflammation

Elevated FFAs due to aberrant activation of obesity-associated lipolysis in WAT contribute to insulin resistance by increasing oxidative stress and inflammation. Indeed, systemic inflammation and oxidative stress are thought to have a causative role in the etiology of insulin resistance.[54–56] High levels of FFAs promote proinflammatory signaling

pathways, such as nuclear factor-κB (NF-κB) and Toll-like receptor 4, and induce expression of the proinflammatory cytokines tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and IL-1β. High FFA levels also stimulate expression of monocyte chemotactic protein-1 (MCP-1), increase free radical concentration, and induce production of reactive oxygen species.[54]

Piceatannol has demonstrated significant radical scavenging activity, even up to 1250-fold higher than resveratrol.[27] In human adipose tissue specifically, piceatannol lowered hydrogen peroxide.[43] Although no difference in hydrogen peroxide generation was detected in adipose tissue of piceatannol-treated obese Zucker rats, lower amine-induced hydrogen peroxide generation was observed when piceatannol was added to these explants *ex vivo*.[44] However, the same group found no change in protein oxidation (3-nitrotyrosine assay), lipid peroxidation (thiobarbituric acid-reactive substrate assay), or superoxide dismutase activity in kidney homogenates.[57] Thus, while piceatannol shows antiradical activity *in vitro*, its effect in more physiologically relevant models remains to be proved.

Piceatannol may reduce inflammation by activating anti-inflammatory pathways. In human endothelial cells, piceatannol increased expression of heme oxygenase-1 (HO-1), an enzyme with antioxidant and anti-inflammatory properties, in a concentration-dependent manner through activation of nuclear factor erythroid 2-related factor 2 (Nrf2) transcriptional activity. Piceatannol's anti-inflammatory action was HO-1 dependent as inhibition of HO-1 abolished piceatannol's effect on TNF-α, IL-6, and NF-κB transcriptional activity and p65 phosphorylation.[53] As further evidence, piceatannol increased HO-1 expression in macrophages, endothelial cells, mammary breast epithelial cells, rat liver, and neuronal cells.[58–63] However, it must be noted that the role of HO-1 in metabolic disorders is not fully understood and has even been shown to be proinflammatory.[64] Given this context, it is possible that piceatannol's anti-inflammatory effects may be mediated by its regulation of the HO-1 upstream activator Nrf2.[61]

Several studies provide evidence of piceatannol's inhibitory role in inflammatory pathways. As reviewed previously, FFAs promote inflammation; palmitic acid, specifically, is one such FFA with proinflammatory properties. Piceatannol prevented the inhibitory effects of palmitic acid on IRS-1 phosphorylation, glucose uptake, endothelial nitric oxide synthase (eNOS) phosphorylation, and nitric oxide (NO) production in human endothelial cells.[53] In addition, piceatannol lowered LPS-induced protein expression of IL-6 and TNF-α and attenuated NK-κB and STAT3 signaling in macrophages; prevented IL-6 secretion and STAT3 signaling in prostate cancer cells; and inhibited the downstream IL-6 mediators STAT3 and STAT5 in human lymphocytes.[58,65–67] Indeed, many others have employed piceatannol as a STAT3 inhibitor and observed decreased expression and signaling of IL-6 and other proinflammatory mediators.[62,68–74] Together, these studies support an anti-inflammatory role of piceatannol.

Cardiovascular disease

As the role of piceatannol in CVD has been extensively reviewed recently by others, here we will focus on key themes and new additions to the literature.[11] In addition, many of the mechanisms previously discussed in this review, such as insulin resistance, oxidative stress, and elevated FFAs, also play contributory roles in the development of CVD.[54] A recent study in obese Zucker rats provides additional insight into piceatannol action in cardiac health. Piceatannol supplementation had no significant impact on heart weight:body ratio, cardiomyocyte transverse area, or degree of fibrosis, suggesting minimal effect on cardiac remodeling during obesity. However, an increase in the cardiac structural protein ephrin-B1 was observed, indicating that piceatannol

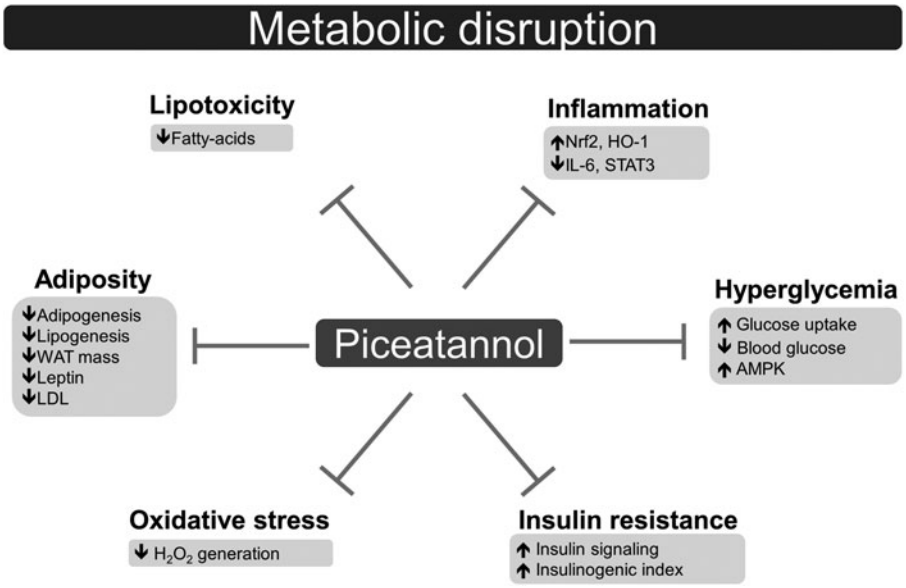


FIG. 1. Mechanisms by which piceatannol may ameliorate metabolic disorders.

may promote cardiac compensation and cardiac muscle structure during weight gain.[44]

CONCLUSION AND FUTURE DIRECTION

In this review, we highlight numerous putative mechanisms of piceatannol in metabolic disease, including inhibited adipogenesis, lowered lipid accumulation, lowered blood glucose, and attenuated oxidative stress and inflammation (Fig. 1). Although piceatannol has shown limited impact on body weight, treating symptoms of metabolic disease has therapeutic potential as adiposity itself is not always causative of metabolic disruption.[75] It should be noted that although current evidence on piceatannol action in metabolic disorders is insufficient to recommend the use of this small molecule to treat and prevent human disease, the beneficial effects of piceatannol observed in several metabolic pathways provide a rationale for further study of this bioactive compound.

The large majority of available literature on piceatannol action is limited to cell and animal models, thus results must be interpreted with caution. In light of these models, limitations of phytochemical studies in general, such as bioavailability, food–matrix interactions, and effects of metabolites, must be taken into account when considering potential dietary relevance.[76] Furthermore, individual variation in genetics and environment will also influence polyphenol metabolism. Indeed, more human studies are required to truly understand piceatannol's effect in metabolic disorders. Studies revealing piceatannol's mechanism and effects on signaling pathways in multiple tissues, crosstalk between metabolic organs, the gut microbiome, and insulin resistance will provide greater insights. Considering the complexity of metabolic disease and the current gaps in the literature, models that examine whole-body metabolism will provide the greatest value.

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AUTHOR DISCLOSURE STATEMENT

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