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NATURAL PRODUCTS: FROM CHEMISTRY TO PHARMACOLOGY (C HO, SECTION EDITOR)

Stilbenes: Chemistry and Molecular Mechanisms of Anti-obesity

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Abstract

Stilbenoids, a class of plant polyphenols abundant in berries, have been found to have many biological actions. Resveratrol, the most well-known of the stilbenes, is used for disease prevention, particularly for anti-obesity. Due to the low bioavailability of resveratrol, other stilbenes and their metabolites are also considered as candidates for anti-obesity. Obesity has numerous known causes, including genetics, diet, lifestyle, the endocrine system, and gut microbiota. Treating obesity can be rather problematic, with calorie intake reductions and increased physical exercise being difficult to maintain, medicines having side effects, and surgery being not suitable for all patients. Many stilbenes tested in animal studies have demonstrated beneficial effects, including reductions of lipid accumulation, regulation of glucose homeostasis, inflammation alleviation, and modulation of gut microbiota. This paper summarizes the molecular mechanisms of four major stilbenes used to treat obesity. Several pathways involved in regulation of fat metabolism affected by stilbenes, such as adipogenesis, lipogenesis, lipolysis, thermogenesis, and gut microbiota, will be introduced. In summary, stilbenes are promising for managing and treating obesity. A comparison of the physiological effects of various stilbenoids and other stilbene derivatives on obesity-associated diseases is warranted.

Keywords Stilbenes · Anti-obesity

Abbreviations

ACC	Acetyl-CoA carboxylase
ATGL	Adipose triglyceride lipase
BAT	Brown adipose tissue
CPT1	Carnitine palmitoyltransferase-1
DAG	Diacylglycerol
FAS	Fatty acid synthase complex
FFA	Free fatty acids
GLUT4	Glucose transporter type 4
HSL	Hormone-sensitive lipase
MAG	Monoacylglycerol
MCE	Mitotic clonal expansion
NAFLD	Non-alcoholic fatty liver disease
NRF-1	Nuclear respiratory factor 1
PGC-1α	Proliferator-activated receptor gamma coactivator 1-alpha
PPARγ	Peroxisome proliferator-activated receptor gamma
SREBP-1c	Sterol regulatory element-binding transcription factor 1c
TG	Triglyceride
UCP1	Uncoupling protein 1
WAT	White adipose tissue

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Introduction

Stilbenoids, natural phytochemicals, are found in grapes, berries, and other medicinal plants. Stilbenes are a type of phytoalexin used by plants as protection against pathogens. They are synthesized by plants in response to various stresses and are derived from the phenylpropanoid pathway [1]. The basic chemical skeleton structure of stilbene compounds is 1,2-diphenylethylene. Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is the most well-known and extensively studied

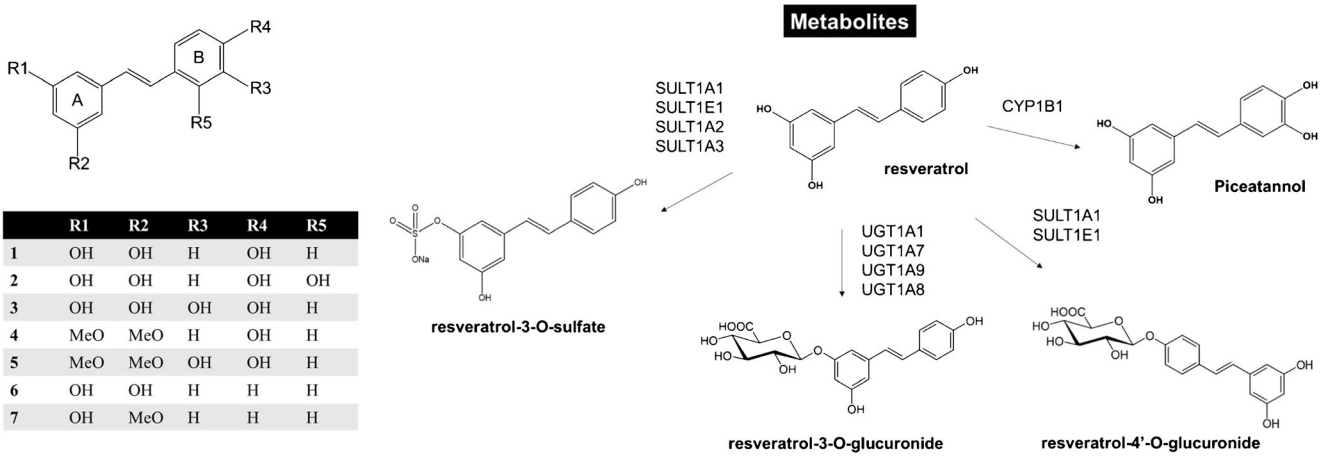
stilbene. Hundreds of studies have illustrated that resveratrol shows a variety of potential benefits such as anti-oxidation, anti-inflammation, anti-carcinogenesis, and particular anti-obesity [2–5]. However, resveratrol is accompanied with low oral bioavailability in humans [6]. Thus, other stilbene compounds including oxyresveratrol, piceatannol, pterostilbene, and its metabolites (Fig. 1) are also considered as candidates for the prevention of obesity. Obesity has become a serious health problem worldwide, particularly in Westernized countries. Obesity is a major risk factor known to contribute to non-alcoholic fatty liver disease (NAFLD), dyslipidemia, cardiovascular disease, type-2 diabetes, and carcinogenesis—primarily breast and colorectal cancers [7]. These metabolic diseases are correlated with inflammation and insulin resistance. Increase of the visceral adipose tissue mass is the main cause of the decrease of insulin sensitivity [8]. Thus, reduction of visceral fat could prevent diseases related to obesity. There are numerous causes of obesity, including genetics, diets, lifestyle, endocrine system, and gut microbiota. Although reducing calorie intake and increasing physical activity are relatively feasible methods for managing body weight, such methods can be difficult to put into practice in real life. Clinically, medicines and surgery are commonly used medical treatments for obesity. However, almost all medicines have side effects, and surgery is not always successful or targeted for everyone. In the past few years, natural phenolic compounds for weight loss have been extensively studied and developed into nutraceuticals. Hundreds of studies have shown that resveratrol is able to reduce obesity both at the cellular level and in animal studies [4]. A deep understanding of the molecular mechanisms of stilbenes on anti-obesity would be useful. This article aims to summarize the molecular mechanisms of anti-obesity by resveratrol, oxyresveratrol, piceatannol, and pterostilbene in vitro and in vivo. Also, several pathways involved in the regulation of fat metabolism, such as adipogenesis, lipogenesis, lipolysis, and thermogenesis, will be introduced in depth in this article.

Mechanisms Regulating the Balance of Adipose Tissue

Energy imbalance is a major cause of obesity, and excessive energy increases adipocyte number (hyperplasia) and size (hypertrophy). Both hyperplasia and hypertrophy are two major key factors for increasing the fat mass [9]. There are several pathways involved in the regulation of fat metabolism, as will now be discussed (Fig. 2):

Characteristics of Adipogenesis

Adipogenesis is the process by which preadipocytes differentiate into fully mature adipocytes. Recent studies on the differentiation and regulation of adipocytes have mostly relied on in vivo systems, and the most commonly used cell lines for this purpose are 3T3-F442A and 3T3-L1. Adipogenesis can be divided into the following stages: cell proliferation, growth arrest, mitotic clonal expansion, early differentiation, and terminal differentiation [10]. In the cell proliferation stage, the number of preadipocytes increases during cell division, but is eventually suppressed by contact inhibition, which marks the beginning of the growth arrest stage. Subsequently, hormone signals prompt growth-arrested preadipocytes to initiate the cell cycle and mitotic clonal expansion (MCE) occurs, which is important for adipogenesis [11]. The critical transcription factors regulating lipid biosynthesis during the MCE stage are CCAAT/enhancer binding proteins (C/EBPs) and PPARs. C/EBPβ appears to be essential in the early differentiation stage, because C/EBPβ and C/EBPδ jointly activate peroxisome



	R1	R2	R3	R4	R5
1	OH	OH	H	OH	H
2	OH	OH	H	OH	OH
3	OH	OH	OH	OH	H
4	MeO	MeO	H	OH	H
5	MeO	MeO	OH	OH	H
6	OH	OH	H	H	H
7	OH	MeO	H	H	H

Fig. 1 Structures of stilbene compounds and resveratrol metabolites. 1, resveratrol; 2, oxyresveratrol; 3, piceatannol; 4, pterostilbene; 5, 3′-pterostilbene; 6, pinosylvin; 7, pinosylvin *O*-methylether. CYP, cytochrome P450; UGT, UDP-glucuronosyltransferase; SULT, sulfotransferase

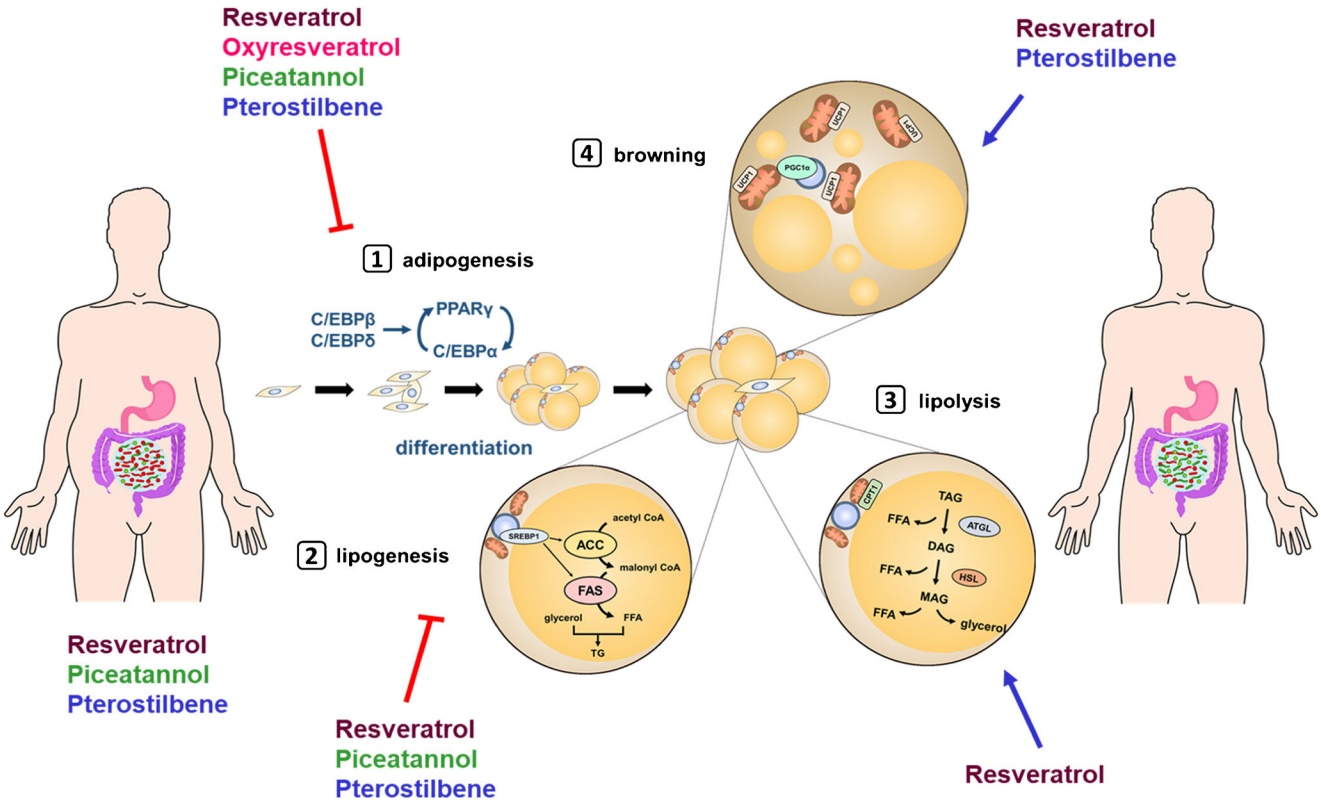


Fig. 2 Fat metabolism pathways regulated by stilbene compounds

proliferator-activated receptor gamma (PPARγ) expression. PPARγ activates the expression of C/EBPα as well as other adipocyte genes. Through a positively regulated feedback loop, C/EBPα functions to maintain the expression of PPARγ. PPARγ and C/EBPα cooperate to promote adipocyte differentiation in the terminal differentiation state [12]. When adipogenesis proceeds to the terminal differentiation stage, the process cannot be reversed. At this stage, the extensive expression of lipogenic proteins induces triglyceride (TG) accumulation in cells, eventually turning them into mature adipocytes.

Characteristics of Lipogenesis

Lipogenesis, which primarily occurs in the liver and adipose tissues, involves de novo fatty acid synthesis and triglyceride synthesis. The sources of acetyl-CoA for fatty acid synthase complex (FAS) are the products of glucose metabolism [13]. As glucose is taken up into cells, it undergoes a series of glycolysis reactions that convert it into acetyl-CoA. Acetyl-CoA then enters the mitochondria and is catalyzed with oxaloacetate into citrate. However, lipogenesis takes place in the cytosol, and citrate is transported to the extracellular compartment, where it is cleaved by the enzyme citrate lyase into oxaloacetate and acetyl-CoA. Subsequently, through the catalysis of acetyl-CoA carboxylase (ACC), acetyl-CoA is converted into malonyl-CoA, which is a critical step in FAS. Acetyl-CoA and malonyl-CoA serve as the substrate for FAS to fatty acid synthesis. Sterol regulatory element-binding transcription factor 1c (SREBP-1c) is one of the main transcription factors that increase expression of FAS and ACC [14]. Furthermore, fatty acids can form TG with glycerol, which is also the product of glycolysis. Glycerol is further converted into glycerol-3-phosphate (G3P), forming TG through the catalysis of glycerol-3-phosphate acyltransferases (GPAT) and other enzymes with fatty acyl-CoA.

Characteristics of Lipolysis and β-Oxidation

When the body is in need of energy, it can be generated through the lipolysis and β-oxidation of adipose tissue. In lipolysis, TG is first hydrolyzed into fatty acids and diacylglycerol (DAG) by adipose triglyceride lipase (ATGL) and further hydrolyzed by hormone-sensitive lipase (HSL) into monoacylglycerol (MAG); more fatty acids are then released. HSL is hormonally regulated and is activated by protein kinase A (PKA) phosphorylation, which is mediated via the accumulation of cAMP [15]. The free fatty acids released by lipolysis can be used to generate more energy through β-oxidation, which occurs primarily in the mitochondria. In this process, fatty acids are first converted into fatty acyl-CoA, which relies on carnitine palmitoyltransferase-1 (CPT1) to enter the mitochondrial matrix.

Characteristics of Thermogenesis

White adipose tissue (WAT) and brown adipose tissue (BAT) are two major types of adipose tissues that play an essential role in regulating energy balance. BATs have a high density of mitochondria, the inner membranes of which contain large amounts of uncoupling protein 1 (UCP1). UCP1 allows the passage of hydrons (H^+), which consume part of the energy that causes the proton gradient in oxidative phosphorylation, rather than being used to drive the synthesis of ATP [16]. This allows additional energy to be released in the form of heat. Furthermore, an increasing number of studies have noted that under certain circumstances (e.g., extreme low temperature or presence of β-3 adrenergic agonist), the number of mitochondria in WATs increases dramatically. This process is called "browning," and this type of WAT is termed "beige" [17]. Beige can generate large amounts of UCP1, enabling the generation of more heat than normal WATs. To date, the expression of UCP1 has been observed to be regulated by proliferator-activated receptor gamma coactivator 1-alpha (PGC1α). PGC-1α is also a cotranscriptional regulation factor that induces mitochondrial biogenesis by activating different transcription factors, including nuclear respiratory factor 1 (NRF-1) and nuclear respiratory factor 2 (NRF-2), which promote the expression of mitochondrial transcription factor A (Tfam) [18].

Obesity and Gut Microbiota

Recent studies have shown a causal link between obesity and the composition of gut microbiota. Moreover, dietary habits are known to be an important factor for the modulation of gut microbiota. The compositional changes of gut microbes affect the host lipid metabolism. The mechanisms linking between gut microbiota and energy metabolism still remain obscure. One of the reasons is that the gut microbiota selectively suppresses the expression of fasting-induced adipose factor (Fiaf) in the intestinal epithelium, leading to upregulation of lipoprotein lipase and deposition of triglycerides in adipose tissues [19]. Otherwise, Firmicutes and Bacteroidetes are the two main dominant bacterial phyla in humans. Studies indicate that obese people who take on a low-calorie or low-carbohydrate diet increase their levels of Bacteroidetes and show decreased Firmicutes levels [20]. Furthermore, probiotics such as *Lactobacillus* and *Bifidobacterium* help reinforce intestinal epithelial barrier function, in order to lower the chances of unhealthy bacteria and viruses invading the intestinal mucosa [21].

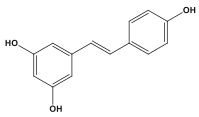
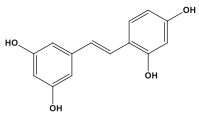
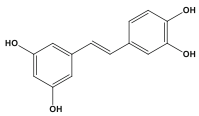
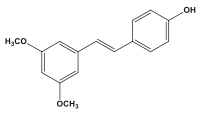
Anti-obesity Properties of Stilbenes

There are several well-known stilbenes which are used for disease prevention such as resveratrol, oxyresveratrol, piceatannol, and pterostilbene. Several studies in this review have demonstrated the potential anti-adipogenic effect of stilbenes under in vitro conditions (Table 1), and the anti-obesity properties in animal models are also described in Table 2.

Resveratrol

Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is found in various foods, such as the skin of grapes, blueberries, raspberries, mulberries, and peanuts [22]. In mouse 3T3-L1 preadipocytes, resveratrol is able to inhibit adipogenesis and induce cell apoptosis, which causes a decrease in fat accumulation [23]. Studies conducted by Kwon et al. showed that 50 μM resveratrol reduced by 55% fat accumulation and decreased the protein level of the transcription factors PPARγ and C/EBPα in 3T3-L1 cells [24]. Also, resveratrol has an impact on preadipocytes to enter G2/M phase and downregulate the expression of Cyclin A and cyclin-dependent kinase 2 (CDK2) [24]. Additionally, resveratrol increases ATGL to promote lipolysis [25] and inhibit lipogenesis to lower fat accumulation [26]. In animal models, a study conducted by Kim et al. showed that supplementation of 0.4% resveratrol [~ 400 mg/kg body weight] effectively reduced the body weight gain by downregulation of CEBP/α and reduction of gene expression of SREBP-1c and its target gene FAS [27]. Furthermore, Lagouge et al. showed that C57BL/6J mice fed with 400 mg/kg/day resveratrol enhanced their capacity for adaptive thermogenesis and increased the production of mitochondria to prevent obesity [28]. Similarly, Wang et al. [29] reported that 0.1% resveratrol enhanced the expression of UCP1 and induced brown-like adipocyte formation in inguinal white adipose tissue. Other studies have reported that resveratrol impacts the regulation of gut microbiota, increasing Bacteroidetes-to-Firmicutes ratio and the growth of *Lactobacillus* and *Bifidobacterium* in high-fat-diet-fed mice [30]. Although resveratrol shows good biological activities in animal models, it had no effect on body weight and visceral fat content in healthy obese men treated with 1500 mg resveratrol for 4 weeks [31]. The current bioavailability research showed that after oral administration 20 mg resveratrol for mice, its highest concentration in plasma is 2.6 ± 1.0 μM and decreased rapidly to almost 0 within 60 min [32, 30]. Otherwise, resveratrol also undergoes rapid and extensive metabolism with low oral bioavailability in humans [6, 32, 33]. Due to this extensive metabolism of resveratrol, Lasa et al. and Eseberri et al. determined whether its metabolites exert any beneficial effect in 3T3-L1 cells. The results indicated that the metabolites of resveratrol such as trans-resveratrol-3-O-glucuronide, trans-resveratrol-4′-O-glucuronide, and trans-resveratrol-3-O-sulfate (Fig. 1) reduced leptin secretion and TG content [34–36].

Table 1 Effects of stilbenes on anti-obesity in vitro studies

Compound	Sources	Experimental design	Doses	Effects	References
Resveratrol 	skin of grapes, blueberries, raspberries, mulberries, roots of Japanese knotweed and peanut	3T3-L1 pre-adipocytes 24, 48 hr	20, 40, 80 μM	↑ apoptosis ↑ cell cycle arrest	[23]
		3T3-L1 pre-adipocytes 16, 24 hr	25, 50 μM	↓ C/EBPα, PPARγ protein expression ↓ adipogenesis	[24]
		3T3-L1 pre-adipocytes SGBS human adipocytes 24 hr	100 μM	↑ ATGL mRNA and protein expression ↑ lipolysis	[25]
		3T3-L1 pre-adipocytes SGBS human adipocytes Day 8, 10	25, 50 μM	↑ p-ACC protein expression ↓ lipogenesis	[26]
Oxyresveratrol 	Moraceae like white mulberry (*Morus alba* L.) and heartwood of *Artocarpus lakoocha*	3T3-L1 pre-adipocytes 24, 72 hr	100 μM	↓ C/EBPα, PPARγ protein expression ↓ adipogenesis ↑ cell cycle arrest	[39]
Piceatannol 	grapes, blueberries, passion fruits and white tea	3T3-L1 pre-adipocytes 16, 24 hr	25, 50 μM	↓ C/EBPα, PPARγ protein expression ↓ adipogenesis ↑ cell cycle arrest	[42]
Pterostilbene 	blueberries, grapes, raspberries and mulberries	3T3-L1 pre-adipocytes 24 hr	6 μM	↓ C/EBPα, PPARγ protein expression ↓ adipogenesis ↑ cell cycle arrest	[48]

SGBS Simpson-Golabi-Behmel Syndrome

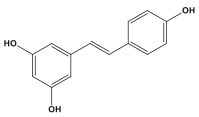
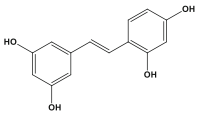
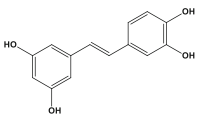
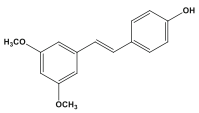
Oxyresveratrol

Oxyresveratrol (2,4,3′,5′-tetrahydroxy-*trans*-stilbene) is present in Moraceae plants, such as white mulberry (*Morus alba* L.) [37] and heartwood of *Artocarpus lakoocha* [38]. Tan et al. [39] used a 3T3-L1 cell model to evaluate the anti-adipogenic properties of oxyresveratrol. The data showed that 100 μM oxyresveratrol significantly lowered the accumulation of triglyceride and reduced the expression of the transcription factors PPARγ and C/EBPα by regulating cyclin D1 and cyclin-dependent kinase 4 (CDK4) to cause cell cycle arrest; this ensures that preadipocytes are retained in the G1 phase, preventing further cell differentiation. Animal studies have indicated that s high-fat diet supplemented with 0.25% and 0.5% oxyresveratrol effectively alleviated obesity in C57BL/6 mice. Results suggested that oxyresveratrol upregulated insulin-dependent glucose transporter type 4 (GLUT4) levels in adipose tissue to regulate lipid and glucose homeostasis. It also improved insulin sensitivity to ameliorated obesity-associated symptoms such as hyperglycemia and hepatic steatosis in high-fat-diet-treated mice [40].

Piceatannol

Piceatannol (3′,4′,3,5-tetrahydroxy-*trans*-stilbene) exists in grapes, blueberries, and passion fruits [22]. It is also known as the metabolite of resveratrol [41]. Cell studies reported that piceatannol effectively inhibits the adipogenesis of preadipocytes 3T3-L1. Kwon et al. reported that 50 μM piceatannol decreases lipid accumulation by approximately 80% and lowers the protein levels of adipogenic transcription factors such as PPARγ and C/EBPα in 3T3-L1 cells. Treated with piceatannol, it simultaneously induced cell cycle arrest and delayed entry into G2/M phase during the MCE process [42]. However, in an animal study, Uchida-Maruki et al. reported no significant weight difference between the groups fed with piceatannol (1, 3, 10, 30 mg/day) for 5 weeks. However, in db/db mice studies, 50 mg/kg piceatannol reduced fasting blood glucose levels [43]. In a study performed in our group, we found that 0.1 and 0.25% piceatannol [~ 370 mg/kg body weight] significantly lower body weight, serum cholesterol, and LDL/HDL ratio. Piceatannol reduced the expression of C/EBPα and PPARγ, and also regulated ACC and FAS protein expression to inhibit triglyceride synthesis. Moreover, Piceatannol has an impact on gut microbiota by increasing the amount of *Lactobacillus* in high-fat-diet-treated mice [44]. Otherwise, the adipocyte hypertrophy was accompanied by increased inflammation, which was the critical factor for metabolic syndrome. Piceatannol is known to exhibit anti-inflammatory properties. In order to clarify the effects of piceatannol on obesity-induced inflammation in a cell model, Yamamoto et al. used the conditioned medium from 3T3-L1

Table 2 Effects of stilbenes on anti-obesity in vivo studies

Compound	Sources	Experimental design	Doses	Effects	References
Resveratrol 	skin of grapes, blueberries, raspberries, mulberries, roots of Japanese knotweed and peanut	C57BL/6J mice 10 weeks	0.4% of diet	↓ C/EBPα mRNA expression ↓ SREBP-1c, FAS mRNA expression ↓ adipogenesis, lipogenesis	[27]
		C57BL/6J mice 15 weeks	400 mg/kg/day	↑ thermogenesis	[28]
		CD1 female mice	0.1% of diet	↑ p-AMPK, UCP1 protein expression ↑ browning	[29]
		Kunming mice 12 weeks	200 mg/kg/day	↑ Bacteroidetes／Firmicutes ratio ↑ *Lactobacillus* ↑ *Bifidobacterium*	[30]
Oxyresveratrol 	Moraceae like white mulberry (*Morus alba* L.) and heartwood of *Artocarpus lakoocha*	C57BL/6J mice 8 weeks	0.25%, 0.5% of diet	↑ GLUT4 mRNA expression	[40]
Piceatannol 	grapes, blueberries, passion fruits and white tea	C57BL/6J mice 5 weeks	30 mg/kg/day	No significantly effect on body weight	[43]
		C57BL/6J mice 18 weeks	0.1%, 0.25% of diet	↓ C/EBPα, PPARγ protein expression ↓ FAS protein expression ↑ *Lactobacillus*	[44]
Pterostilbene 	blueberries, grapes, raspberries and mulberries	OLETF rats 4 weeks	0.5% of diet	↓ FAS mRNA expression ↓ lipogenesis	[49]
		Zucker (*fa*/*fa*) rats 6 weeks	15, 30 mg/kg/day	↑ UCP1, NRF-1 mRNA expression	[50]
		Zucker (*fa*/*fa*) rats 6 weeks	15 mg/kg/day	↓ Firmicutes	[51]

OLETF Otsuka Long-Evans Tokushima fatty

adipocytes to culture RAW264.7 macrophages. The results showed that 30 μM piceatannol suppressed inflammatory cytokines TNF-α and IL-6 in 3T3-L1-conditioned medium-treated cells [45]. Similarly, Li et al. reported that in a cocultured adipocyte and macrophage system, 10 μM piceatannol significantly reduced the release of TNF-α and monocyte chemoattractant protein-1 (MCP-1) [46]. In summary, piceatannol not only regulates lipid accumulation but also effectively alleviates the inflammation caused by obesity.

Pterostilbene

Pterostilbene (3,5-dimethoxy-4′-hydroxy-*trans*-stilbene), the dimethylether analog of resveratrol, is naturally present in almost the same sources of foods as resveratrol. Kapetanovic et al. [47] reported that pterostilbene exhibits better oral bioavailability than resveratrol, but had lower tolerance. In a 3T3-L1 preadipocyte model, a study showed that 6 μM pterostilbene was required to decrease the lipid accumulation by suppressing adipogenesis under differentiation conditions [48]. During the MCE stage, pterostilbene markedly decreased the expression of C/EBPα and PPARγ to decelerate the progression of adipogenesis. In animal studies, a 0.5% pterostilbene diet for 4 weeks markedly enhanced energy expenditure and reduced abdominal WAT weight. This study suggested that pterostilbene suppressed lipogenesis by decreasing FAS mRNA levels in WAT [49]. Additionally, Aguirre et al. [50] reported that pterostilbene dissipated surplus calorific energy by increasing UCP1 and NRF-1 mRNA levels in interscapular BATs from obese rats. Furthermore, the same research team reported that Zucker (*fa*/*fa*) rats supplemented with pterostilbene exerted anti-obesity effects which could be associated with changes in gut microbial profiles [51]. Taken together, these studies suggest that pterostilbene can effectively prevent obesity through modulation of various lipid metabolism-related genes.

Conclusion

In this review, we highlight numerous lipid regulating pathways of stilbenoid compounds such as resveratrol, oxyresveratrol, piceatannol, and pterostilbene. The large amount of available literature suggests that stilbenes have promising applications for the management and treatment of obesity. Although there are many different administration routes and formulations for these studies over the past few decades, the effective doses of each stilbene remain uncertain. Therefore, further in vitro and in vivo studies for comparison of these stilbenes are needed using physiological concentrations

or the currently effective doses at the same time. Moreover, only a few number of studies have been reported for oxyresveratrol, piceatannol, and pterostilbene in clinical trials so far. Thus, the physiological effects of various stilbenoids and other stilbene derivatives in human research on obesity-associated diseases would be necessary to investigate for in the future.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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