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## Hypoglycemic effects and associated mechanisms of resveratrol and related stilbenes in diet†

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Hyperglycemia has become a global health problem due to changes in diet and lifestyle. Most importantly, persistent hyperglycemia can eventually develop into type II diabetes. While the usage of current drugs is limited by their side effects, stilbenes derived from fruits and herbal/dietary plants are considered as important phytochemicals with potential hypoglycemic properties. Herein, the most common stilbenoids in consumed foods, *i.e.* resveratrol, pterostilbene, piceatannol, oxyresveratrol, and 2,3,5,4'-tetrahydroxystilbene-2-*O*- $\beta$ -glucopyranoside (THSG), are reviewed in this paper. These stilbenes are found to regulate glucose homeostasis *via* (a) modulation of feeding behaviour and nutrition absorption; (b) restoration of insulin signalling by enhancing insulin production/insulin sensitivity; (c) improvement of gut permeability, gut microbial profile and resulting metabolomes; and (d) amelioration of circadian rhythm disruption. In this review, we have summarized the underlying mechanisms for the hypoglycemic effects of the five most common dietary stilbenoids listed above, providing a comprehensive framework for future study and applications.

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### 1. Introduction

Hyperglycemia, elevated blood sugar level especially during fasting status, is an essential risk factor for various diseases including diabetes mellitus (DM), metabolic syndrome, coronary heart disease and even some cancers.<sup>1,2</sup> Depending on the abnormality, hyperglycemia can be divided into two categories: impaired fasting glucose (prediabetes) which ranges from 100 to 125 mg dL<sup>-1</sup> and type II diabetes which exceeds 125 mg dL<sup>-1</sup>.<sup>3</sup> According to the CDC National Diabetes Statistic Report 2020, 34.5% of all US adults had prediabetes based on their fasting glucose or hemoglobin A1C level. Moreover, once hyperglycemia persists and develops into type II diabetes mellitus (T2DM), there is no cure and patients have to live with it life-long. Hyperglycemia often occurs when the insulin-responding organs and tissues, mainly the liver, muscles, and adipose tissues, become insulin-resistant or when the body is under various stresses either from physical or mental health issues. In the case of T2DM, insulin resistance (IR) featuring

an impaired biological response of organs and tissues to insulin commonly occurs, and the stress in producing excess insulin to cover the inefficiency caused by IR would compromise the body's original function and ultimately lead to a reduction in insulin level.<sup>4</sup> In the past few decades, efforts have been made to reveal the root causes of such symptoms and the involvement of, among others, unhealthy diet or overload nutrition-induced obesity and physical inactivity was widely recognized.<sup>5</sup> These risk factors can initiate and accelerate the progression of various pathological issues, such as IR, loss of function and apoptosis of pancreatic  $\beta$ -cells, and alterations in the gut environment and gut microbiota, and ultimately impact hyperglycemia and related disease. Aiming to reduce hyperglycemia, particularly in patients with T2DM, different targets are interfered with by several types of drug in current therapy: (1) promotion of insulin secretion by insulin secretagogues such as sulphonylureas, meglitinides, dipeptidylpeptidase 4 inhibitors, glucagon-like peptide 1 (GLP-1) agonists *etc.*; (2) reduction of hepatic glucose output, which can be achieved by metformin without affecting the level of insulin; (3) improvement of insulin sensitivity, for which thiazolidinediones and related drugs serve as peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) agonists; and (4) suppression of glucose uptake in the intestine by  $\alpha$ -glucosidase inhibitors; and a decrease in the reabsorption of glucose in the kidneys and the excretion of extra glucose through the urine by sodium-glucose cotransporter 2 (SGLT-2) inhibitors.<sup>6,7</sup> However, although these therapeutics can help ameliorate

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certain symptoms of diabetes, their significant side effects, such as weight gain, heart failure and potential intolerance, remain unexplored.<sup>7</sup> Most importantly, it has been suggested that the majority of cases in T2DM are preventable in the stage of solely hyperglycemia, which is also closely related to other metabolic diseases. Based on the above considerations, new therapy and treatment with fewer side effects and with an emphasis on the prevention of persistent hyperglycemia are needed.

The intake of fruits, nuts and their products has been associated with some health benefits and is considered as part of a healthy eating diet. Grapes and related products are shown to promote health status. For instance, the consumption of grape powder, grape skin extract and grape seed oil successfully prevented increased fasting blood glucose and dyslipidemia in mice, and red grape pomace extract, which comes from wine-making by-products, was able to suppress postprandial hyperglycemia (PPHG).<sup>8</sup> These grape products are also capable of decreasing oxidative stress and inflammation and promoting cardiac health.<sup>9</sup> Blueberry, a “superfruit” that is commonly consumed in Western countries and has gained increasing popularity in Asia in recent years, is well-linked to several health-promoting effects. Dietary supplementation of whole blueberry, blueberry juice, and blueberry leaf extract has been proved to improve IR as well as postprandial glucose management.<sup>10</sup> Mulberry (*Morus alba* L.), another edible berry mainly consumed in Asia, is also known for its health-promoting functions. Research on dietary supplementation with mulberry fruit extracts has shown their protective effects against hyperglycemia, IR, neurotoxins, atherosclerosis and tumors *via* antioxidant and immunomodulatory properties.<sup>11</sup> Moreover, consistent with the fact that mulberry branches are used as a traditional medicine for DM patients in Asia, the bark powder<sup>12</sup> was proved to significantly improve hyperglycemia and regulate insulin secretion. The functional properties of these fruits have been attributed to abundant phenolic compounds within them, *i.e.*, anthocyanins, phenolic acids and flavonoids. Nevertheless, the antioxidant capacity of many products depends not only on the total amount of phenolic compounds but also on the exact polyphenol profile. Therefore, it is also important for us to study other polyphenols such as stilbene compounds.

Stilbenes, commonly secreted secondary metabolites as protective agents against stress, such as environmental threats, occur naturally in plants. They are a group of phenolic compounds known for diverse biological activities, including antioxidant, anti-inflammatory, anti-obesity, anti-diabetic and other properties.<sup>13</sup> Recent studies have revealed the hypoglycemic and anti-diabetic effects of several stilbene compounds commonly found in grapes, berries and other foods, these effects being attributed to their influence on food intake and nutrient absorption, glucose homeostasis, apoptosis and function of pancreatic  $\beta$ -cells, gut permeability, composition of gut microbiota as well as circadian rhythm. Since most abovementioned mechanisms are similar to those of currently used medicines, these stilbenes are considered as potential agents to control hyperglycemia, or as preventive dietary supplements with less safety concern.

In this review, common dietary stilbenoids, that is, resveratrol, pterostilbene, 2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -glucopyranoside (THSG), piceatannol, and oxyresveratrol, are discussed in-depth in terms of structure, dietary source and pharmacokinetics. Recent study results regarding their preventive and therapeutic effects on hyperglycemia and diabetes are summarized, and the potential mechanisms of their actions are discussed. Although compared with resveratrol and pterostilbene, there is significantly less research concerning THSG, piceatannol, and oxyresveratrol, they are included here due to their structural similarity to resveratrol, better bioavailability and excellent activities in preventing other diseases.

## 2. Overview of resveratrol, pterostilbene, THSG, piceatannol and oxyresveratrol

Structures of stilbenes can be characterized by C6–C2–C6, a basic 14-carbon skeleton of 1,2-diphenylethylene, in other words, two aromatic rings linked by an ethylene moiety. Owing to various modifications such as hydroxylation, glycosylation, methylation and polymerization that take place at different positions of the basic stilbene structure, many stilbenes have been identified.<sup>13</sup> The chemical structures of selected stilbenoids are shown in ESI Fig. S1.†

Resveratrol (*trans*-3,5,4'-trihydroxystilbene), one of the most extensively studied monomeric stilbene compounds in the past few decades, is present in a variety of plants such as berries and grapes and reaches the highest concentration in the seeds of *Paeonia suffruticosa*.<sup>14</sup> According to current reports, resveratrol possesses quite a few biological functions, ranging from antioxidant, anti-cancer, and anti-aging to cardioprotective and neuroprotective effects.<sup>15</sup> Through studying the analogues of resveratrol, it was found that structural differences, particularly the number and position of hydroxyl groups on the ring, were closely related to its free-radical scavenging capacity, which was believed to play an essential role in its overall bioactivities.<sup>16</sup>

Pterostilbene (*trans*-3,5-dimethoxy-4'-hydroxystilbene), a natural dimethylated analog of resveratrol predominately found in blueberries, exhibits similar or better biological functions.<sup>17,18</sup> The replacement of the two hydroxyl groups on the A-benzene ring of resveratrol with two methoxy groups is believed to increase lipophilicity and reduce overall reactions with phase II metabolic enzymes like glucuronidase in the human body.<sup>19,20</sup> Therefore, in comparison with resveratrol, pterostilbene may have a higher membrane permeability and stronger metabolic stability, thus achieving a better bioavailability.<sup>17,19,21</sup> Compared with resveratrol, pterostilbene was also proved to exert additional protective effects against aging, demonstrated by the improvement of cognitive behavioural deficits, memory loss, and dopamine release.<sup>22</sup>

THSG is a stilbene glycoside and one of the major bioactive phytochemicals found in the medicinal plant named *Polygonum multiflorum* (PM), which is popularly grown and



consumed in Southeast Asia since it is traditionally known for an anti-aging effect and the ability to darken hair. Different from resveratrol, THSG possesses an extra hydroxyl group at the 2-position connected with a 2-O-glycoside. Once the sugar moiety is dissociated *in vivo*, an additional hydroxyl group will present at the *ortho*-position, giving it a much higher antioxidant activity and stronger protective effect against oxidative stress induced by reactive oxygen species (ROS).<sup>23</sup>

Piceatannol (*trans*-3,5,3',4'-tetrahydroxystilbene) is a hydroxylated metabolite of resveratrol and it can be naturally found in white tea, passion fruit, peanuts, berries, and the skin of grapes. Although piceatannol was at first less noticed due to its relatively low content in wine, it was later found that a considerable amount of piceatannol was present in the seeds of passion fruit (*Passiflora edulis*) with an amount of 4.8 mg g<sup>-1</sup> freeze-dried seed.<sup>24</sup> Meanwhile, piceatannol exhibits similar or even better biological properties compared with resveratrol. For instance, piceatannol is more metabolically stable and possesses a better antioxidant capacity due to the additional hydroxyl group at the 3'-position which facilitates the formation of a semiquinone structure.<sup>25</sup> As a result, piceatannol has gradually drawn the attention of scientists in the last decade.

Oxyresveratrol (*trans*-2,4,3',5'-tetrahydroxystilbene), another hydroxylated derivative of resveratrol, is a natural stilbenoid that has similar biological activities to resveratrol.<sup>26</sup> However, due to an extra hydroxyl group at the 2-position, oxyresveratrol exhibited a stronger antioxidant and anticancer effect than resveratrol.<sup>27</sup> The distribution of oxyresveratrol occurs in certain plants sporadically and concentrates in two genera from the Moraceae (or mulberry family), namely *Artocarpus* (jackfruit) and *Morus* (mulberry). Commonly, oxyresveratrol is extracted from the bark and root of *Morus* plants, *i.e.* *Morus alba*.<sup>26</sup>

The contents of these five stilbenes reported in common foods and edible plants are listed in Table 1. Of note, these compounds are not only present in the fruit of the plant but also in other parts which are commonly treated as waste, including the stems and leaves. Therefore, the extraction of stilbenes from the waste after fruit-picking or even juicing allows a more complete utilization of the entire plant. Methods such as UV-C radiation and cotreatment with other compounds can be used to stimulate the accumulation of stilbenes and increase their levels in the fruits and stems. For instance, in common grapes, the resveratrol content increased from 0.78 µg g<sup>-1</sup> to 1.63 µg g<sup>-1</sup> after UV-C radiation<sup>28,29</sup> while in peanut callus cotreated with chitin, the resveratrol content can rise to 10.43 µg g<sup>-1</sup>.<sup>30</sup> Detailed information of other experiments is summarized in Table 1.

### 3. Hypoglycemic effect of resveratrol and related stilbenes and potential mechanisms

Several studies have demonstrated the efficacy of these five stilbenes, *i.e.* resveratrol, pterostilbene, oxyresveratrol, picea-

tannol, and THSG, to relieve hyperglycemia and improve insulin sensitivity in rodent models of IR and T2DM. Animal studies that used resveratrol, pterostilbene, THSG, piceatannol, and oxyresveratrol as dietary intervention managed to improve some symptoms including lowered fasting blood glucose level, improvement in glucose tolerance and insulin sensitivity, alleviation of loss in β-cell functions, reduced weight gain, improved lipid profile and others. They will be discussed in the following sections. Commonly used dosages, durations, and outcomes for related research are listed in Tables 2 and 3. For a better comparison of dosages between animal studies and clinical trials, the conversion of human dosages to animal equivalent doses can be calculated using the FDA drafted guideline, in which the dosages for mouse and rat are approximately calculated as multiplying the human dosage (mg kg<sup>-1</sup>) by 12.3 and 6.2 respectively.<sup>31</sup> Commonly, body weight is assumed as 60 kg per person. Therefore, since resveratrol treatment in clinical trials (discussed in section 4) ranged from 100–1000 mg day<sup>-1</sup> (1.67–16.7 mg kg<sup>-1</sup>), its corresponding dosages for mice and rat are 20.5–205.4 mg kg<sup>-1</sup> and 10.3–103.5 mg kg<sup>-1</sup> respectively. The dosage used in most of the studies fell into this range. For studies applying stilbenes in water (0.005% to 0.02%) and in feed (2 or 4 g kg<sup>-1</sup>), the corresponding dosage is calculated as 12 to 48 mg kg<sup>-1</sup> and 480 to 960 mg kg<sup>-1</sup> (water and food intake for mice assumed as 6 mL and 6 g respectively).<sup>32</sup> Since mice sometimes tend to gnaw the food without eating it, actual food intake could be much less than the 6 g that was recorded, and thus 2 g kg<sup>-1</sup> might still be reasonable. However, the dosages used in some experiments were extremely high, reaching 400 mg kg<sup>-1</sup> or even 800 mg kg<sup>-1</sup> *via* oral gavage for several months, and hence these experiments were marked specifically with symbols (\*\*\*) in Tables 2 and 3. The regulatory effect of these stilbenes on hyperglycemia may be ascribed to the aspects listed below and they are also briefly depicted in Fig. 1.

#### 3.1 Influence on food intake and nutrition absorptions

Long-term exposure to elevated levels of free fatty acid (FFA) and glucose has been considered as the cause of IR, which is an important biomarker in patients with persistent hyperglycemia prior to the onset of T2DM.<sup>5</sup> Consequently, controlling elevated levels of both plasma FFA and glucose can prevent or alleviate hyperglycemia. Since both substances are used as energy fuels in the body, this could be achieved by promoting energy expenditure and reducing energy intake. Regulation of feeding behavior and satiety by neuropeptides and hormones, as well as modulation of nutrient absorption in the gut, are effective ways to alter this energy balance and they are reported to be part of the mechanisms through which resveratrol and pterostilbene exert their hypoglycemic functions.

The regulatory effect of resveratrol on food consumption has been examined. Neuropeptide Y (NPY) and agouti-related peptide (AgRP) were postulated to exert powerful stimulation on feeding behaviour. However, in mice injected with resveratrol, a decline in accumulative food intake over 48 h was



**Table 1** Content of stilbenes found in common food and edible plant

Food	Scientific name	Stilbene compounds	Content in different parts of plant	Ref.
Common grapes	<i>Vitis vinifera</i>	Resveratrol	Fruit: 36.6 $\mu\text{g g}^{-1}$	14
		Resveratrol	Fruit: 3.18 $\mu\text{g g}^{-1}$ before UV-C radiation 8.13 $\mu\text{g g}^{-1}$ after UV-C radiation	28
		Resveratrol	Stem: 50 $\mu\text{g g}^{-1}$	
		Resveratrol	Pinot noir cane after storage: up to around 2800 $\mu\text{g g}^{-1}$ dried weight	174
		Piceatannol	Fruit: 0.78 $\mu\text{g g}^{-1}$ before UV-C radiation 1.63 $\mu\text{g g}^{-1}$ after UV-C radiation	28
		Piceatannol Pterostilbene	Stem: 5 $\mu\text{g g}^{-1}$ Pinot noir cane after storage: up to around 800 $\mu\text{g g}^{-1}$ dried weight Fresh weight: 0.2–4.7 $\mu\text{g g}^{-1}$	174 29
Red wine		Resveratrol	Skin of grapes after UV radiation: 0.8–20 $\mu\text{g g}^{-1}$ fresh weight	
		Piceatannol	0.27 mg per 100 ml 0.58 mg per 100 ml	175 Phenol-explorer
Mulberry	<i>Morus sp.</i>	Resveratrol	Fruit: 7.95 $\mu\text{g g}^{-1}$	14
		Resveratrol	3.3 $\mu\text{g g}^{-1}$	176
		Piceatannol	Fruit: 2–10.19 $\mu\text{g g}^{-1}$	177
		Oxyresveratrol	Bark to stem: 150–680 $\mu\text{g g}^{-1}$	178
		Oxyresveratrol	Fruit: up to 29.5 $\mu\text{g g}^{-1}$ Fruit marc: up to 37.3 $\mu\text{g g}^{-1}$ Leave: up to 179.9 $\mu\text{g g}^{-1}$ depending on cultivar	176
		Resveratrol	0.4 $\mu\text{g g}^{-1}$	175
Peanut	<i>Arachis hypogaea</i>	Resveratrol	Dry-blanching peanut skin: 3.6 $\mu\text{g g}^{-1}$	179
		Resveratrol	Peanut callus after UV-C radiation: up to 11.97 $\mu\text{g g}^{-1}$	180
		Resveratrol	Peanut callus cotreated with chitin: 10.43 $\mu\text{g g}^{-1}$	30
		Piceatannol	Peanut callus after UV-C radiation: up to 5.31 $\mu\text{g g}^{-1}$	180
		Piceatannol	Peanut callus cotreated with chitin: 2.55 $\mu\text{g g}^{-1}$	30
		Pterostilbene	N/A	181
Blueberries	<i>Vaccinium sect. Cyanococcus</i>	Resveratrol	Fruit: 6.7 $\mu\text{g g}^{-1}$	175
		Pterostilbene	Dried fruit: up to 0.151 $\mu\text{g g}^{-1}$	182
		Piceatannol	Dried fruit: up to 0.422 $\mu\text{g g}^{-1}$	182
Deerberry	<i>Vaccinium stamineum L.</i>	Pterostilbene	Dried fruit: 0.52 $\mu\text{g g}^{-1}$	182
		Piceatannol	Dried fruit: up to 0.195 $\mu\text{g g}^{-1}$	182
Lingonberries		Resveratrol	30 $\mu\text{g g}^{-1}$	175
Heshouwu	<i>Polygonum multiflorum thunb.</i>	THSG	Root tuber (edible part): 5%	183
Sugarcane	<i>Saccharum spp.</i>	Resveratrol	Billet stalks after 7 days incubation: 73 $\mu\text{g g}^{-1}$ ; juice: 1.2 mg L <sup>-1</sup>	184
		Piceatannol	Billet stalks after 7 days incubation: 1659 $\mu\text{g g}^{-1}$ ; juice: 8.5 mg L <sup>-1</sup>	184
Jackfruit	<i>Artocarpus heterophyllus Lam.</i>	Oxyresveratrol	N/A	185
Passion fruit	<i>Passiflora edulis</i>	Piceatannol	Raw passion fruit seed: 2.2 mg g <sup>-1</sup>	24
		Resveratrol	Raw passion fruit seed: 0.1 mg g <sup>-1</sup>	24

noticed and resveratrol was shown to downregulate both NPY and AgRP<sup>33</sup> in neuron cells. In line with this study, another research study found that intervention with resveratrol caused a concomitant decrease in energy intake and an increase in metabolic rate, leading to a reduced body mass in non-human primates.<sup>34</sup> Nevertheless, future works focusing on the detailed changes of biomarkers of satiety are necessary to investigate the effect of resveratrol on feeding behaviours in mice with hyperglycemia. In addition, GLP-1, an incretin hormone mainly produced by the intestinal endocrine cells, seems to be involved in the regulatory effect of resveratrol. It can reduce food intake by delaying the process of emptying the stomach, reducing bowel movement and glycogen secretion. Upregulation of GLP-1 in mice with hyperglycemia was reported after supplementation with resveratrol for 8 weeks.<sup>35,36</sup> Together, these results indicate that resveratrol is effective in modulating food consumption.

Once the food is ingested, the next step to reduce energy intake is to modulate nutrition absorption *in vivo*, which can be accomplished by regulating enzymatic activity and nutrient transporters.  $\alpha$ -Glucosidase, a membrane-bound enzyme in the GI tract, is responsible for the hydrolysis of polysaccharides to glucose and other monosaccharides. When a large amount of glucose generated from the hydrolysis is taken up by the gut and enters the circulation, PPHG occurs. Therefore, suppression of  $\alpha$ -glucosidase can alleviate PPHG and subsequently lessen the stress for insulin production, thus protecting the normal functions of the pancreas. *In vitro* experiments have illustrated the ability of resveratrol to significantly repress the enzyme activity of both yeast and mammalian  $\alpha$ -glucosidase.<sup>37,38</sup> Further *in vivo* research in obese mice demonstrated that the administration of resveratrol prior to sucrose or starch loading can indeed lower postprandial blood glucose.<sup>37</sup> Besides managing PPHG, another key point is to



**Table 2** Effect of resveratrol on glycemic control in different diabetic animal models

Animal models	Dose/dosing method/period	Hypoglycemic and anti-diabetic function	Involvement of mechanisms	Ref.
High fat diet-induced obese wild type C57BL/6J mice with insulin resistance and GLP 1r <sup>-/-</sup> mice	60 mg kg <sup>-1</sup> day <sup>-1</sup> ; mixed in diet; 5 weeks	Glucose tolerance↑ Insulin level↑	Increasing GLP-1 level and promoting its further action	35
High fat diet-fed C57BL/6J mice with insulin resistance	30 mg kg <sup>-1</sup> ; oral gavage; one time	Postprandial blood glucose after sucrose-loading or starch-loading↓	Inhibition of α-glucosidase	37
High fat diet-induced obese Wistar rats	20 mg kg <sup>-1</sup> ; dissolved in saline; daily basis; 8 weeks	Plasma triglycerides↓ Fecal triglycerides level↑ Insulin sensitivity↑ HOMA-IR↓ Blood glucose↓	Inhibition of pancreatic lipase	39
High fat diet-fed C57BL/6J mice with insulin-resistance	100 mg kg <sup>-1</sup> ; daily basis; intragastric administration; 6 weeks	Blood glucose and serum insulin level↓ The quantitative insulin sensitivity check index (QUIACKI)↑	Modulation of lncRNAs in the insulin signalling pathway (G6PC, FOXO1 and suppressor of cytokine signalling 3 (SOCS3)↓; phosphorylation of Akt and FOXO1↑)	51
High fat diet-fed C57BL/6J mice with insulin-resistance	100 mg kg <sup>-1</sup> ; daily basis; intragastric administration; 6 weeks	Significantly enhanced PI3K/Akt insulin signaling pathway	Mmu-miR-363-3p expression↑	52
High fat diet-fed C57BL/6J mice with insulin-resistance	100 mg kg <sup>-1</sup> ; oral administration; 8 weeks	QUIACKI↑; insulin sensitivity↑ Blood glucose and serum insulin level↓ Lipid accumulation↓	Expression of AMPK kinase: ataxia-telangiectasia mutated (ATM) ↑ Phosphorylation of AMPK↑	54
Insulin-resistant KKA <sup>y</sup> mice	2 or 4 g kg <sup>-1</sup> diet; 12 weeks	Blood glucose and serum insulin level↓ Insulin and glucose tolerance↑	COXIV↑ Upregulation of Sirt1 protein in liver and muscle and consequent AMPK activation	49
Methylglyoxal-induced insulin-resistant Balb/C mice	10 mg kg <sup>-1</sup> ; daily basis; oral gavage; 12 weeks	Serum glucose level↓ Significantly lower ITT Insulin level↓	Phosphorylation of Nrf2 in pancreas and Tyr-phosphorylated IRS-1 level in liver↑	50
C57BL/KsJ-db/db mice	0.005%, 0.02%; diet; 6 weeks	Hepatic glycogen and blood glucose↓ Serum free fatty acid and triglycerides↓ Plasma insulin level↑	Activation of AMPK and downstream targets Hepatic gluconeogenic enzymatic activity↓ Upregulation of GLUT4 protein and protection of pancreas	99
Monosodium glutamate-induced T2DM CD1 mice	30 mg kg <sup>-1</sup> ; dissolved in water; 60 days	Plasma insulin, glucose and triglyceride level↓	Slc2a4 mRNA (GLUT 4 encoding gene), GLUT4 protein and nuclear Sirt1 protein expression↑; Slc2a2 mRNA (GLUT 2 encoding gene) and GLUT2 protein expression level in liver↓ Pck1 mRNA expression level↓	105
Sprague-Dawley rats with chronic intermittent hypoxia induced-insulin resistance	3, 30, 60 mg kg <sup>-1</sup> ; daily basis; oral gavage; 28 days	Improved IR; HOMA-IR↓	Insulin receptor and GLUT2 expression in liver↓ Phosphorylation of PI3K and AKT↑ Activation of Sirt1	104
STZ-induced diabetic rats supplemented with insulin	10 mg kg <sup>-1</sup> ; daily basis; intraperitoneal injection; 30 days	Improved glycemic control	Slc2a2 mRNA and GLUT2 protein expression level in liver↓; Pck1 and G6pc mRNA expression↓	103
Goto-Kakizaki rats	20 mg kg <sup>-1</sup> ; daily basis; oral gavage; 10 weeks	Improved glucose tolerance, blood glucose↓, insulin level↑; better preservation of islets	Protein expression level of Akt and its phosphorylation↓ ACC level and its phosphorylation in muscle↓	61
Male C57BL/6J mice	400 mg kg <sup>-1</sup> ; daily basis; oral administration (dissolved in saline); 16 weeks***	Function of insulin secretion both <i>in vitro</i> and <i>in vivo</i> ↑ Improved insulin resistance Blood glucose and FFA↓ Improved islet morphology including less islet hypertrophy	Elevating Sirt1 expression and inhibiting UCP2 expression in islets; pancreatic cell apoptosis and oxidative stress↓	65
STZ-nicotinamide-induced Wistar rats	5 mg per kg body weight; daily basis; oral administration; 30 days	Blood glucose↓ Glycosylated hemoglobin↓ Plasma insulin↑ Protection of pancreatic β-cells	Antioxidative function↑ Oxidative stress↓ (elevating level of SOD, GPx, GST, GSH, vitamin C and E) Level of inflammatory cytokines↓	74





Table 2 (Contd.)

Animal models	Dose/dosing method/period	Hypoglycemic and anti-diabetic function	Involvement of mechanisms	Ref.
STZ-induced diabetic Wistar rats	1, 5, 10 mg per kg body weight; daily basis; oral treatment; 30 days	Fasting blood glucose↓ Total antioxidant capacity↑ Total oxidant status↓	RAGE expression↓ Antioxidant content (in liver)↑	77
STZ-induced diabetic Wistar rats	1, 5, 10 mg per kg body weight; daily basis; oral treatment; 30 days	Fasting blood glucose↓ Serum insulin level↑ Total antioxidant capacity↑	RAGE expression↓ Antioxidant content (in kidney)↑	76
C57BL/6 with CML-induced pancreatic dysfunction	10 mg kg <sup>-1</sup> ; intraperitoneal injection; 12 weeks	Improved OGTT; blood glucose↓  Insulin sensitivity↑ Insulin level↑ Inhibited pancreatic damage and elevated numbers of islets	PDX-1, PPAR $\gamma$ , Nrf2 and GCL (rate-limiting enzyme in GSH production) expression↑ C/EBP $\beta$ expression in pancreas↓ GSH level↑ Phosphorylation of Akt and Nrf2 in muscle and liver↑	78
STZ-nicotinamide-induced rats	10 mg kg <sup>-1</sup> ; oral aqueous suspension; 30 days	Improved insulin tolerance	Normalizing the mRNA and protein expression level of Nrf2, Keap1 and other related genes Serum level of AGE↓	75
STZ-induced T1DM mice	50 mg kg <sup>-1</sup> ; daily basis; intraperitoneal injection; 12 days	Proinflammatory cytokines level in kidney↓ Level of antioxidant in kidney↑ Fasting blood glucose level↓ Serum insulin level↑  Food intake↓	Inhibited expression of CXCL16/NF- $\kappa$ B Normalized CD45 and CXCL16 (T cell regulators) expression in islets Inhibited macrophage infiltration Serum level of GSH↑ Level of MDA↓ F4/80 (murine macrophage marker)↓	84
High fat diet-fed C57BL/6J mice with insulin-resistance	200 mg kg <sup>-1</sup> or 400 mg kg <sup>-1</sup> ; daily basis; oral gavage; 18 weeks***	Blood glucose↓ HOMA-IR↓; insulin sensitivity↑	Serum cytokine↓ Reduced macrophage infiltration and inflammation <i>via</i> CCR2 (regulates monocyte mobilization) modulation in adipose tissue	90
High fat diet-induced obese C57/BL6J mice	4 g kg <sup>-1</sup> diet; 16 weeks	Improved insulin and glucose tolerance Fasting blood glucose↓ HFD-induced inflammation in skeletal muscle↓	Downregulation of MAPK pathway  Expression of TLR2 and TLR4↓ Enhanced percentage of T regulatory cells Switched from M1 to M2 macrophage	86
High fat diet-induced insulin resistant C57BL/6J mice	100 mg kg <sup>-1</sup> ; daily basis; oral gavage; 12 weeks	Ameliorate insulin resistance, dyslipidaemia, hyperglycemia, inflammation and endotoxemia	Expression of tight junction proteins↑ Modifying the composition of intestinal microbiome	125

reduce the elevated level of FFA, of which dysregulation can ultimately contribute to IR and further persistent hyperglycemia. The inhibitory effect on pancreatic lipase, an enzyme that cleaves triglycerides to fatty acids, along with the drastically higher level of triglycerides in faeces, was observed after resveratrol treatment, implying delayed and reduced FA absorption by the intestinal enterocytes.<sup>38,39</sup> Besides, reduced intestinal glucose uptake from isolated porcine jejunum and ileum was reported *in vitro* after pre-incubation with resveratrol, and the inhibition of SGLT-1, a transporter that is predominately in charge of dietary glucose uptake in the small intestine, was postulated as the underlying mechanism.<sup>40-42</sup> However, further *in vivo* experiments are needed to establish such a direct relationship. These studies illustrate the ability of resveratrol to interfere with digestion and nutrient absorption in general, thus ameliorating hyperglycemia.

Similar to resveratrol, oxyresveratrol exhibits some of the functions mentioned above, such as inhibition of  $\alpha$ -glucosidase. However, a recent study stated that its inhibitory

effect was greatly compromised when applied to membrane-bound  $\alpha$ -glucosidase in differentiated Caco-2 cells.<sup>43</sup> Piceatannol, on the other hand, presented convincing information on its ability to attenuate PPHG *in vivo*.<sup>37</sup> As for pterostilbene and THSG, data are rather limited yet pterostilbene has been shown to be effective in inhibiting  $\alpha$ -glucosidase with relatively limited efficacy when compared with resveratrol.<sup>37</sup>

### 3.2 Regulation of glucose homeostasis

The maintenance of glucose homeostasis plays a crucial role in the prevention and treatment of hyperglycemia. In healthy individuals, different levels of insulin are released into the circulation to maintain glucose homeostasis under different situations. In post-absorptive states, a low level of insulin is released in pulses to ensure the necessary protein synthesis and maintain a normal level of hepatic glucose production. However, in the postprandial period, the insulin level is rapidly upregulated in response to glucose absorption in the gut, which will subsequently enhance glucose uptake in



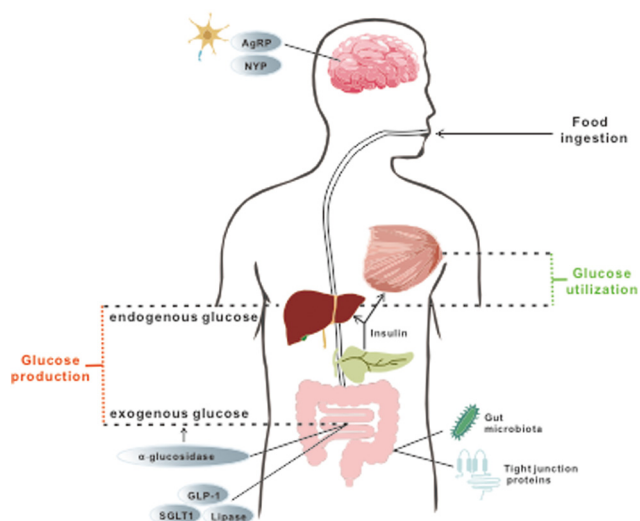
**Table 3** Effect of pterostilbene, piceatannol and oxyresveratrol on glycaemic control in diabetic animal models

Animal models	Dose/dosing method/period	Anti-diabetic function	Involvement of mechanisms	Ref.
Pterostilbene Fructose-induced diabetic Sprague-Dawley rats	20, 40 mg kg <sup>-1</sup> ; daily basis Oral gavage; 8 weeks	Fasting blood glucose↓ Improved OGTT Fasting serum insulin level↓ HOMA-IR↓ Insulin sensitivity index↑ Glycated haemoglobin↓	Reduction of hepatic oxidative stress <i>via</i> increasing level of hepatic SOD and GSH while decreasing TBARS (lipid peroxidation marker)	57
Mice with AGE-induced insulin resistance	200 mg kg <sup>-1</sup> pterostilbene added in high-AGE diet	Fasting blood glucose↓ Lower AGE accumulation Improved hepatic insulin signaling	AGE accumulation in liver and serum↓	58
STZ-induced diabetic Swiss Albino mice	5, 10 mg kg <sup>-1</sup> ; intraperitoneal injection; 5 weeks	Improved blood glucose level Insulin level↑ Preserve a better structure for insulin-positive cells	Nrf2 and its downstream targets expression in pancreas↑ Restoring glycogen level in liver Enzymatic activity of hexokinase, G6PD↑ Enzymatic activity of G6P and F1, 6BP↓ Inflammatory cytokines such as TNF-α and IL-6↓	62
STZ-induced diabetic Sprague-Dawley rats	20, 40, 80 mg kg <sup>-1</sup> ; daily basis; oral gavage; 8 weeks	Improved fasting blood glucose and glucose tolerance Increased insulin level and improved insulin resistance Improved histopathology of pancreas	Reducing oxidative stress by upregulating SOD level and decreasing MDA level Protein expression level of PI3K, p-Akt and GLUT4, IRS-1 and PPAR-γ↑	64
Obesogenic diet-fed Wistar rats	15, 30 mg kg <sup>-1</sup> ; mixed with diet; 6 weeks	Basal glucose and insulin↓ HOMA-IR↓ Improved glucose tolerance	Enzymatic activity of GK↑ Phosphorylated Akt/total Akt ratio↑; expression of GLUT4 in muscle↑	106
STZ-induced diabetic Swiss Albino mice	5, 10 mg kg <sup>-1</sup> ; intraperitoneal injection; 5 weeks	Fasting blood glucose↓ Insulin level↑ Pancreatic islet apoptosis↓ Improved pancreatic islet structure	Serum pro-inflammatory cytokines↓ Activating Nrf2 and its downstream genes iNOS expression, nitrate and nitrite level in pancreas↓	63
Piceatannol HFD-induced obese mice	0.1% or 0.25% piceatannol in feed; 18 weeks	Blood glucose↓	Modulation of gut microbiota Reduced lipid accumulation and adipocyte size <i>via</i> increasing pAMPK and decreasing PPARγ expression	186
High fat diet-induced diabetic C57BL/6J mice	3, 10, 30 mg kg <sup>-1</sup> ; oral gavage; daily basis; 5 weeks	Fasting blood glucose↓	NA	187
T2DM db/db mice	50 mg kg <sup>-1</sup> in suspension; intubated; 3 weeks	Fasting blood glucose↓ Improved glucose tolerance	NA	110
High fat diet-fed diabetic C57BL/6J mice	10 mg kg <sup>-1</sup> ; daily basis; oral gavage; 4 weeks	Improved glucose control (OGTT test)	Hepatic gene expression of insulin receptor, AMPK, Sirt1, Sirt3, Sirt6, PGC1-α and FOXO1↑ TNF-α↓	111
Oxyresveratrol STZ-induced diabetic ICR mice	600 mg kg <sup>-1</sup> ; once daily; oral administration; 22 days***	Fasting blood glucose↓ Glycogen level↑	GLUT2 transcription↑	188
High-fat diet-induced C57BLKS/J db/db mice	800 mg kg <sup>-1</sup> ; once daily; oral gavage; 14 weeks***	Pancreatic insulin↓ Plasma insulin↑	Insulin secretion↑ Pancreatic ROS level↓ Improved pancreatic inflammation	67
High-fat diet-induced C57bl/6 diabetic mice	0.25% and 0.5%	Fasting blood glucose↓ Plasma insulin↑	Expression of glucose-6-phosphatase and GLUT4 ↑ Expression of IRS1, AMPKα2, PGC-1α, Sirt1↑	112

tissues and organs and reduce hepatic glucose output by inhibiting gluconeogenesis and glycogenolysis.<sup>44,45</sup> By contrast, in patients with hyperglycemia, disruption of glucose homeostasis occurs because of the abnormality in insulin function or secretion. Hyperinsulinemia would commonly be observed in the first stage as it is proposed as a compensatory mechanism for progressing IR, in which responses to insulin in the targeted tissues and organs are significantly compromised.<sup>5</sup> On the other hand, decreased levels of insulin may also occur when pancreatic β-cells, which are responsible for insulin pro-

duction, are exhausted under excessive stress. Both situations not only alter normal hepatic enzymatic activities which in turn lead to excessive gluconeogenesis and glycogenolysis during the fasting state but also impair glucose transportation and uptake by the target tissues, producing insufficient clearance of blood glucose after meals.<sup>46</sup> Therefore, the improvement not only in IR but also in insulin secretion *via* protecting pancreatic structure and function, along with the subsequent enhancement in glucose deposition to the responding tissues and organs and in the recovery of related hepatic enzymatic





**Fig. 1** Organs, tissues and downstream targets that are involved in the maintenance of glucose homeostasis during treatment with selected stilbenoids. The stilbenes are found to exert regulatory effects on glucose homeostasis *via* a few aspects, including (a) management of exogenous glucose intake by modulating feeding behavior and nutrition absorption (targets are marked in grey circles); (b) improvement of glucose utilization and endogenous glucose production through restoration of insulin production and further signalling (details are elaborated in Fig. 2); and (c) attenuation of systemic oxidative stress and inflammation *via* enhancing gut permeability and positively altering gut microbial profile and related metabolomes.

activities, might be considered as potential mechanisms in the prevention and treatment of hyperglycemia and related diseases. Resveratrol and other stilbenes mentioned above were reported to exert hypoglycemic functions through the proposed mechanisms summarized in Fig. 2.

**3.2.1 Improvement of insulin resistance.** Insulin resistance, also known as impaired insulin actions, is characterized by a reduced response of the liver, muscles and other organs and tissues to insulin. Several factors are proposed as contributors in the development of IR, including direct harmful effects posed by excess lipids and glucose on the metabolism in organs and tissues, activation of the endoplasmic reticulum (ER) stress pathway and enhanced inflammatory reactions. A detailed review of the molecular and metabolic mechanisms of insulin resistance is done by Muoio and Newgard.<sup>47</sup> In brief, the excess glucose and lipids in the liver will reduce the lipid oxidation and promote the production of lipid with a signalling property that further results in the inactivation of key insulin signalling molecules, whereas, in muscle, upregulation of fatty acid oxidation caused by excess lipids is not accompanied by the concurrent upregulation of downstream metabolic processes such as the tricarboxylic acid cycle, thus compromising insulin signalling due to the incomplete lipid metabolism in the mitochondria. Besides the changes in lipid metabolism, reduced glucose uptake and metabolism are also commonly observed, characterizing the impaired insulin actions during IR. In particular, the inhibition of insulin receptor substrate-1 (IRS-1) plays a key part in this process.

IRS-1 is an important mediator that transmits the signal from the insulin receptors to intracellular pathways for glucose uptake. Under normal conditions, tyrosine phosphorylation of IRS-1 by the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) cascade is required for insulin actions, which further influence glucose uptake through glucose transporter 4 (GLUT4) and glucose metabolism (glycogen synthase kinase 3 *etc.*) (see section 3.2.3. for a detailed explanation). However, the phosphorylation of IRS-1 on serine residues is involved in the negative feedback loop that terminates insulin signalling, and such phosphorylation could be induced by common agents such as free fatty acids, cytokines, and cellular stress.<sup>48</sup> Nutrition overload and related metabolic changes are linked to the ER stress-induced activation of c-Jun-N-terminal kinase (JNK), which can phosphorylate insulin receptor substrate-1 (IRS-1) and further interfere with insulin signalling.<sup>47</sup>

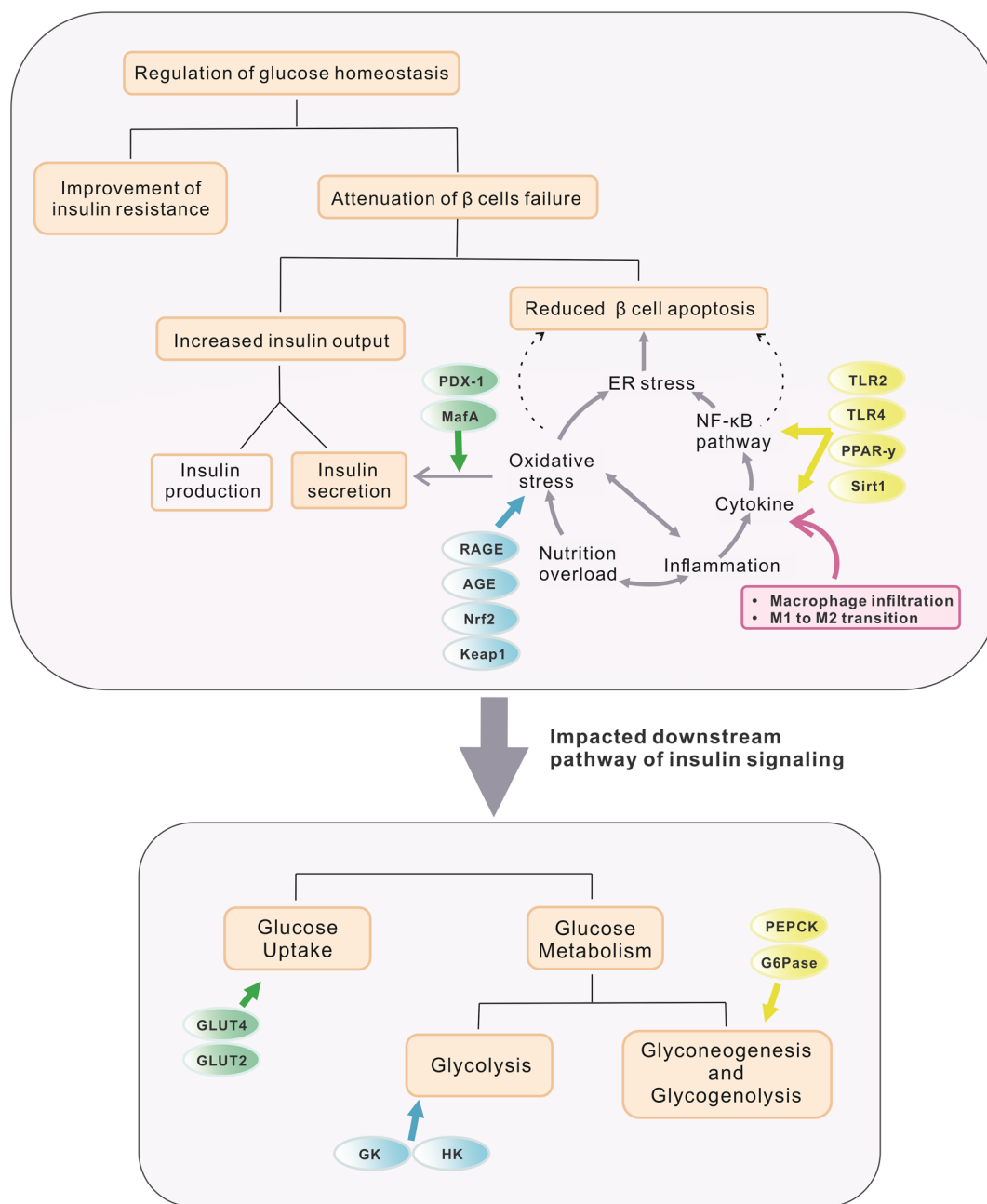
The ability of resveratrol to ameliorate IR was reported in several studies. In cells and rodents with IR, overproduction of insulin was observed yet a decreased insulin level, together with an improvement in glucose tolerance, was reported after resveratrol treatment.<sup>49–51</sup> These results indicated an effective attenuation of IR, which could be attributed to the regulation in long noncoding RNA (lncRNA)<sup>51</sup> and micro RNA<sup>52</sup> that potentially regulates the interaction of the encoded transcript and protein in the insulin signalling pathway, restoration of autophagic flux,<sup>53</sup> improvement in fatty acid oxidation efficiency and activity of key enzymes in the respiratory electron transport chain: cytochrome oxidase subunit IV(COIV),<sup>54</sup> oxidative stress and subsequent apoptosis in insulin-responding cells and tissues and others.<sup>55,56</sup>

A similar function of pterostilbene was also reported. Recent *in vitro* and *in vivo* studies indicated that pterostilbene administration can effectively decrease the homeostasis model assessment (HOMA)-IR<sup>57</sup> and rescue symptoms of IR *via* enhancing (IRS-1)/(PI3K)/Akt insulin signalling<sup>58</sup> or reversing the activation of c-Jun N-terminal kinase (JNK) which in turn alters the IRS-1/Akt/glycogen synthase kinase-3 $\beta$  insulin signalling pathway.<sup>59</sup>

**3.2.2 Improvement of insulin production and secretion.** Apart from the amelioration in IR, the promoting effect of resveratrol on the production and secretion of insulin is also a key part in the regulation of glucose homeostasis. Depending on the time point when the rodents were sacrificed, a decline in insulin level was also observed in diabetic animal models,<sup>60</sup> but resveratrol was reported to elevate insulin production.<sup>61</sup> The pancreas is one of the most important organs in maintaining a normal glucose level. There are several types of cell in the pancreatic islets such as  $\alpha$ ,  $\beta$ , and  $\delta$ -cells, among which  $\beta$ -cells are responsible for the production and secretion of insulin. As mentioned above, IR associated with chronic exposure to elevated levels of FFA and glucose and a further requirement for the overproduction of insulin can ultimately result in progressive  $\beta$ -cell failure, which includes mainly two aspects, a decrease in  $\beta$ -cell mass (cell number decrease) and the impairment of  $\beta$ -cell function (reduced output of insulin). The main form of cell death in  $\beta$ -cell failure is apoptosis,







**Fig. 2** Proposed mechanisms and targeted genes through which selected stilbenes exert hypoglycemic and anti-diabetic functions. The light orange rectangles mark major aspects affected in glucose deposition and metabolism. The gray circle illustrates the main pathway involved in  $\beta$  cell apoptosis (mainly oxidative stress and inflammation). Ellipses in different colors represent targeted genes modulated by selected stilbenes. The pink rectangle shows the effects of stilbenes on macrophages. Regulation of glucose homeostasis can be achieved mainly through improving IR and increasing insulin output (reduce  $\beta$ -cell apoptosis and enhance  $\beta$ -cell function in insulin productivity and secretion). Meanwhile, downstream targets of insulin signalling were also upregulated by stilbenoids, thus ameliorating hyperglycemia.

induced either by cytokines, nutrient overload, or the combination of both and they may involve the activation of ER stress and increased oxidative stress.<sup>4</sup> Therefore, protecting  $\beta$ -cells from excessive apoptosis and functional damage caused by free radicals like ROS and increased pro-inflammatory cytokines, should be beneficial for the prevention of hyperglycemia and related diseases.

A few studies have illustrated a positive role of selected stilbenes in the stimulation of insulin production, potentially through protecting  $\beta$ -cells from apoptosis and reducing pancreatic functional damage. Histologic analysis showed an improved insulin secretion (more positive staining for insulin) and better preservation of pancreatic  $\beta$ -cells (better morphology with less distorted  $\beta$ -cells) after treatment with resver-



atrol and pterostilbene.<sup>50,61–64</sup> This was further confirmed by a decreased expression level of B cell leukemia/lymphoma 2 (Bcl2)/Bcl2-associated X and reduced activation of caspase 3, the main executor of apoptosis.<sup>63,65,66</sup> As for oxyresveratrol and piceatannol, although there are no available data concerning their influence on the pancreas, they were reported to lower fasting blood glucose. Oxyresveratrol can increase plasma insulin level *in vivo* and stimulate insulin secretion in a pancreatic cell line.<sup>67</sup> Study results attributed the above benefits to the anti-oxidative and anti-inflammatory properties of these stilbenes and the underlying mechanisms will be discussed in the following sections.

**3.2.2.1 Improvement of oxidative stress-related pancreatic damage and insulin secretion.** Excessive oxidative stress is a common feature associated with long-term hyperglycemia. Several mechanisms have been proposed, which mainly refer to the direct promotion of ROS generation or compromised cellular antioxidant defense mechanisms.<sup>46</sup> Regulation of cellular redox homeostasis primarily happens at the transcriptional level, and the nuclear factor erythroid 2-related factor-2 (Nrf2)/kelch-like ECH-associated protein 1 (Keap1)/antioxidant response elements (ARE) pathway is the primary mediator of this response. However, dysfunction of this pathway is commonly seen in patients with hyperglycemia and diabetes, thus weakening their ability to clear ROS and contributing to an imbalanced redox state.<sup>68</sup> In addition, such an imbalance can deteriorate by the accumulation of advanced glycation end products (AGEs) mediated through their cell surface receptor widely expressed in the tissues, that is, RAGE. AGE-ligand interaction can lead to activation of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system,<sup>46</sup> which along with the mitochondria serves as the major source of ROS production in the biological system.<sup>69</sup> Even worse, owing to the naturally low expression level of free radical-scavenging enzymes, pancreatic  $\beta$ -cells are particularly sensitive to oxidative stress-mediated damage when compared with other cell types. Consequently, the imbalanced redox state brings about impaired pancreatic  $\beta$ -cell functions and further interrupts insulin secretion potentially through reducing the expression level of related transcription factors, mainly pancreatic and duodenal homeobox-1 (PDX1) and V-Maf avian musculoaponeurotic fibrosarcoma oncogene homolog A (MafA).<sup>68</sup> PDX1 is an essential insulin transcription factor in both the development of the pancreas and normal insulin secretion. Increased oxidative stress can reduce the transcriptional activity of PDX-1 by inhibiting its translocation from the cytoplasm to the nucleus and this process is associated with the activation of JNK, through forkhead box O1 (FOXO1).<sup>70</sup> Similarly, MafA, another important transcriptional factor for cell differentiation in the pancreas and insulin secretion<sup>71</sup> was found to be down-regulated in glucotoxic pancreatic cells. It was further reported that the use of antioxidants can preserve its protein expression and its binding to the insulin promoter, hence underscoring the role of oxidative stress in pancreatic dysfunction.<sup>72</sup> In addition, overexpression of uncoupling protein 2 (UCP2), which is known to be upregulated in pancreatic islet patients

with T2DM, could result in the reduction of insulin secretion through decreased mitochondrial function and increased ER stress through an oxidative stress-mediated pathway.<sup>73</sup> Therefore, the ability to suppress ROS production and to remove ROS from the current overall oxidative environment is crucial for the survival of  $\beta$ -cells and the restoration of their functions.

Resveratrol has been reported to improve redox balance and attenuate the apoptosis and dysfunction of pancreatic cells. In isolated human islets, resveratrol significantly reduced hypoxia and oxidative stress-induced pancreatic cell apoptosis.<sup>66</sup> In parallel, increased ROS, reduced non-enzymatic antioxidants such as glutathione (GSH) and vitamin C in plasma, along with diminished activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione-S-transferase (GST) in the pancreas, were observed in diabetic rats. However, resveratrol treatment reversed the aforementioned diminished enzyme activities and significantly reduced lipid peroxide, hydroperoxides, and glycated proteins nearly to normalcy,<sup>74</sup> which may be attributed to their regulatory effects on the following aspects. Firstly, in diabetic rats, resveratrol significantly reduced serum AGE level<sup>75</sup> and RAGE expression in organs,<sup>76,77</sup> thus suppressing ROS production. However, up to now, there is no report regarding the effect of resveratrol on pancreatic RAGE expression. Therefore, its direct effect on the pancreas needs further confirmation. Secondly, studies have suggested that in hyperglycemic or diabetic mice, resveratrol administration can not only promote Nrf2 phosphorylation in the pancreas<sup>50</sup> and the liver and muscle tissues,<sup>78</sup> but also normalize renal expression of Nrf2/Keap1 and their downstream targets.<sup>75</sup> Furthermore, recovery of oxidative stress-influenced insulin secretion was noticed after resveratrol treatment, evidenced by (1) the elevated PDX-1 expression *via* activation of silencing information regulator 2 related enzyme 1 (Sirt1)<sup>79</sup> in glucose-stimulated cells and *via* activation of PPAR- $\gamma$  and Nrf2 in mice with pancreatic dysfunction;<sup>78</sup> and (2) the reinstated reduction in transcriptional activity of MafA *via* activation of Sirt1 in pancreatic  $\beta$  cells with palmitate-induced dysfunction.<sup>80</sup>

Similarly, the administration of pterostilbene has been shown to reduce oxidative stress *via* inhibiting the accumulation of AGEs in both the liver and serum.<sup>58</sup> It also activated anti-oxidative genes (heme oxygenase-1, SOD, CAT, and GPx) and increased pancreatic Nrf2 expression, thus preserving pancreatic structure and insulin secretion. Moreover, pterostilbene can promote Nrf2 binding to ARE, further inducing the expression of a set of cytoprotective genes.<sup>62</sup>

**3.2.2.2 Improvement of cytokine-induced  $\beta$ -cell inflammation and related damage.** Besides the stress brought about by ROS, the elevated level of inflammatory cytokines has been considered as one of the major causes for the impaired functions and apoptosis of pancreatic  $\beta$ -cells. Islet inflammation, characterized by increased immune cell infiltration, cell death, and others, are observed under diabetes, and this inflammation is associated with hyperglycemia.<sup>4</sup> Studies have proposed a role of macrophage-secreted cytokines in this process as cytokine



treatments including interleukin 1 $\beta$  (IL-1 $\beta$ ), tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), and interferon gamma (IFN- $\gamma$ ) can result in a marked decrease in islet dysregulation possibly through nuclear factor kappa B (NF- $\kappa$ B)-induced excessive nitric oxide (NO) production.<sup>81–83</sup> Concordantly, a significant reversal occurred with the addition of a competitive NO synthase inhibitor, proving the essential role of NO in cytokine-induced  $\beta$ -cell apoptosis,<sup>83</sup> as elevated NO may result in a disrupted mitochondrial membrane potential that causes bioenergetic stress, increased BAX/Bcl-2 ratio (indicator for increased apoptosis) and activation of executioner protease for cell apoptosis, caspase-3.<sup>63</sup> Therefore, the ability to reduce the levels of macrophage-secreted cytokines and suppress their following pathways should be helpful in reducing inflammation-induced  $\beta$ -cell damage, including apoptosis and loss of functions.

Administration of resveratrol has been reported to lower the levels of cytokines and ameliorate cytokine-induced inflammation *in vitro* and *in vivo*. Resveratrol has been proved to suppress macrophage infiltration to pancreatic islets in diabetic rats.<sup>84</sup> Moreover, research proposed that the shift of overall macrophage polarity towards the pro-inflammatory M1-like phenotype contributes to islet inflammation and further  $\beta$ -cell dysfunction,<sup>85</sup> yet resveratrol effectively prevented the accumulation of macrophages in skeletal muscle tissue while promoting the M2 polarization of macrophages rather than M1,<sup>86</sup> thus reducing cytokine production and related inflammation. However, no data regarding the M1/M2 macrophages in the pancreas after supplementation of resveratrol are currently available and future experiments are needed. Resveratrol also reduced the expression of Toll-like receptor 2 (TLR2) and/or TLR4 in skeletal muscles and liver, which are essential mediators of inflammation in both muscles and islets.<sup>86–88</sup> In line with this, resveratrol reinstated the elevated levels of cytokines in different tissues of diabetic mice, including TNF- $\alpha$ , IL-1 $\beta$ , and interleukin 6 (IL-6).<sup>84,89,90</sup> Through all these improvements in the whole body, overall systemic inflammation may be attenuated, hence reducing the exposure of pancreatic  $\beta$ -cells to cytokines. Moreover, resveratrol can directly protect  $\beta$ -cells by inhibiting transcriptional NF- $\kappa$ B activity and suppress downstream nitric oxide synthase (iNOS) expression and NO production, potentially *via* the activation of PPAR- $\gamma$  and Sirt1.<sup>91,92</sup>

Studies have reported similar inhibitory effects of pterostilbene on cytokine production and pancreatic apoptosis. Administration of pterostilbene was found to reduce serum TNF- $\alpha$  levels and increase the M1/M2 macrophage ratio in adipose tissue.<sup>93</sup> It also significantly enhanced the protein expression of PPAR- $\gamma$ , PI3K, and p-Akt<sup>64</sup> and inhibited JNK activation,<sup>59</sup> which may suppress NF- $\kappa$ B expression and ameliorate inflammation. In addition, pterostilbene treatment was shown to reduce NO production in the pancreas of diabetic mice *via* inhibition of iNOS while attenuating islet cell apoptosis, demonstrated by a reduced BAX/Bcl-2 ratio and caspase 3 level.<sup>63</sup> Administration of oxyresveratrol also improved pancreatic inflammation and insulin secretion.<sup>67</sup>

Although currently there is no comparative study for anti-inflammatory effects between resveratrol and its analogues in islet cells, related data are available from an experiment that applies microglial neurological cells, in which excessive NO was also proposed to mediate macrophage-dependent inflammation. In this study, pterostilbene demonstrated the strongest ability to reduce the level of LPS-induced proinflammatory cytokine secretion, followed by THSG, oxyresveratrol and resveratrol. Pterostilbene also exhibited the best suppression effect on NO production, followed by resveratrol, oxyresveratrol and THSG.<sup>94</sup>

**3.2.3 Influence on the insulin downstream pathway.** The improvement by stilbenes in IR, insulin production and secretion has been addressed previously, but the mechanisms through which these changes affect glucose homeostasis remain to be elaborated in detail. In fact, they may be bridged by the modulation of glucose uptake and metabolism in the responding organs and tissues. GLUT4, an essential transporter in the glucose uptake of muscles and adipose tissue, contributes to the control of whole-body glycemia critically. Commonly, GLUT4 is distributed in the plasma membrane and several intracellular compartments including endosomes and vesicles. Upon insulin stimulation, GLUT4 could be released from these intracellular compartments *via* exocytosis and get further transported to the plasma membrane, thus enhancing the shuttling of glucose into the muscles and adipose tissue.<sup>95</sup> The activation of the PI3K/Akt cascade through the insulin signalling pathway, which is previously mentioned in section 3.2.1, is known to stimulate such GLUT4 translocation to the plasma membrane. Besides PI3K, Akt can also be activated by AMP-activated protein kinase (AMPK) under stresses and its activation can lead to the phosphorylation, in other words, the deactivation of FOXO1, a major regulator that promotes the expression of gluconeogenic genes and glucose production.<sup>96</sup> In addition, PPAR- $\gamma$  coactivator (PGC-1 $\alpha$ ), another essential transcriptional factor for gluconeogenic actions, also requires FOXO1 to exert robust functions.<sup>97</sup> Therefore, the regulation of Akt by insulin and other bioactive compounds can greatly affect the utilization and metabolism of glucose in the liver. Key genes involved in these processes are discussed in section 3.2.3.2.

**3.2.3.1 Modulation of glucose uptake in insulin-responding organs and tissues.** The modulatory effect of resveratrol on glucose uptake has been illustrated in several studies. In mice with IR, resveratrol treatment successfully restored the insulin-mediated glucose uptake<sup>98</sup> and such an effect may be attributed to the upregulation in the expression of GLUT4.<sup>99</sup> In cells or animals with IR, a reduction in GLUT4 expression was observed yet resveratrol greatly reversed the reduction in the muscles and adipocytes.<sup>98–101</sup> Concordantly, these effects were ascribed to the activation of the Sirt1-pAMPK-pAkt and Sirt1-PIRS-pAkt pathways, which further promote the GLUT4 translocation to the plasma membrane, hence improving insulin sensitivity and promoting glucose uptake in the responding tissues.<sup>49,100</sup> In addition, an elevated level of GLUT2, another major glucose transporter that serves as an important regula-



tor of hepatic glucose output, was reported in the liver of diabetic mice<sup>102,103</sup> or IR mice,<sup>104</sup> yet such a change was restored by resveratrol, which potentially led to a direct reduction in hepatic glucose efflux and an improvement in glycemic control.<sup>103,105</sup>

Similar modulatory effects of the other four selected stilbenes on glucose uptake were also recorded. In insulin-resistant and diabetic rats fed with pterostilbene, the expression of GLUT4 was upregulated due to the elevated phosphorylation of Akt.<sup>106</sup> Research demonstrated that the cytokine cardiotrophin-1 can regulate glucose homeostasis *via* the activation of Akt<sup>107</sup> and increased PPAR- $\gamma$  was potentially involved.<sup>64</sup> In regard to piceatannol, an enhancement in glucose uptake was also reported, possibly through increased phosphorylation of IRS-1 in the insulin signalling pathway,<sup>108</sup> upregulation of Akt and FOXO1 phosphorylation,<sup>109</sup> promotion of GLUT4 translocation *via* AMPK activation<sup>110</sup> and increased hepatic insulin receptors.<sup>111</sup> For oxyresveratrol, increased GLUT 4<sup>112</sup> was observed along with elevated glycogen content in supplemented mice, suggesting the stimulation of hepatic glucose uptake and glycogen storage. Meanwhile, PM extract rich in THSG was shown to enhance insulin signalling *via* the insulin receptor- $\alpha$ /IRS-1/GLUT4 pathway.<sup>113</sup>

**3.2.3.2 Modulation of hepatic glucose metabolism.** Besides glucose deposition after food digestion and absorption, glucose metabolism, consisting of glycolysis, gluconeogenesis and glycogenesis and glycogenolysis, is also important in maintaining glucose homeostasis. Elevated hepatic glucose production, mainly resulting from abnormal gluconeogenesis and glycogenolysis, is a major contributor to long-term hyperglycemia, and several rate-limiting hepatic enzymes including glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) are involved.<sup>52,105</sup> Meanwhile, glucokinase (GK), a key enzyme in both glycogen synthesis and glycolysis, and pyruvate kinase (PK), a rate-limiting enzyme in glycolysis, are both inhibited in diabetic rats. Since hepatic glycogen is one of the main storage forms of glucose in the body, suppressed GK activity will result in reduced glucose utilization. In parallel, decreased PK activity can lead to reduced glucose consumption and metabolism; hence the imbalance between total glucose production (from both dietary uptake and endogenous production) and glucose utilization exacerbates hyperglycemia and compromises glucose homeostasis.<sup>99</sup> A decrease in the activity of these enzymes and the mRNA expression of gluconeogenic coding genes for PEPCK and G6Pase, *pepck1* and *g6pc*, was noticed after resveratrol treatment<sup>52,99,105</sup> whereas a boost in the activity of glycolytic enzymes including GK and PK, which facilitated the utilization and clearance of glucose in the blood, was reported.<sup>99</sup> Therefore, by suppressing hepatic glucose production and promoting glucose consumption, resveratrol effectively reduced the net hepatic glucose output and assisted the regulation of glucose homeostasis.

Such alterations in enzymatic activities were also seen after the administration of other selected stilbenes. Pterostilbene reduced the production of glucose *via* inhibiting the activity of

G6Pase and PEPCK in diabetic rats<sup>62,114</sup> and such effects may be partially attributed to the activation of AMPK and subsequent downregulation of FOXO1 and PGC-1 $\alpha$  based on the result of cell study.<sup>59,115</sup> For both *trans* and *cis*-THSG, significant suppression in the transcription of PEPCK was observed in HepG2 cells, implying their potential use as hypoglycemic agents.<sup>116</sup> Meanwhile, an improvement in glucose utilization was reported after the stilbene supplement. While both pterostilbene and oxyresveratrol increased the activity of glucokinase,<sup>106,117</sup> pterostilbene also markedly promoted the activity of three other glycolytic enzymes, namely hexokinase, glucose-6-phosphate dehydrogenase and fructose-1,6-bisphosphates, in diabetic mice,<sup>62</sup> further increasing glycolysis and the usage of glucose for energy production. For piceatannol and oxyresveratrol, upregulation of PGC-1 $\alpha$  was also recorded.<sup>111,112</sup>

### 3.3 Improvement of gut permeability and modulation of gut microbiota

As previously described, relatively low bioavailability is a common feature of resveratrol and some derivatives, majorly due to poor aqueous solubility and extensive metabolism. Hence, increased attention to stilbenes has been paid to the influence on the gut and the interaction with gut microbiota, as a great part of the stilbenoids is metabolized in the gut.<sup>118</sup> Studies have proposed that resveratrol, pterostilbene, and THSG can alleviate hyperglycemia through protecting the intestinal barrier and modulating gut microbiota, which are detailed below.

**3.3.1 Improvement of gut permeability and related intestinal inflammation.** Loss of gut barrier integrity can facilitate the progression of IR and cause damage in the islets by not only allowing the progressive leakage of antigens, pathogens, and microbial metabolites from the lumen to the blood that further leads to endotoxemia<sup>119,120</sup> and potentially systemic inflammation<sup>121–123</sup> but also triggering the activation of islet-reactive T cells.<sup>124</sup> Therefore, the ability to improve gut permeability and reduce intestinal inflammation should be important targets of hypoglycemic treatment.

Resveratrol and pterostilbene have been shown to enhance barrier functions that were once disrupted by hyperglycemia *via* increasing tight junction proteins (TJPs) and promoting the proliferation of intestinal epithelial cells. TJPs, mainly consisting of occludins, claudins, and zonula occludens (ZO), seal the adjacent intestinal epithelial cells (IECs) with junction adhesion molecules to form a strict defence line. Upon the dysregulation of TJPs, luminal microbes may enter the circulation through passing between the IECs.<sup>121</sup> Reduction of TJP expression was observed in IR mice, yet resveratrol administration partially reversed such changes.<sup>125,126</sup> In line with this, resveratrol can restore the impaired production of TJPs in IECs by improving the activity of SOD, CAT, and GPx *via* the P13K/Akt-mediated Nrf2 signalling pathway and inhibiting the activation of protein kinase C (PKC) and p38 mitogen-activated protein kinase (MAPK) phosphorylation possibly by the upregulation of heme oxygenase-1(HO-1).<sup>127,128</sup> Moreover, a similar





modulatory effect on TJPs was observed in mice with severe intestinal barrier defects, which potentially involved inhibiting the phosphorylation of multiple inflammatory signalling molecules, including NF- $\kappa$ B, stress activated-phosphokinase (SAPK)/JNK and extracellular signal-regulated kinase (ERK) 1/2.<sup>126</sup> These results proved that resveratrol helped to maintain the integrity of the gut barrier under various challenges. Likewise, injection of pterostilbene was reported to alleviate the intestinal damage and inflammation resulting from lipopolysaccharides (LPS) challenge in broiler chickens and this might be attributed to its resistance to oxidative stress.<sup>129</sup> Reduced phosphorylation of p38 MAPK and ERK1/2 was also proposed as the mechanism for attenuating the effect of pterostilbene on the gut barrier.<sup>130</sup> Further experiments are still needed to confirm the involvement of these pathways in the regulation of TJPs by resveratrol and pterostilbene using IR or diabetic animal models.

Regulatory effects of oxyresveratrol on gut permeability were also reported in recent studies, manifesting the enhanced production of TJPs and mucin in Caco-2 cells and goblet cells after exposure to oxyresveratrol or conditioned culture with oxyresveratrol.<sup>131–133</sup> Such effects might be associated with the activation of the PKC and MAPK pathways<sup>132</sup> and the upregulation of trefoil factor 3.<sup>133</sup>

**3.3.2 Modulation of gut microbiota.** The gut microbiota plays a key role in the modulation of the host immune system and the development of organs and host physiology. A large body of evidence demonstrated that the dysbiosis of gut microbiota is associated with the development of hyperglycemia and diabetes, yet most results remain observational without determining a causal relationship between these two.<sup>120,134</sup> A previous study has shown that in contrast to normal mice on an HFD, germ-free mice were protected from IR and gained less weight when fed the same diet, yet this effect was abolished and they developed IR and glucose intolerance after receiving a fecal transplant from conventionally raised mice, indicating that the gut microbiota was closely related to the development of persistent hyperglycemia and related diseases.<sup>135</sup> Recent studies regarding the dietary intervention of selected stilbenes indicated their ability to partially abort microbial changes induced by hyperglycemia and to manipulate the structure of the microbial profile, functional pathways, and metabolome in a way that was different from normal mice.

**3.3.2.1 Stilbenes modulated microbiota composition, metabolome, and functional pathway.** Modulation in the structural profile of the gut microbiota was noticed after supplement of resveratrol in several studies. Compared with obese/diabetic mice, a reduction in the *Firmicutes* to *Bacteroidetes* ratio was observed in normal or hyperglycemic mice that received resveratrol treatment,<sup>136</sup> yet the alteration in specific microbiota varied from one study to another. Detailed changes in microbial structure in each study are listed in Table 4. Generally, the promotion of certain beneficial bacteria by resveratrol has been observed, including *Parabacteroides* and *Alistipes*, which have been found to be negatively correlated with inflammation, IR or obesity, some other short-chain fatty

acid (SCFA)-producing bacteria such as *Ruminococcaceae*, *Blautia*, *Alloprevotella*, and *Odoribacter* and other microbes.<sup>137,138</sup> Generated by microbes in the fermentation of non-digestible carbohydrates, SCFAs are considered as signalling molecules in the crosstalk between the host and the gut microbiota, exerting significant metabolic functions and a crucial impact on intestinal health. They are essential substrates in maintaining the mucosal integrity of the gut and in improving insulin sensitivity by modulating metabolism in the adipose, liver, and muscle tissues.<sup>139</sup> Meanwhile, the suppression of the growth of some other bacteria was observed after resveratrol treatment, such as of *Lachnospiraceae*, *Enterococcus* and *Proteobacteria*,<sup>136,140,141</sup> indicating an improved disease state as such microbes are commonly related to obesity and other metabolic disorders.<sup>142–144</sup> In particular, a bloom of *Proteobacteria* is often viewed as characteristic of diseases like intestinal inflammation and it was positively correlated with the levels of two pro-inflammatory substances, phosphatidylcholines and sphingomyelin, in obese mice with hyperglycemia.<sup>136,140</sup>

A consequentially profound impact brought by the shift in microbial structure is the marked separation of the gut metabolome. Apart from SCFAs, phosphatidylcholines and sphingomyelin mentioned before, some other metabolites also showed a strong correlation with microbial composition. In a recent study, non-targeted metabolomic analysis in faeces has identified a significant increase in the abundance of metabolites involved in amino acid biosynthesis and metabolism after resveratrol treatment, among which 4-hydroxyphenylacetic acid (4-HPA) and 3-hydroxyphenylpropionic acid (3-HPP) appeared to be the gut metabolites of resveratrol that improve lipid metabolism. Consistently, metabolites involved in fatty acid and methane metabolism, which were once elevated in obese mice, were restored to a normal level, including palmitic acid, stearic acid, and cholesterol.<sup>141</sup> In another study, acylcarnitine was proposed to correlate with *Verrucomicrobiota* and *Actinobacteria*.<sup>140</sup>

An alteration in dominant functional pathways was also recorded in a few studies. Sung *et al.* (2017)<sup>140</sup> predicted a shift in dominant pathways from bacterial chemotaxis, flagellum assembly and motility in obese mice to carbohydrates, amino acids, and energy metabolism as well as replication and repair pathways in resveratrol-fed obese mice. However, a significant enrichment of carbohydrate metabolism, along with other new pathways in obese mice and a further reversal by resveratrol treatment, was reported by Wang and colleagues.<sup>141</sup>

Likewise, in pterostilbene-fed obese mice, an alteration in microbial profile was observed from phylum to genus or further species level, yet the description of a pterostilbene-induced change in gut microbiota is rather limited due to the lack of research. A similar reduction in *Firmicutes* to *Bacteroidetes* ratio and a significant increase in *Verrucomicrobia* at the phylum level and *Rikenellaceae* at the family level were observed in obese rats fed with pterostilbene. In particular, certain SCFA-producing bacteria were enriched by pterostilbene treatment, including *Odoribacter splanchnicus*, which has



**Table 4** Changes in microbial structure and related key functions caused by resveratrol, pterostilbene and THSG treatment

Animal experiment	Dose/method/period	Changes of key microbes	Examples of key functions	Reported effects	Ref.
Resveratrol db/db and db/dm mice	10 mg kg <sup>-1</sup> daily for 12 weeks <i>via</i> oral gavage	<i>Firmicutes/Bacteroidetes</i> ↓ <i>Bacteroides</i> , <i>Alistipes</i> , <i>Alloprevotella</i> , <i>Odoribacter</i> , <i>Parabacteroides</i> , <i>Rikenella</i> ↑	NA	Intestinal barrier function↑ Intestinal permeability and inflammation↓ Bacterial richness, α-diversity↑	137
Male db/db mice (FMT)	200 μL microbe suspension <i>via</i> oral gavage for 7 days	<i>Firmicutes</i> , <i>Tenericutes</i> , <i>Deferribacteres</i> ↓ <i>Turicibacter</i> , <i>Alistipes</i> , <i>Odoribacter</i> , <i>Rikenella</i> ↑ <i>Enterococci</i> ↓	NA	Improved renal functions↑ Intestinal characteristics↑  Inflammatory response↓ (IL-6, IL-1β, IFN-γ and TNF-α)↓ Changed microbial structure	137
High-fat diet-fed mice	300 mg kg <sup>-1</sup> daily for 16 weeks <i>via</i> intra-gastric injection***	<i>Firmicutes/Bacteroidetes</i> ↓ <i>Blautia</i> , <i>Parabacteroides</i> , <i>Lachnospiraceae</i> , <i>Lachnospiraceae_NK4A136_group</i> , <i>Ruminiclostridium_9</i> ↑	NA	Insulin sensitivity↑ weight gain↓ Intestinal barrier integrity and function↑ Improvement of intestinal morphology Reduced oxidative stress and inflammation↓	138
High-fat diet-fed mice (FMT)	200 μL microbe suspension <i>via</i> oral gavage for 16 weeks	<i>Bacteroidetes</i> ↑  <i>Proteobacteria</i> ↓  <i>Desulfovibrio</i> , <i>Ruminiclostridium</i> , <i>Anaerotruncus</i> , <i>Oscillibacter</i> ↓ <i>Allobaculum</i> ↑	NA	Insulin sensitivity↑ weight gain↓ Intestinal barrier integrity and function↑ Improvement of intestinal morphology Reduced oxidative stress and inflammation↓	138
High-fat diet-fed mice	300 mg kg <sup>-1</sup> daily <i>via</i> oral gavage for 16 weeks***	<i>Bacteroidetes</i> ↑  <i>Blautia</i> , <i>Lachnospiraceae</i> ↓  <i>Desulfovibrio</i> ↓  <i>Lachnospiraceae_NK4A136_group</i> ↓	CAZy subsystem relating to degradation of dietary plant polysaccharide↑ Gene-encoding products associated with carbohydrate, amino acid and energy metabolism↑ Reversed HFD-induced enrichment in nutrient processing, including phosphotransferase system (PTS), ATP-binding cassette (ABC) transport, methane metabolism, LPS biosynthesis and carbohydrate metabolism Amino acid cofactor and vitamin metabolism↑ Pathway involved in small metabolite generation↑	Body weight↓, insulin resistance↑  mRNA expression of lipogenic gene and thermogenic genes↑  Intestinal ROS level↓	141
High-fat diet-induced mice (FMT)	200 μL microbe suspension daily <i>via</i> oral gavage for 16 weeks	<i>Allobaculum</i> , <i>Bacteroides</i> and <i>Alistipes</i> ↑  <i>Desulfovibrio</i> ↓	Pathway involved in small metabolite generation↑ Promotion in gut metabolite production in amino acid biosynthesis and metabolism such as glycolic acid, tartaric acid, aminomalonic acid and 4-HPP	Fasting glucose; insulin concentration↓ Glucose and insulin tolerance↑ mRNA expression level of lipogenic, fatty acid oxidation and thermogenic genes↑ Intestinal barrier integrity and function↑ Improved glucose homeostasis	141
High fat/high sugar diet-fed mice	0.4% Resveratrol in diet for 8 weeks	<i>Turicibacteraceae</i> , <i>Moryella</i> , <i>Lachnospiraceae</i> , <i>Akkermansia</i> ↓ <i>Bacteroides</i> , <i>Parabacteroides</i> ↑ <i>Firmicutes/Bacteroidetes</i> ↓	Top discriminative microbial pathways include carbohydrate, amino acid and energy metabolism, along with replication and repair pathways	Altered acylcarnitine and phosphatidylcholine metabolism	140
High fat/high sugar diet-fed (FMT)	200 μL microbe suspension <i>via</i> oral gavage at day 1, 3, 5	<i>Allobaculum</i> , <i>Bacteroides</i> and <i>Alistipes</i> ↑ <i>Desulfovibrio</i> ↓	Glycan biosynthesis, genetic information processing, and replication and repair pathways↑	Improve glucose homeostasis without reduction in body weight; alteration in metabolic profile: butyrylcarnitine (C4)↓; (independent of direct supplementation of SCFAs)	140
High-fat diet-fed mice (FMT)	50, 75 and 100 mg kg <sup>-1</sup> <i>via</i> drinking water, 16 weeks	<i>Firmicutes/Bacteroidetes</i> ↓ <i>Enterococcus faecalis</i> ↓  <i>Desulfovibrionaceae</i> ↓ (compared with HFD group)	NA	Reduced blood glucose level Reduced serum triglyceride level, cholesterol and LDL protein Improved antioxidative state and inflammation Increased gut microbiota diversity	136

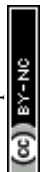


Table 4 (Contd.)

Animal experiment	Dose/method/period	Changes of key microbes	Examples of key functions	Reported effects	Ref.
Pterostilbene Zucker (fa/ fa) rats	15 mg kg <sup>-1</sup> daily <i>via</i> oral gavage for 6 weeks	<i>Firmicutes</i> , <i>Gammaproteobacteria</i> ↓ <i>Verrucomicrobia</i> , <i>Rikenellaceae</i> ↑ <i>Odoribacter</i> , <i>Akkermansia</i> ↑	NA	Improved glucose tolerance and HOMA-IR index; reduction in serum insulin Attenuated adiposity	145
THSG HF-HSD induced IR rats	12 mg kg <sup>-1</sup> daily <i>via</i> oral gavage for 12 weeks	<i>Firmicutes</i> / <i>Bacteroidetes</i> ↓ <i>Parabacteroides</i> ↓ <i>Bacteroides</i> spp.↑ <i>Bifidobacterium</i> spp.↑ <i>Clostridium</i> spp.↓ <i>Desulfovibrio</i> spp.↓ <i>Oscillibacter</i> spp.↓	Amino acid metabolism↑ Energy metabolism↑	Relieved insulin resistance Fasting blood glucose↓ Glucose tolerance↑	146

a strong inverse correlation with body weight and *Akkermansia muciniphila*, which was negatively correlated with adiposity.<sup>145</sup> Depletion of *Gammaproteobacteria* was also reported after pterostilbene treatment.<sup>145</sup>

Changes in gut microbiota after THSG treatment were also observed, although only one report was published using IR rats. Like the other two stilbene compounds mentioned above, dietary intervention with THSG resulted in a reduction in the *Firmicutes* to *Bacteroidetes* ratio. It also significantly elevated the abundance of some beneficial bacteria such as *Bacteroides* spp. and *Bifidobacterium* spp. while reducing the levels of *Clostridium* spp., *Desulfovibrio* spp., and *Oscillibacter* spp. In addition, KEGG metabolic pathway analysis reported that under IR conditions, the pathway related to amino acid metabolism was downregulated. This was reversed by THSG, concomitantly with the upregulation of genes in the energy metabolism pathway.<sup>146</sup>

**3.3.2.2 Hypoglycemic effect of stilbenes was partially mediated through gut microbiota.** Although alterations in bacterial profile were observed after treatment with stilbenoid compounds, it remains to be clarified whether the hypoglycemic effects exhibited by these compounds depends on the selectively altered microbiota. While the exact mechanisms linking microbes to hyperglycemia and related diseases need further exploration, these changes in microbial composition are believed to cause corresponding functional changes and convey the benefits of dietary supplementation *via* multiple mechanisms, which can be proved by conducting fecal microbial transplantation (FMT).<sup>120</sup>

Transplantation of gut microbiome from resveratrol-fed donor mice to diet-induced obese or diabetic mice was able to reproduce multiple modulatory effects once seen in mice directly given resveratrol treatments, including improved glucose homeostasis, insulin sensitivity, intestinal permeability, as well as systemic inflammation and oxidative stress.<sup>137,138,140,141</sup> Microbiota collected from resveratrol-fed donor mice was suggested to exert benefits on recipient mice through two aspects. One was to protect the gut barrier in the recipients *via* the reduction in proinflammatory cytokines, ROS and malondialdehyde (MDA), enhancement in SOD and total antioxidant capacity, as well as upregulation of TJPs and major

mucin genes and related transcription factors resistin-like molecule  $\beta$  and regenerating islet-derived protein 3 gamma (Reg3 $\gamma$ ).<sup>138</sup> The increased expression of mucins, along with antimicrobial peptide Reg3 $\gamma$ , which can influence the structure of the microbial community and promote spatial segregation in the outer mucus layer,<sup>147</sup> are believed to reinforce the whole mucus barrier covering the luminal surface of the epithelial cells and prevent the colonization of the epithelium by gut microbiota and potential pathogens. Another aspect was that the FMT process altered the microbial structure in recipient mice to a certain extent, which is consistent with resveratrol-fed donor mice. For instance, an increased *Bacteroidetes* to *Firmicutes* ratio and some SCFA-producing bacteria were also observed in mice that received FMT.<sup>137,140</sup> In general, these results indicated that changes in the microbiota at least partially mediated the overall benefits brought about by the administration of resveratrol. However, to determine whether the direct impact of resveratrol on the intestinal environment outweighs the effect mediated by microbes, future experiments applying germ-free mice or antibiotic treatment will be needed.

### 3.4 Improvement of the circadian clock

To adapt to the cyclic environment, notably the natural light-dark cycle and fluctuation of the temperature, organisms have evolved a circadian rhythm to align biological processes including metabolism, energy expenditure and food intake to external changes. The synchronization of the endogenous timing system in both the central circadian and peripheral circadian rhythm is fundamental for proper and robust homeostasis within the body and the misalignment of such a system may negatively impact the overall health condition. The impact of circadian rhythm on wellness was previously reviewed by others.<sup>148</sup> In brief, the crosstalk between the circadian clock and metabolism is achieved through a transcriptional-translational feedback loop consisting of several clock genes, such as circadian locomotor output cycles kaput protein (CLOCK), brain and muscle arnt-like protein-1 (BMAL1), period proteins (PERs) and cryptochromes (CRY). The heterodimer of BMAL1 and CLOCK activates the transcription of many downstream genes including *Per* and *Cry*, the accumulation of which would



result in new dimer formation and in turn give negative feedback. Together with other loops, rhythmic oscillations in gene expression are formed.

Currently, limited research and data are available to reveal the underlying molecular mechanisms associating circadian rhythm and hyperglycemia, yet many observational studies supported this theory. For instance, consuming a greater share of total calories early in the day improved insulin resistance compared with a longer feeding period.<sup>149</sup> It was also demonstrated that from the *meta*-analysis of observational studies, people with shift work had a 9% higher risk of diabetes when compared with people without shift work.<sup>150,151</sup> Furthermore, the risk of diabetes for people with rotating shifts is even higher than in ones with fixed shifts.<sup>152</sup> Since circadian rhythms were observed for many components involved in the action of insulin,<sup>148</sup> it is not surprising that circadian misalignment or disruption by interfering behavioural cycles or external cues can result in the decrease of insulin sensitivity and further IR.<sup>149</sup> However, treatment with resveratrol was shown to elevate insulin level or attenuate IR by improving disturbed circadian rhythms in mice exposed to various interferences,<sup>153</sup> in human skeletal muscle,<sup>154</sup> in FFA-treated HepG2 cells<sup>155</sup> and in HFD treated-mice.<sup>156–158</sup> These processes may involve the activation of Sirt1, which is also an important downstream circadian regulator in insulin signaling, secondly, the recovery of bidirectional communication between inner-mitochondrial genes and rhythmic gene expression<sup>154</sup> and lastly, the modulation of glucose and lipid metabolism *via* regulating BMAL1-dependent phosphorylation of acetyl-CoA carboxylase, AMPK, AKT and IRS-1.<sup>155</sup>

Similar regulatory effects on circadian rhythm were also observed after treatments with pterostilbene and oxyresveratrol. Pterostilbene has been shown to decrease fasting blood glucose and ameliorate circadian misalignment in sleep-restricted mice *via* restoring the rhythm of AMPK phosphorylation activity, Sirt1 and PGC-1 $\alpha$  deacetylation activity, which in turn interact with clock genes.<sup>159</sup> Moreover, pterostilbene managed to prevent increased food intake and weight gain as well as produce a recomposition of gut microbial profiles in mice with circadian rhythm dysregulation.<sup>160</sup> Likewise, in PER::LUC mice with a high fat diet, a significant delay in the phase change of PER2 had been observed and the administration of oxyresveratrol successfully advanced the rhythm, thus potentially preventing circadian disturbance.<sup>161</sup> Hence, since circadian rhythms are closely interrelated with overall metabolism, the effects of stilbenes against circadian dysregulation highlight their potential as precautionary therapeutics, especially under various disruptions stemming from changes in modern lifestyle.

#### 4. Human studies of resveratrol and related stilbenes in managing diabetes and its complications

According to the review published by Zhu *et al.* in 2017,<sup>162</sup> a systemic review and *meta*-analysis of data from 9 previous clinical

trials showed that resveratrol significantly improved the fasting plasma glucose and insulin level, as well as HOMA-IR index while showing no significant effect on low or high-density cholesterol. The author also pointed out that resveratrol treatment >100 mg day<sup>-1</sup> revealed a significant difference in fasting plasma glucose. To further investigate the effect of resveratrol, clinical trials of resveratrol on diabetes and some diabetic complications published mainly in the past 5 years were reviewed here. In total, 7 clinical trials are found. The majority of them are randomized, double-blind and placebo-controlled trials. Among these trials, except one study that reported no measurable effects of resveratrol in T2DM patients<sup>163</sup> and another study that only reported changes in oxidative stress markers,<sup>164</sup> all other studies recorded positive results upon resveratrol administration, showing that resveratrol alone, or together with another anti-diabetic drug, can improve insulin resistance, increase antioxidant capacity, and reduce the levels of insulin, proinflammatory cytokines and blood glucose.<sup>165–169</sup> Variation in the modulation of biomarkers may be observed in different trials and to better compare the method, duration, dosage and outcome among trials, related information is listed in Table 5. In general, the number of participants ranges from 13–112 people, with the dosage varying from 100 mg day<sup>-1</sup> to 1000 mg day<sup>-1</sup> for a duration of 1–6 months. In most studies, a dosage of 500 mg day<sup>-1</sup> was applied, and no major adverse reactions were reported. In particular, resveratrol administration significantly contributed to the reduction in urinary albumin excretion when patients with diabetic nephropathy were cotreated with the drug losartan, thus proving the potential usage of resveratrol as an effective adjunct for certain medicines.<sup>137</sup>

In a few most recent clinical studies, some molecular alterations after resveratrol treatment were also explored. For instance, regulations in several micro RNAs, including micro RNA-34a which is a tumor suppressor, micro RNA-375 which regulates  $\beta$  cell development and function, and micro RNA-21 which regulates apoptosis and inflammation, among others, were observed.<sup>165</sup> Also, the upregulation of Nrf2 was noticed.<sup>164</sup>

For other stilbenes, limited clinical trials were found, especially on hyperglycemia and diabetes. In a clinical study, patients with hypercholesterolemia were given 125 mg pterostilbene twice a day for 52 days and no adverse drug side effects on hepatic, renal and blood glucose markers were reported, proving that pterostilbene is safe for use at a dosage of 250 mg day<sup>-1</sup>.<sup>170</sup> Another clinical trial has revealed the effect of pterostilbene in reducing blood pressure also at 250 mg day<sup>-1</sup>.<sup>171</sup> For oxyresveratrol, no clinical study was found using the pure compound but two human studies with the administration of leaf extract of mulberry (in which oxyresveratrol is commonly present) reported significantly decreased postprandial plasma glucose levels and lower insulin levels compared with the control group within 120 min.<sup>172,173</sup> In one of the studies, the intake of 3.3 g mulberry leaf extract per day successfully reduced the postprandial glucose from 209 mg dL<sup>-1</sup> to 148 mg/mg dL<sup>-1</sup> in the patients' group and from 125 mg dL<sup>-1</sup> to 97 mg dL<sup>-1</sup> in healthy people.<sup>172</sup>





**Table 5** Clinicals trials of effects of resveratrol on T2DM and related complications

Number of participants	Dose/method period	Anti-diabetic function	Involvement of mechanisms	Ref.
Resveratrol N = 110	200 mg; daily basis; oral administration; 6 months	Fasting blood glucose↓ Insulin level↓	Downregulation of micro RNA 34a, 375, 21 and 196 Upregulation of micro RNA 126 and 132	165
Double-blind, randomized, placebo-controlled N = 48	800 mg; daily basis; oral administration; 2 months	Insulin resistance↓ No significant changes in plasma glucose, insulin and HOMA-IR compared with control	Inflammatory cytokines↓ Increased plasma total antioxidant capacity Increased Nrf2 and SOD expression	164
Double-blind, randomized, placebo-controlled N = 13	500 mg twice daily; oral administration; 2 months	Significantly decreased in fasting blood glucose at 2 months but not 1 month No significant differences in insulin level and HOMA-IR	Increased plasma total antioxidant capacity Decreased MDA	166
Exploratory clinical trials (type: N/A) N = 60	500 mg, daily basis; oral administration; 3 months Cotreatment with losartan	Reduced urinary albumin excretion in diabetic nephropathy	N/A	167
Double-blind, randomized, placebo-controlled N = 192	40, 500, daily basis; oral administration; 6 months	No significant differences in all measured markers	N/A	163
Double-blind, randomized, placebo-controlled N = 472	500 mg, daily basis; oral administration 6 months	Improved glucose metabolism and insulin tolerance	Inflammatory cytokines↓	168
Single-blind, randomized, controlled N = 56	500 mg, daily basis, oral administration 1 month	Fasting blood glucose↓	Increased total antioxidant capacity Activation of PPAR-γ and Sirt1	169
Double-blind, randomized, placebo-controlled		Insulin sensitivity↓ Insulin resistance↓		

## 5. Conclusion

Over the past several decades, dietary intervention with natural bioactive compounds from plants has gained broad interest and was intensely investigated as an alternative approach to prevent and treat hyperglycemia, obesity, diabetes, and other metabolic complications. One type of representative compound is stilbenes, which include the most studied resveratrol and others that are less noticed, such as pterostilbene, THSG, piceatannol, and oxyresveratrol. A line of cell and animal studies has illustrated the potential hypoglycemic effect of these five stilbenes and their ability to improve IR. Both resveratrol and pterostilbene have been shown to exert bioactivity *via* multiple mechanisms, including reducing food intake, inhibiting nutrition absorption, regulation of glucose homeostasis by improving IR, insulin production, and downstream signalling targets, enhancing gut permeability and modulating gut microbiota, and ameliorating disruptions in circadian rhythm. To further confirm the effect of stilbenes on reducing food intake and inhibiting nutrition absorption, an *in vivo* study applying a diabetic mouse model should be conducted with detailed changes of biomarkers of satiety being recorded. Also, attention should be paid to future studies on the molecular mechanisms explaining the correlation between hyperglycemia and disrupted circadian rhythm, and consequently the future studies on the influence of stilbenes on these molecular

mechanisms. In addition, research regarding the changes in microbiota structure brought about by stilbene administration and their impacts on the amelioration of symptoms has emerged in the last decade. However, the underlying mechanisms through which gut microbiota exhibit their benefits, and the importance of their existence remains obscure. Meanwhile, due to the influence caused by the environment, the resulting changes in specific microbial species in each report can vary dramatically and limit their value as reference standards. Therefore, future experiments using germ-free mice will be necessary and investigation should be extended to the level of single species or strains. Moreover, as the development of delivery systems can greatly improve the bioavailability of resveratrol and its derived stilbenes, more studies can be performed to construct an ideal system and investigate their potential application in the improvement and prevention of hyperglycemia-related diseases.

Of note, even though some research has also been conducted for THSG, piceatannol, and oxyresveratrol to explore and confirm these related hypoglycemic mechanisms, data are quite limited due to a dearth of reports. Therefore, further detailed investigations on these three stilbenes are warranted. Moreover, comparative studies applying multiple stilbenes would give more straightforward results when trying to select the stilbene with better hypoglycemic effects. A comprehensive measurement of related parameters, including all the aspects



mentioned in this review, for both the liver, intestine, muscles and pancreas, will further contribute to a solid comparative study. Another important aspect is that dosage and duration should be carefully considered in the experimental design. While the applied dosage and duration of most animal studies were below the highest dosage and time applied in the human clinical trials (no obvious side effects are observed), some studies use much higher dosages for a long time. Therefore, the potential toxicity of such high dosages of stilbene should be verified for better results. Also, currently, there are no available clinical trials except for resveratrol and pterostilbene, with the latter only establishing a safety use limit up to 250 mg day<sup>-1</sup>. Therefore, more animal studies or clinical trials should be conducted to explore and establish the highest dosage and proper duration for future studies.

## Author contributions

Jie Peng: conceptualization, writing – original draft, review & editing; Chenyang Lu: conceptualization, writing – review & editing; Yue Luo: investigation, writing – review & editing. Xiurong Su: supervision, funding acquisition. Chi-tang Ho: supervision, writing – review & editing. Shiming Li: conceptualization, supervision, writing – review & editing.

## Conflicts of interest

The authors declare no conflicts of interest.

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