Bioactive Flavonoids from Citrus Fruit Peels

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Obesity is associated with a significantly increased risk of cardiovascular and metabolic diseases such as diabetes mellitus. A growing body of evidence shows that phytochemicals, especially many flavonoids, place an inhibitory regulatory effect on adipogenesis, obesity and diabetes. With computer-aided drug discovery, the action modes of more and more bioactive flavonoids are being identified and confirmed at the molecular level. Citrus fruit peels are particularly rich in bioactive flavonoids which have demonstrated strong therapeutic potentials in regulating lipid metabolisms.

flavonoid citrus fruit fruit waste obesity diabetes

1. Introduction

Over the past three decades, Obesity prevalence has doubled globally, leading to a dramatic increase in associated diseases including type 2 diabetes mellitus, nonalcoholic fatty liver disease, cancer, and cardiovascular diseases [1][2][3]. Pathophysiologically, obesity is characterized by increased mass of adipose tissue. Besides storing energy in the format of fat, adipose tissue also functions as a major endocrine organ which secrets adipokines, cytokines, and hormones, affecting inflammation, insulin sensitivity and bioenergetic homeostasis [3]. As such, dysfunction of adipose tissue plays an essential role in obesity and related metabolic syndrome [3][4]. Enhanced adipogenesis, derived from excessive accumulation of triglycerides (TGs) in adipocytes, is the essential process which leads to obesity [3]. During adipogenesis, adipocyte differentiation is the determining step which is characterized by a series of morphological and biochemical transition of confluent preadipocytes [5]. After terminal differentiation, a well-controlled stimulation of lipid mechanism-related genes will be enhanced [5]. Several key transcriptional factors dominate this process, including CCAAT/enhancer-binding proteins (C/EBPs), peroxisome proliferator activated receptors (PPARs), and sterol regulatory element-binding proteins (SREBPs) [6][7]. Insulin-like growth factor-1 (IGF-1) signaling and adenosine monophosphate-activated protein kinase (AMPK) signaling are also well-acknowledged to be key influencers involved in adipocyte differentiation and energy homeostasis [8][9].

Among obese population, overt diabetes cases are considerably less than cases diagnosed as prediabetes, an intermediate state before developing into diabetes which is also characterized by fasting hyperglycemia, inflammation and elevated oxidative stress [4][10]. Insulin resistance (IR), a deteriorated phenotype in blood glucose control, is well acknowledged as a classical feature of prediabetes [4][10]. An increase in liver fat has recently been proved to be associated with elevated fasting plasma glucose and insulin levels, as well as impaired glucose tolerance [3][11]. Thus, fatty liver is another key factor predisposing obese people to the development of insulin resistance. Emerging evidence also suggest that macrophages infiltration into adipose tissue and consequent

metabolic inflammation are the key contributors to the pathogenesis of obesity-associated insulin resistance and metabolic disorders [3][12]. Chronic insulin resistance, combined with a deteriorated β-cell function, leads to the elevated blood glucose level and subsequently, full-blown diabetes [4][10].

Recently, a growing body of evidence shows that phytochemicals, especially flavonoids from a variety of fruits such as cherries and grapes, were potent in suppressing adipogenesis and development of obesity and diabetes [13][14][15]. The previous studies showed that peel from *Averrhoa carambola* L., commonly known as star fruit, is rich in polyphenols such as (-)epicatechin and proanthocyanidins. Extracts from star fruit peel exhibits antiobesity potential by repressing adipocyte differentiation, which was likely mediated via downregulation of PPARγ and C/EBPα expressions as well as upregulation of PPARα expression [16]. Interestingly, the peels of fresh and dried citrus fruits are also rich sources of bioactive compounds such as flavonoids, terpenes and coumarins [17][18][19]. Among them, flavonoids are of particular interest, as on one hand, they are the major constituents of polyphenols in citrus fruits [20][21]; on the other hand, they have been linked to a reduced risk of various chronic diseases due to their potent antioxidant and anti-inflammatory properties [13][15][20].

Citrus flavonoids such as hesperidin and naringin have exhibited impressive capacities in regulating lipid synthesis, storage and utilization both in vitro and in vivo [11][19][22][23][24][25][26][27][28]. Oral administration of neohesperidin at a dose of 50 mg/day/kg body weight for 12 weeks attenuated the body weight gain by 15.01% in HFD-fed obese mice [29]. Similarly, treatment of diosmetin at a dose of 50 mg/day/kg body weight for 8 weeks reduced the bodyweight gain by 17.95% in HFD-fed obese mice [30]. Emerging evidence also suggest that citrus flavonoids process therapeutic effects on obesity and diabetes-associated pathological conditions in humans [31][32][33]. Impressively, in Japanese individuals prone to developing diabetes, a daily consumption of sudachi peel extract power which contains 4.9 mg sudachitin for 12 weeks significantly reduced the ratio of visceral fat to subcutaneous fat by around 3.6%, compared with the placebo group [33]. Waist circumference, another metabolic syndrome marker, was also moderately reduced by around 4% [33]. Recently, researchers have also employed machine learning methods such as virtual screening to study flavonoids in greater detail as well as identify and design novel compounds with potential therapeutic utility [34][35]

However, in the routine practice of the juice and fruit processing industry, the peels of fresh citrus fruits and relevant byproducts are usually thrown away after consuming the flesh [13][20][21][36][37]. Rapid growth of industrial waste from citrus fruits even causes some environmental problems [13][20][21][36][37]. Thus, proper revaluation and recycling of citrus fruit waste adapting the concept of circular economy should be developed to minimize waste and promote the continual use of resources through the creation of closed-loop systems [20][21][37]. Extraction of useful phytochemicals from citrus fruit peels for the development of novel pharmaceuticals offers such a sustainable solution, as it could not only reduce the amount of landfill waste and subsequent emissions of greenhouse gas, but also have the potential to create new revenue streams and reduce the demand for virgin resources [20][21][37].

2. Bioactive Flavonoids from Citrus Fruit Peels

2.1. Flavanones

2.1.1. Didymin

To evaluate the antidiabetic potential of didymin, a bioactive flavonoid glycoside found in various citrus fruits, Ali et al., first employed a series of cell-free enzymatic inhibitory assays and they discovered that didymin was a potent inhibitor of α-glucosidase, PTP1B, rat lens and human recombinant aldose reductase, which was further supported by the molecular docking analysis [38]. Treatment of didymin in insulin-resistant HepG2 cells also led to downregulation of PTP1B and enhanced glucose uptake. This improved insulin sensitivity was mediated via activation of IRS-1, PI3K, Akt, and GSK-3 via enhanced phosphorylations while downregulation of key enzymes involved in gluconeogenesis such as PEPCK and G6Pase [38].

2.1.2. Eriocitrin (Eriomin)

Eriocitrin (Eriomin) is an abundant flavanone in the peels of various citrus fruits including *C. latifolia*, *C. limon*, *C. grandis* cv Hirado, and *C. leiocarpa* [17][39]. Using HFD-fed and HCD-fed obese rats, Miyake et al. have proved the strong lipid-lowering effects of eriocitrin [39]. Using HepG2 cells and a diet-induced obese zebrafish model, Hiramitsu et al. further demonstrated that eriocitrin could ameliorate dyslipidemia and hepatic steatosis via upregulating PPARα, NRF1, ATP5J, and COX4I1, thus activating mitochondrial biogenesis [39]. The antiobesity potential of Eriocitrin was further confirmed in HFD-fed obese mice [40][41]. Kwon et al. discovered that dietary eriocitrin reduced adipose tissue mass and hepatic steatosis via decreasing lipogenesis and increasing FA oxidation in adipose tissue and liver respectively, as well as enhancing energy expenditure in adipose tissue and skeletal muscle [40]. Furthermore, insulin sensitivity was improved by eriocitrin as a result of reduced gluconeogenesis and proinflammatory responses in the liver [40]. Ferreira et al. also found that eriocitrin supplementation at 25 mg/kg body weight for 4 weeks could significantly enhance insulin sensitivity and reduce hepatic TG accumulation which were associated with the inhibitory effect of eriocitrin on oxidative stress and systemic inflammation [41].

Of note, Cesar et al. recently showed that in a randomized crossover clinical study, a 200 mg/day eriomin administration for 12 weeks was able to reduce hyperglycemia and improve diabetes-related parameters in patients with hyperglycemia above 110 mg/dL via its anti-inflammatory effect and upregulation of GLP-1, indicating the therapeutic potential of eriomin for the glycemic control in prediabetic and diabetic populations [42].

2.1.3. Hesperidin

Hesperidin is a flavonoid commonly found in citrus fruits, with especial high amount in the peels of *C. tangerine*, *C. succosa*, *C.suhuiensis*, and *C. kinokuni* [17]. In 3T3-L1 cells, hesperidin has shown potent inhibitory effects on adipogenesis and free fatty acid (FFA) secretion derived from adipocyte lipolysis, repressing FFA-induced IR [43]. This is executed through inhibition of tumor necrosis factor-alpha (TNF- α) stimulated NF-κB and ERK pathways, as well as downregulation of antilipolytic genes including perilipin and PDE3B [43]. In HepG2 cells, hesperidin efficiently blocks pancreatic lipase (PL) activity via interacting with PL by hydrogen bonds and van der Waals forces, showing therapeutic potential in managing obesity [44]. Rajan et al. further showed in palmitate (PA)-treated HepG2 cells, besides reducing TG content, hesperidin increased glucose uptake in an insulin-independent manner

[45]. Further elucidation of the molecular mechanism revealed that hesperidin activated AMPK signaling, increasing phosphorylation of acetyl-CoA carboxylase (ACC) and glycogen synthase kinase 3 beta (GSK3β) while decreasing expression of HMG-CoA reductase (HMGCR) and SREBP-2 [45]. In primary bovine aortic endothelial cells, hesperidin and its metabolite hesperetin improved endothelial function via stimulation of NO production and reduction of inflammation [31].

Interestingly, in high fat diet (HFD)-fed LDLr(-/-) mice, hesperidin also exerted protective effect against atherosclerosis via pleiotropic effects such as antioxidative and anti-inflammatory effects, improvement of insulin sensitivity, reduction of hyperlipidemia and hepatic steatosis, and blockage of macrophage foam cell formation [46]. Similarly, in obesogenic cafeteria diet (CAF)-fed obese rat, hesperidin supplementation also showed therapeutic potential against metabolic syndrome via improving insulin sensitivity and lowering cholesterol, FFA and inflammation levels [47]. Hesperidin also showed significant antidiabetic effect in nicotinamide/streptozotocin (NA/STZ)-induced diabetic rats via remarkable improvements in the insulin sensitivity and antioxidant defense system [25].

Salden et al. found that in obese individuals with a flow-mediated dilation ≥ 3%, supplementation of hesperidin 2S at 450 mg/day for 6 weeks could significantly improve endothelial function and blood pressures via reduction of soluble vascular adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1) [32].

Yet, hesperidin has relatively lower water solubility and thus poor oral bioavailability, so the scientific community have tried to modify hesperidin to α-monoglucosyl hesperidin using cyclodextrin glucanotransferase [48]. Nishikawa et al. discovered that compared with hesperidin, α-monoglucosyl hesperidin is more potent in inducing brown-like adipocyte formation and thus suppressing white adipose tissue accumulation in mice [48]. Yoshida et al. also found that although not improving the insulin sensitivity, α-monoglucosyl hesperidin did ameliorate hyperglycemia and macrophage infiltration into the adipose tissue in HFD-fed obese mice [49]. Moreover, hesperetin, the metabolite of hesperidin and an aglycone of α-monoglucosyl hesperidin, efficiently block the monocyte chemotactic protein 1 (MCP-1) expression when 3T3-L1 adipocytes cultured alone or cocultured with RAW264 macrophages [49].

2.1.4. Naringenin

Naringenin is a well-studied bioactive flavonoid extracted from citrus fruit peels. Using 3T3-L1 and coculture of 3T3-L1 and RAW264 macrophages, Yoshida et al. and Tsuhako et al. found that naringenin could be a potent antiobesity nutritional supplement due to its efficient inhibitory effects on adipogenesis and adipose tissue inflammation [12][43][50][51]. Detailed examination revealed that naringenin, besides suppressing TNF-α-stimulated FFA secretion, blocked toll-like receptor 2 (TLR2) expression during adipocyte differentiation in 3T3-L1 which is partially executed via activation of PPARγ [43][51]. Naringenin was discovered to be an activator of PPARα and PPARγ while an inhibitor of LXRα [52]. Later it was also found that naringenin reduced adiponectin protein expression and dose-dependently inhibited insulin-stimulated glucose uptake via suppressing tyrosine phosphorylation of IRS-1 [53]. Furthermore, in 3T3-L1 and macrophages coculture, naringenin suppressed TNF-α-induced TLR2 expression via attenuating activation of NF-κB and JNK pathways in differentiated adipocytes [51].

Noticeably, MCP-1 and MCP-3 expression were also consistently downregulated in adipocytes, macrophages, and a co-culture of adipocytes and macrophages [12][50]. These effects were also observed in HFD-fed obese mice and were correlated with amelioration of hyperglycemia and adipose tissue inflammation, especially, macrophage and neutrophil infiltration into adipose tissue [12][50][51]. Using human white adipocyte cultures (hADSC), Rebello et al. found that naringenin enhanced energy expenditure, and upregulated key genes involved in thermogenesis and insulin sensitivity including UCP1, PGC1α, ChREBP, and GLUT4 [54]. In human umbilical vein endothelial cells (HUVECs), Zhang et al. also discovered naringenin ameliorated high glucose-induced endothelial dysfunction via upregulating the protein level of intracellular heat shock protein 70 (iHSP70) [55].

With HFD-fed LDLr(-/-) mice, Mulvihill et al. and Burke et al. investigated the therapeutic effect of naringenin on obesity associated metabolic dysfunctions [56][57][58][59]. Naringenin supplementation to a HFD was able to reverse obesity via increased energy expenditure and hepatic fatty acid (FA) oxidation, which was accompanied by an amelioration of dyslipidemia, a reduction of inflammation and improvements in insulin sensitivity [56][57][58][59]. Elucidation of the relevant molecular mechanism revealed that naringenin stimulated PPARα-mediated transcription while downregulated SREBP-1-mediated lipogenesis both in liver and muscles [60]. Although in these mice, atherosclerotic lesions were unchanged in size, they displayed a much less macrophage content and a more stable plaque phenotype [56]. Besides this atheroprotection effect, naringenin also displayed the ability to promote atherosclerosis regression [61]. Using HFD-fed Fgf21(-/-) mice, Assini et al. found that naringenin ameliorated hyperinsulinemia and impaired glucose tolerance, partially through induction of PGC1α [62]. Ahmed et al. further discovered that in NA/STZ-induced diabetic rats, naringenin treatment potently reversed diabetic symptoms via its insulinotropic effects and insulin improving action which is partially mediated through modulating insulin receptor, GLUT4 and adiponectin expression in adipose tissue [63].

Using HFD-fed obese ovariectomized mice, Ke et al. discovered that naringenin administration placed beneficial effects on metabolic health and tumorigenesis of obesity-related postmenopausal breast cancer via activation of AMPK signaling and induction of cell death in tumor cells [64]. Similarly, Snoke et al. also found that in a colon-26 cancer cachexia mouse model, naringenin administration improved insulin sensitivity while suppressed inflammation and adenocarcinoma growth [65].

2.1.5. Naringin

Naringin is also commonly found in the peels of various citrus fruits including *C. aurantium*, *C. natsudaidai*, *C. paradise*, and *C. grandis* cv. Hirado [17]. Although also displayed strong anti-inflammatory and antioxidant activities, naringin is less studied compared with its aglycone naringenin and its effect on obesity and associated metabolic disorders remains to be fully elucidated.

In a rat model of diabetes, Ahmed et al. found that similar to naringenin, naringin also stimulated adipose tissue expression of insulin receptor β-subunit, GLUT4 and adiponectin which partially explains its alleviation effects on the content of serum insulin, C-peptide, and liver glycogen content [63]. Using an in vitro cardiomyoblast model of diabetes, Chen et al. also demonstrated the protective potential of naringin on diabetes-associated cardiomyocyte

injury [66]. In H9C2 cells, naringin attenuated high glucose-induced apoptosis by inhibiting excessive ROS production, the dissipation of mitochondrial membrane potential, and the activation of the p38 MAPK signaling induced by leptin [66].

2.1.6. Narirutin

Abundant in the peels of *C. shunkokan*, *C. sulcata*, *C. nobilis* var Knep, and *C. leiocarpa* [17], narirutin is another flavone glycoside which shows potent capacities in suppressing adipogenesis and intracellular triglyceride accumulation. Rajan et al. recently found that in insulin resistant HepG2 cells, narirutin enhanced glucose uptake in an insulin-independent manner mainly through activation of the AMPK pathway [45]. Molecular docking analysis revealed that narirutin might activate AMPK by binding to the CBS domains in the regulatory gamma-subunit of AMPK. Activation of AMPK leads to enhanced phosphorylation of metabolic enzyme ACC and GSK3β as well as decreased expression of HMGCR and SREBP-2, resulting in enhanced fatty acid oxidation and reduced lipid biosynthesis [45].

2.1.7. Neohesperidin

Neohesperidin is a flavonoid enriched in the peels of *C. aurantium*, *C. bergamia*, *C.glaberrima*, *C. hassaku*, and *C. changshanensis* [17][67]. Using HepG2 cells, Zhang et al. found that neohesperidin dramatically increased glucose uptake and this was associated with activation of AMPK signaling [67]. In vivo studies also showed that, similar to hesperidin, neohesperidin exhibited impressive potency in suppressing intracellular triglyceride accumulation and improving insulin sensitivity [29][68]. In HFD-fed obese mice, neohesperidin administration attenuated gain of body weight, inflammation and insulin resistance [29]. This was associated with an improved diversity of gut microbiota and the modified abundance of bacteroidetes and firmicutes, indicating the potential of flavonoid-induced gut microbiota therapy against obesity [29]. Using diabetic KK-A(y) mice, Jia et al. discovered that the antidiabetic potential of neohesperidin was associated with hepatic activation of the AMPK pathway and the subsequent regulation of its target genes including stearoyl-CoA desaturase 1 (SCD-1), fatty acid synthase (FAS), and acyl-CoA oxidase (ACOX) [68].

2.2. Flavones

2.2.1. Diosmetin

Diosmetin, a monomethoxyflavone, is naturally present abundantly in the peels of citrus fruits such as *C. medica* var. 2 and *C. suhuiensis* [69][70]. Xie et al. discovered that in 3T3-L1 cells, normal diet–fed ob/ob mice and in HFD-fed obese mice, diosmetin functioned as an agonist for estrogen receptors (ERs) which subsequently provoked energy expenditure via stimulation of thermogenesis in brown adipose tissue (BAT) and acceleration of white adipose tissue (WAT) browning [30]. Diosmetin-induced upregulation of ERs in matured adipocytes and in mice adipose tissue was indispensable for the observed metabolic benefits that diosmetin placed in obese mice, as ER blockage by the antagonist fulvestrant abolished the metabolic benefits including reduction of weight gain and fat mass as well as improved insulin sensitivity [30]. Using 3T3-L1 and RAW264 macrophages coculture, Lee et al.

found that diosmetin also displayed strong anti-inflammatory and antilipolytic activities [70]. These activities were mediated via downregulation of iNOS and inhibition of MAPK phosphorylation and nucleus translocation in macrophages and adipocytes which lead to suppression of inflammatory mediators such as NO, TNF-α, and MCP [70]. As such, diosmetin-rich dietary therapy may be suitable for the management of obesity-related metabolic syndromes.

Interesting, in HFD-fed SD rats, Meephat et al. further discovered that diosmetin efficiently prevent metabolic syndrome and associated cardiac abnormalities in these insulin resistant rats as diosmetin treatment improved insulin sensitivity, restored ejection faction, and decreased left ventricular hypertrophy and fibrosis [69]. Detail investigation indicates that suppression of the Ang II/AT1 receptor/NF-κB pathway was underlying these rescue effects of diosmetin [69].

2.2.2. Diosmin

Jain et al. found that diosmin, a flavone enriched in the peels of *C. montana*, *C. latifolia*, *C. lumia*, and *C. kinokuni*, was able to suspend the progression of early diabetic neuropathy in a rat model of HFD/STZ-induced type 2 diabetes [17][71]. After successful induction of diabetes as evidenced by insulin resistance and dramatically elevated blood glucose, 4 weeks of diosmin supplementation dose-dependently improved thermal hyperalgesia, cold allodynia and walking function in vivo [71]. This was associated with normalized malondialdehyde, and nitric oxide as well as restored glutathione levels and superoxide dismutase activity of diabetic mice [71].

2.2.3. Nobiletin

Nobiletin is a well-studied polymethoxylated flavone (PMF) which is extensively found in the peels of various citrus fruits [17][72]. Nobiletin has been shown to suppress adipogenesis and obesity in various in vitro and in vivo models [45]. In 3T3-L1 cells, Miyata et al. found that besides inducing adipocyte apoptosis, nobiletin increased the secretion of adiponectin while decreased the secretion of MCP-1 and resistin, thus improving the insulin sensitivity [73]. Apart from downregulating PPARγ2, Kanda et al. found that nobiletin suppressed adipogenesis via reducing the phosphorylation of CREB while enhancing the phosphorylation of STAT5 [74]. Lone et al. further demonstrated that nobiletin exerted dual modulatory effects on 3T3-L1 preadipocytes, on one hand, nobiletin reduced intracellular stress and key transcription factors involved in lipid metabolism; on the other hand, it accelerated browning in 3T3-L1 white adipocytes via induction of multiple beige-specific genes [75]. Using HepG2 and Ampkβ1-/- primary mouse hepatocyte, Morrow et al. proved that nobiletin placed a metabolic protection effect on hepatocytes via activation of AMPK and ACC [76]. Rajan et al. also observed the similar effect induced by nobiletin in PA-treated HepG2, in addition, they found that nobiletin also upregulated GSK3β while downregulated SREBP-2 and HMGCR [45]. In addition, Tsuboi showed that in J774.1 mouse macrophages, nobiletin increased cell release of high-density lipoprotein cholesterol via activation of AMPK and subsequently the LXRα-PPARγ loop pathway which upregulated ABCA1 and ABCG1 [77].

The therapeutic potentials of nobiletin against obesity, diabetes and atherosclerosis are evidenced by multiple in vivo studies [78][79]. Lee et al. showed that in diabetic ob/ob mice and HFD-fed obese mice, nobiletin significantly

improved insulin sensitivity and glucose homeostasis via decreasing inflammatory adipokines such as interleukin (IL)-6 and MCP-1, while simultaneously upregulating GLUT4 and GLUT1 in various tissues [78][80]. Zhang et al. found that in both HFD-fed obese mice and rat, gut microbiota was modified by long-term oral administration of nobiletin which led to improved biotransformation, indicating the crucial contribution of gut microbiota in the in vivo antiobesity effect of nobiletin [81][82].

By employing mice with hepatic AMPK deficiency, hepatic ACC dysfunction and mice with adipocyte-specific AMPK deficiency, Morrow et al. proved the metabolic protective effect of nobiletin against HFD/HCD-induced obesity, hepatic steatosis, and dyslipidemia, in vivo [76]. Bunbupha et al. further examined nobiletin-induced protective effect on nonalcoholic fatty liver disease (NAFLD) and they found that nobiletin-treated HFD-fed rat exhibited a much less severe NAFLD phenotype including ameliorated adiposity, hyperlipidemia, insulin resistance, hepatic lipids accumulation and fibrosis [79]. This protective effect was mediated through upregulation of hepatic adiponectin receptor 1 (AdipoR1) and plasma adiponectin levels, as well as downregulation of hepatic NADPH oxidase subunit gp91(phox) [79]. Similarly, in nonobese mice, Kim et al. also observed nobiletin-induced protective effect on nonalcoholic fatty liver disease (NAFLD) and HCD-induced hypercholesterolemia [83]. This effect was associated with a reduction of systematic inflammation and atherosclerosis-associated cardiovascular markers [83]. Consist with this, Burke et al. have also demonstrated that nobiletin exhibited a strong therapeutic potential on metabolic dysfunction and cardiovascular disease as nobiletin supplement in HFD-fed LDLr(-/-) mice led to a more stable plaque phenotype of atherosclerotic lesions, in which the macrophage content was much less [56].

2.2.4. Sinensetin

Sinensetin is a rare polymethoxylated flavone which is found in certain citrus fruits including *C. sunki*, *C. sinensis* cv Valencia, *C. tachibana*, and *C. tangerine* [17][84]. Compared with other parts of the fruit, it is more abundantly found in the peels of the citrus fruits [85][86]. Kang et al. observed a strong inhibitory effects of sinensetin on adipogenesis in 3T3-L1 cells [84]. Its antiadipogenic property was partially explained by a downregulation of SREBP1c expression as well as an increased phosphorylation of PKA and hormone-sensitive lipase, indicating the involvement of the cAMP-mediated signaling pathway [84]. In 3T3-L1 cells, sinensetin blocked insulin-stimulated glucose uptake by suppressing the IRS and Akt phosphorylation while it enhanced phosphorylation of AMPK and ACC to stimulate FA oxidation [84]. Similarly, Rajan et al. found that in PA-treated HepG2 cells, sinensetin also increased AMPK, ACC, and GSK3β phosphorylation levels and decreased SREBP-2 and HMGCR expression. Nevertheless, an increase in 2-NBDG glucose uptake was observed in PA-treated HepG2 cells, indicating the tissue-specific regulation pattern of sinensetin [84], Yet, to this date, the physiological relevance of these antiadipogenic effect induced by sinensetin still need to be further investigated in vivo.

2.2.5. Sudachitin

Sudachitin is a rare polymethoxylated flavone found in the peels of *C. sudachi* [33][87]. Studies have shown that in cellular and animal models, the extracts from *C. sudachi* peel which is enriched in sudachitin, could ameliorate hyperlipidemia and obesity, possibly due to an augmented AMPK activity and PPARα transcription [87]. Shikishima et al. further proved that in a randomized controlled trial, although not affecting glycemic control and lipid profile,

consumption of sudachi peel extract capsules (including sudachitin 4.9 mg/day) for 12 weeks could considerably decreased the ratio of visceral fat to subcutaneous fat, and moderately reduced waist circumference in Japanese patients at risk for developing diabetes [33].

In HFD-fed obese mice and db/db mice, sudachitin displayed strong capacity in stimulating energy expenditure and limiting weight gain via improving glucose and lipid metabolism and promoting mitochondrial biogenesis and function [88]. Elucidation of the underlying molecular mechanism in primary myocytes revealed that sudachitin placed a favorable effect on Sirt1 and PGC1α upregulation in the skeletal muscle [88].

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