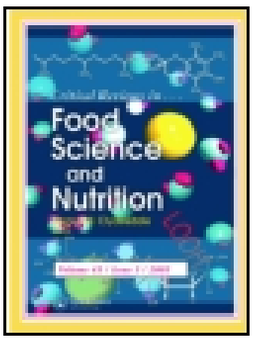

Taylor & Francis
Taylor & Francis Group

Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

Sweet tea (*Lithocarpus polystachyus* rehd.) as a new natural source of bioactive dihydrochalcones with multiple health benefits

Ao Shang , Hong-Yan Liu , Min Luo , Yu Xia , Xiao Yang , Hang-Yu Li , Ding-Tao Wu , Quancai Sun , Fang Geng , Hua-Bin Li & Ren-You Gan

To cite this article: Ao Shang , Hong-Yan Liu , Min Luo , Yu Xia , Xiao Yang , Hang-Yu Li , Ding-Tao Wu , Quancai Sun , Fang Geng , Hua-Bin Li & Ren-You Gan (2020): Sweet tea (*Lithocarpus polystachyus* rehd.) as a new natural source of bioactive dihydrochalcones with multiple health benefits, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2020.1830363

To link to this article: https://doi.org/10.1080/10408398.2020.1830363

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2020.1830363

Taylor & Francis
Taylor & Francis Group

REVIEW

Sweet tea (*Lithocarpus polystachyus* rehd.) as a new natural source of bioactive dihydrochalcones with multiple health benefits

Ao Shang[a,b,c], Hong-Yan Liu[a,b], Min Luo[c], Yu Xia[a,b], Xiao Yang[a,b], Hang-Yu Li[c], Ding-Tao Wu[d], Quancai Sun[e], Fang Geng[f], Hua-Bin Li[c], and Ren-You Gan[a,b,f]

[a]National Agricultural Science & Technology Center, Chengdu, China; [b]Institute of Urban Agriculture, Chinese Academy of Agricultural Sciences, Chengdu, China; [c]Guangdong Provincial Key Laboratory of Food, Nutrition and Health, Department of Nutrition, School of Public Health, Sun Yat-Sen University, Guangzhou, China; [d]Institute of Food Processing and Safety, College of Food Science, Sichuan Agricultural University, Ya'an, Sichuan, China; [e]School of Food and Biological Engineering, Jiangsu University, Zhenjiang, China; [f]Key Laboratory of Coarse Cereal Processing (Ministry of Agriculture and Rural Affairs), School of Food and Biological Engineering, Chengdu University, Chengdu, China

ABSTRACT

Sweet tea (*Lithocarpus polystachyus* Rehd.) has been consumed as herbal tea to prevent and manage diabetes for a long time. Recent studies indicate that sweet tea is rich in a variety of bioactive compounds, especially a class of nonclassical flavonoids, dihydrochalcones. In order to provide a better understanding of sweet tea and its main dihydrochalcones on human health, this review mainly summarizes related literature in the recent ten years, with the potential molecular mechanisms emphatically discussed. Phlorizin, phloretin, and trilobatin, three natural sweeteners, are the main dihydrochalcones in sweet tea. In addition, sweet tea and its dihydrochalcones exhibit plenty of health benefits, such as antioxidant, anti-inflammatory, antimicrobial, cardioprotective, hepatoprotective, antidiabetic, and anticancer effects, which are associated with the regulation of different molecular targets and signaling pathways. Therefore, sweet tea, as a rare natural source of dihydrochalcones, can be processed and developed into nutraceuticals or functional foods, with the potential application in the prevention and management of certain chronic diseases.

KEYWORDS

Sweet tea; dihydrochalcone; health benefits; antioxidant; antidiabetic; anticancer

Introduction

Lithocarpus polystachyus Rehd., or called *Lithocarpus litseifolius* (Hance) Chun, belonging to the genus Fagaceae, is an evergreen tree (Zhang, Lin, et al. 2019). The leaves of *L. polystachyus* have both medicinal and edible functions, and have been used as herbal tea to prevent and manage diabetes for a long time. Due to its herbal tea with an evident sweet taste, *L. polystachyus* is, therefore, called "sweet tea" in the folk. It has already been approved as new food materials in China since 2017. Recent studies report that sweet tea contains diverse bioactive compounds, and is rich in a class of nonclassical flavonoids, dihydrochalcones, such as phlorizin, phloretin, and trilobatin (Yang et al. 2018; Zhao et al. 2014). Meanwhile, sweet tea and its dihydrochalcones have a variety of health benefits (Figure 1), especially with an excellent blood sugar-lowering effect for the management of diabetes (Chang, Huang, and Liou 2012; Ehrenkranz et al. 2005; Hou et al. 2012; Lin et al. 2014; Park et al. 2012; Sun, Li, and Liu 2015). It is also worth mentioning that phlorizin is traditionally thought to be rich in apple peels and contributes to the health benefits of apples (Muceniece et al. 2016). Phlorizin is reported to be about 0.825 mg/g in apples (Gutierrez, Zhong, and Brown 2018). In comparison, the content of phlorizin is more than 100 times higher in sweet tea than in apples, suggesting that sweet tea is an excellent natural resource of phlorizin (Zhang, Li, et al. 2018).

In order to provide state-of-the-art research progress of sweet tea, related literature in the recent ten years is mainly collected from Web of Science Core Collection and Pubmed databases. This review first introduces the main bioactive dihydrochalcones in sweet tea, and next summarizes the health benefits of sweet tea and its main dihydrochalcones from in vitro and in vivo preclinical studies, with the emphasis on discussing related molecular mechanisms. We hope that this review paper can attract more attention to its further research and application in the prevention and management of certain chronic diseases, such as diabetes.

Bioactive dihydrochalcones in sweet tea

Sweet tea contains diverse bioactive compounds. Polyphenols are the most abundant bioactive compounds in sweet tea, with a total content of about 9.0–13.4 g gallic acid equivalent/100 g dry weight (Meng et al. 2020). Sixty-eight phenolic compounds have been identified, with flavonoids as the most predominant compounds in it (Zhao et al. 2014).

Dihydrochalcones are the main flavonoids as well as natural sweeteners in sweet tea (Yang et al. 2018), including

CONTACT R. Y. Gan ganrenyou@caas.cn; ganrenyou@yahoo.com National Agricultural Science & Technology Center, Chengdu 610213, China

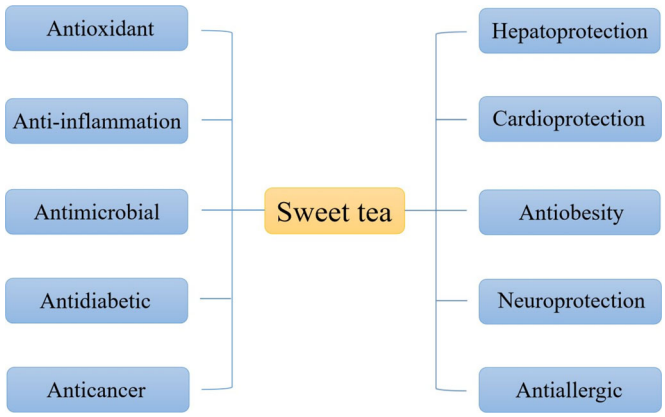

Figure 1. The main health benefits of sweet tea and its dihydrochalcones. Sweet tea has a variety of health benefits, including antioxidant, anti-inflammatory, antibacterial, antidiabetic, anticancer, hepatoprotective, cardioprotective, anti-obesity, neuroprotective, and antiallergic activities.

phloridzin, phloretin, trilobatin, 3-hydroxyphlorizin, and 2′,6′-dihydroxy-4′-methoxyl-dihydrochalcone, with their chemical structures shown in Figure 2. Among them, the sweetness of trilobatin is amazingly 300 times higher than that of sucrose (Yang, Zhong, and Xiao 1991). The content of phloretin in sweet tea is much less compared to phlorizin and trilobatin, while phlorizin can be metabolized into phloretin by the action of lactase-phlorizin hydrolase, β-glucosidase, and intestinal flora in the intestinal tract (Wang, Gao, Wang, Wang, et al. 2019; Zhang et al. 2012). In addition, the contents of dihydrochalcones can be influenced by harvesting location, harvesting time, and leaf age (Yang et al. 2018). For example, the content of phlorizin is higher in older leaves and branches, accounting for a maximum of 9.04%, while trilobatin has higher content in tender leaves up to 24.35% (Zhang, Li, et al. 2018). Overall, sweet tea is rich in dihydrochalcones, with phlorizin and trilobatin as the most predominant dihydrochalcones.

Health benefits of sweet tea

Antioxidant activity

Oxidative stress refers to the imbalance between the oxidative and antioxidant systems of cells and tissues, and excessive oxidative stress is a potential factor in the occurrence and development of many metabolic diseases (Rani et al. 2016). Natural antioxidants have gained a lot of attention, and a great number of studies reports that many vegetables, fruits, fungi, spices, and medicinal plants have excellent antioxidant activity (Li et al. 2017; Shang et al. 2019; Zhang, Li, et al. 2018; Zhou et al. 2019).

Recent studies report that sweet tea and its dihydrochalcones exhibit potent in vitro antioxidant activity. Sweet tea extract exhibits strong antioxidant activity, including 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity about 50.5–72.5 g trolox/100 g DW, 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical scavenging activity about 43.2–77.7 g trolox/100 g DW, and ferric ion reducing antioxidant power (FRAP) activity about 5.0–10.6 g butylated hydroxytoluene/100 g DW (Meng et al. 2020). Dihydrochalcones in sweet tea, including phloridzin, trilobatin, and phloretin, can also effectively scavenge DPPH free radicals (Sun, Li, and Liu 2015). For phloretin, its antioxidant pharmacophore is reported to be 2,6-dihydroxyacetophenone (Rezk et al. 2002). Additionally, phloretin exhibits synergistic antioxidant activity with caffeic acid and glutathione, based on in vitro reducing power, DPPH, and ABTS free radical scavenging assays (Sun, Yu, and Cao 2013). In addition, the pair comparison of FRAP, DPPH, and ABTS values demonstrates that phloretin has the highest antioxidant activity, followed by phloridzin and trilobatin (Li, Wang, et al. 2018). The difference in the antioxidant capacity between phloretin and phloridzin is mainly due to the glycosylation. At the position of 2′-OH of phloretin, phloridzin is glycosylated with β-D-glucoside, thus decreasing the number of phenolic-OH group, which significantly contributes to the antioxidant activity (Figure 2). On the other hand, the difference in the glycosylation position may contribute to the difference in the antioxidant capacity of phloridzin and trilobatin. However, according to another research on the chemical structure of dihydrochalcones, ABTS assay mainly reflects the antioxidant activity of the A ring (Figure 2), while the result of DPPH assay is associated with the antioxidant activity of the B ring, and 3-hydroxyphlorizin displays a better antioxidant property than phloridzin and trilobatin (Xiao et al. 2017).

Sweet tea and its dihydrochalcones also exhibit antioxidant activities in cell models. In hydrogen peroxide (H_2O_2)-stimulated human neuroblastoma, sweet tea can increase cell viability, probably by reducing the accumulation of reactive oxygen species (ROS) in cytoplasm and mitochondria via activating the silent mating-type information regulation 2 homolog 3 (Sirt3) signaling pathway (Gao, Liu, et al. 2018). Moreover, phloretin can alleviate tert-butyl hydroperoxide-induced oxidative damage in rat primary hepatocytes by upregulating the expression of heme oxygenase 1 (HO-1) and glutamate-cysteine ligase (GCL), and subsequently increasing the intracellular content of antioxidant glutathione through the extracellular signal-regulated kinase 2 (ERK2)/nuclear factor erythroid 2-related factor 2 (Nrf2) pathway (Yang et al. 2011). Similarly, phloretin is reported to reduce the oxidative stress induced by high levels of palmitic acid in the human umbilical vein endothelial cells, via upregulating the expression of p-Nrf2 and HO-1 through the adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK)/Nrf2 pathway (Yang et al. 2019). Other dihydrochalcones like trilobatin are reported to reduce the oxidative injury induced by H_2O_2 in PC12 cells via regulating the homeostasis of mitochondrial ROS, which is partially related to the AMPK/Nrf2/Sirt3 signaling pathway (Gao, Liu, et al. 2018).

These results suggest that the dihydrochalcones are the main antioxidants in sweet tea, and their antioxidant mechanisms involve the activation of ERK, AMPK, Nrf2, and Sirt3 signaling pathways, which finally induce antioxidant defense system in cells. In the future, the in vivo antioxidant effect of sweet tea and its dihydrochalcones needs to be verified to provide more reliable evidence for developing natural antioxidant-related functional foods.

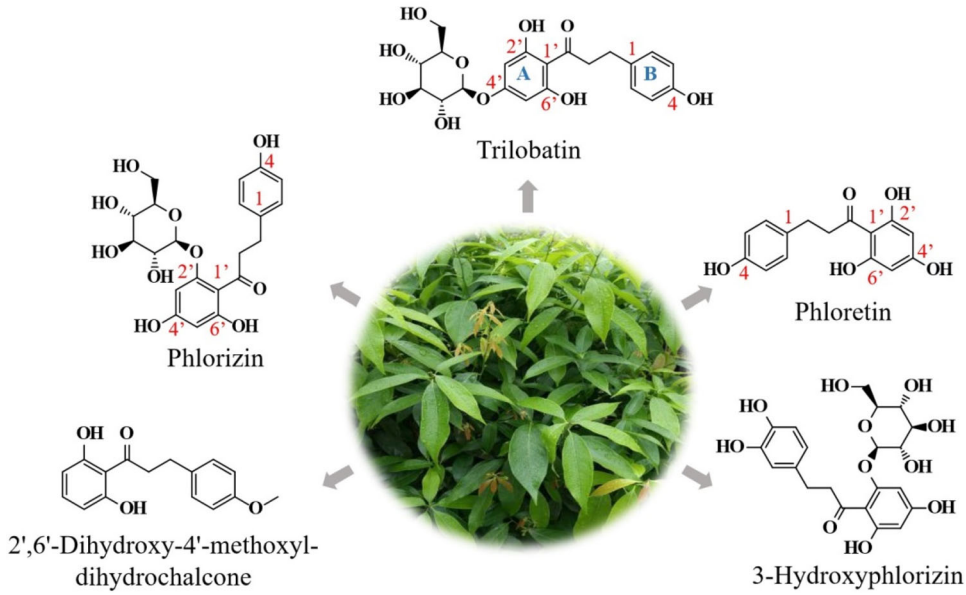

Figure 2. The chemical structures of the main dihydrochalcones in sweet tea. The main dihydrochalcones in sweet tea include trilobatin, phlorizin, phloretin, trilobin, 2′,6′-dihydroxy-4′-methoxyl-dihydrochalcone, and 3-hydroxyphlorizin. The letters A and B stand for the A and B rings in the molecular structure of dihydrochalcones, respectively.

Anti-inflammatory activity

Inflammation is the response of the immune system to stimuli, such as pathogen (bacterial, viral, or fungal) infection, tissue damage, or non-physiological cell death, and is considered as a latent promoter of several chronic diseases (Du et al. 2015). Although the anti-inflammatory effect of sweet tea as a whole has not been reported, its dihydrochalcones, such as phloretin and phlorizin, have been demonstrated to possess excellent anti-inflammatory activity.

Phloretin exhibits an anti-inflammatory effect in cell-based studies. The treatment of phloretin at 10 μM markedly decreases the levels of inflammatory cytokines, including nitric oxide (NO), prostaglandin E (PGE)-2, interleukin (IL)-6, tumor necrosis factor (TNF)-α, inducible NO synthase (iNOS), and cyclooxygenase (COX)-2 through suppressing phosphorylated-MAPK and the nuclear translocation of nuclear factor-kappa B (NF-κB) p65 subunit in lipopolysaccharide (LPS)-induced RAW264.7 cells, while phlorizin has no significant effect (Chang, Huang, and Liou 2012). Similarly, Huang et al. demonstrate that phloretin is more effective in inhibiting inflammatory response than phlorizin in cellular experiments (Huang et al. 2013). In addition, phloretin exerts the anti-inflammatory effect through blocking the NF-κB and MAPK pathways in human lung epithelial cells, and it can also inhibit the expression of COX-2, intercellular adhesion molecule (ICAM)-1, and chemokines in keratinocytes (Huang et al. 2015a, 2015b). Besides, phloretin downregulates the level of phosphorylated-JNK, which is involved in the inflammatory response caused by *Propionibacterium acnes* in keratinocytes (Cheon et al. 2019). Phloretin is also a toll-like receptor (TLR) 2/1 inhibitor, and can inhibit TLR2-mediated inflammation in human embryonic kidney (HEK) 293-hTLR2 cells (Kim et al. 2018).

On the other hand, phloretin can also alleviate arthritis, sepsis, airway inflammation, and ulcerative colitis in animal models, suggesting its potential therapeutic effects on inflammation-related diseases (Aliomrani et al. 2016; Wang, Huang, et al. 2016; Wang et al. 2018; Zhang, Lin, et al. 2019). In addition, phlorizin also displays in vivo anti-inflammatory activity. In the high-fat diet (HFD)-fed mice, phlorizin can decrease the elevation of monocyte chemotactic protein 1 (MCP-1), tumor necrosis factor (TNF)-α, IL-1, and IL-6 levels in the serum and adipose tissues (Tian et al. 2017). Besides, trilobatin from sweet tea exhibits the ability to inhibit the expression of pro-inflammatory cytokines in mouse models, with the mechanism similar to phloretin (Fan et al. 2015).

Collectively, the in vitro and in vivo studies support the anti-inflammatory activity of phloretin and trilobatin, and their anti-inflammatory mechanisms are related to the regulation of NF-κB, MAPK, and JNK signaling pathways. However, phlorizin exhibits no significant in vitro anti-inflammatory effect, but evident in vivo anti-inflammatory effect, suggesting the discrepancy of its anti-inflammatory effects in vitro and in vivo, probably associated with the different physiological environments in vitro and in vivo. Overall, sweet tea is rich in dihydrochalcones with an anti-inflammatory effect, therefore, it has the potential to be used to prevent and manage inflammation-related diseases in the future.

Antidiabetic activity

Diabetes is a metabolic disease characterized by hyperglycemia (Meng et al. 2019; Rolo and Palmeira 2006). α-Amylase and α-glucosidase play a critical role in promoting the hydrolysis of dietary sugars to induce the increase of postprandial blood glucose levels (He, Chen, and Li 2019). Insulin is the most crucial hormone for blood glucose regulation, and the maintenance of normal blood glucose level depends on the balance of insulin secretion and action. Insulin resistance occurs when insulin becomes retarded, and has an insufficient capability to inhibit glucose disposal

in the skeletal muscle and hepatic glucose production, driving the development of diabetes (Stumvoll, Goldstein, and van Haeften 2005).

In recent years, the antidiabetic effects of sweet tea and its dihydrochalcones have been increasingly concerned. Sweet tea exhibits excellent hypoglycemic ability (Meng et al. 2020), which is mainly due to its dihydrochalcones with inhibitory effects on α-amylase and α-glucosidase. Trilobatin, a main dihydrochalcone in sweet tea has been found to noncompetitively inhibit α-glucosidase and α-amylase (Dong et al. 2012). Another main dihydrochalcone of sweet tea, phloretin, also has an inhibitory effect on α-glucosidase (Han et al. 2017). Moreover, phloretin improves insulin sensitivity and glucose uptake in 3T3L1 cells via activating cyclin-dependent kinase 5 and suppressing peroxisome proliferation-activated receptor (PPAR)-γ (Kumar et al. 2019). Also, phloretin enhances glucose tolerance by promoting the translocation of GLUT4 and activating the PI3K/Akt pathway in L6 myotubes (Shen et al. 2017).

In addition, the hypoglycemic activity of sweet tea and its dihydrochalcones has been confirmed in vivo. The treatment of the flavonoid-rich extract of sweet tea for four weeks significantly decreases the fasting serum insulin and C-peptide levels, and improves the insulin tolerance in type 2 diabetic rats (Hou et al. 2011). In another study, the treatment of sweet tea extract increases the intracellular glucose uptake, and decreases blood glucose and liver glycogen synthesis, accompanied with upregulating the expression of glucokinase, glucose transporter 2 (GLUT2), insulin receptor (IR), and insulin receptor substrate (IRS) in the liver tissue of type 2 diabetic mice (Wang, Huang, et al. 2016). Its hypoglycemic mechanism is associated with the suppression of liver glucose production mediated by phosphoenolpyruvate carboxykinase (PEPCK) and/or glucose-6-phosphatase (G-6-Pase). Interestingly, the hypoglycemic effect of sweet tea leaf extract is more effective than that of trilobatin and phlorizin alone.

The hypoglycemic activity of phlorizin has been verified by in vivo studies. Phlorizin is regarded as a glucopenic drug lacking the insulin-mimetic property in the treatment of diabetes mellitus (Amessou et al. 1999; Lu et al. 2012). It can partially restore the insulin response to glucose in T2DM Goto-Kakizaki rats (Gaisano et al. 2002). The combination of phlorizin with a glucose-lowering factor 5-aminoimidazole-4-carboxamide can block the response of glucagon to the hypoglycemia in T1DM biobreeding (BB) rats and improves the hypoglycemia-specific glucagon secretory defect (McCrimmon et al. 2002). Additionally, the combination of phloretin with metformin demonstrates a better antidiabetic effect in T2DM rats compared with phloretin or metformin alone (Shen et al. 2020). The combination reduces postprandial blood glucose by 76%, while phloretin and metformin only reduced it by 41% and 42%, respectively, and the glucose tolerance and insulin sensitivity are improved more effectively by the additive effect of phloretin and metformin.

Furthermore, phloretin and phlorizin can improve the secondary complications of diabetes in vivo. Phloretin can downregulate the level of blood glucose, and decrease the activity of aldose reductase, a key enzyme associated with diabetic chronic complications in HFD-fed mice, accompanied with reduced accumulation of total advanced glycation end products (AGEs) (Sampath, Sang, and Ahmedna 2016). On the other hand, phlorizin is reported to prevent proteinuria, glomerular hyperfiltration, and renal hypertrophy caused by hyperglycemia in diabetic Fischer rats (Malatiali, Francis, and Barac-Nieto 2008). As a well-known sodium-glucose cotransporter (SGLT) inhibitor, phlorizin can prevent the progress of hyperglycemia, hypertension, and diabetic renal complications via inhibiting the expression of SGLT2 in diabetic rats (Osorio et al. 2010). It is also observed that phlorizin can reduce blood glucose by inhibiting SGLT2 and inducing renal glucose excretion in cynomolgus monkeys (Nagata et al. 2014). Another study suggests that the blood sugar-lowering effect of phlorizin may be related to the reduction of lipopolysaccharides and the change of gut microbiota in T2DM mice (Li et al. 2019; Mei et al. 2016). In addition, phlorizin can also improve other diabetic complications, including nephropathy, neuropathy, cardiomyopathy, hepatic injury, vascular disease, and retinopathy, with the specific mechanisms of action shown in Table 1.

In general, sweet tea and its dihydrochalcones exhibit excellent anti-diabetic potential, and prevent and improve diabetic complications, including diabetic nephropathy, cardiomyopathy, and retinopathy, with the molecular mechanisms summarized in Figure 3. Phloretin, phlorizin, and trilobatin are the main hypoglycemic dihydrochalcones in sweet tea, but it is still not clear which compound plays the most critical role in the antidiabetic effect of sweet tea, and whether the gut microbiota also involves in its antidiabetic effect, which is interesting to be revealed in the future.

Anticancer activity

Current research has shown that sweet tea and its dihydrochalcones, especially phloretin, possess anticancer activity against different cancer cells in vitro, such as gastric, colon, liver, and lung cancers (Table 2). The aqueous extract of sweet tea is reported to effectively inhibit the proliferation and colony formation, and induce apoptosis in breast cancer cells, with the decreased expression of cyclin D1 and B cell lymphoma-2 (Bcl-2) and the elevated expression of PPAR-γ, Bcl-2 associated X (Bax), and caspase-3 (Lin et al. 2014). Phloretin is one of the major dihydrochalcones in sweet tea. Many studies have demonstrated that phloretin exhibits different anticancer effects, which are discussed below together with potential molecular mechanisms in detail.

Phloretin has been reported to effectively inhibit cancer cell growth and induce cancer cell apoptosis in vitro. It can induce apoptosis and inhibit the proliferation of BGC823 gastric cancer cells by increasing the cleavage of PARP and blocking the expression of Bcl-2 (Lu et al. 2015). In HT-29 colon cancer cells, it can promote cell apoptosis by altering the mitochondrial membrane permeability, activating caspases, including caspase-8, -9, -7 and -3, and inducing the cleavage of poly (ADP-ribose) polymerase (PARP) (Park et al. 2007). As a GLUT inhibitor, it leads to HepG2 cells apoptosis by regulating Akt, the Bcl-2, intrinsic, and extrinsic apoptotic pathways (Wu et al. 2009). It is reported to

Table 1. Effects of sweet tea and its dihydrochalcones on diabetes mellitus and diabetic complications.

Product	Extracts/Compounds	Subjects/Cell lines	Treatments	Main effects and related mechanisms	Ref.
In vitro ***studies***					
Lithocarpus polystachyus leaves	Extract	α-Glucosidase Protein tyrosine phosphatase 1B	1.25 mg/mL	Inhibiting α-glucosidase and protein tyrosine phosphatase 1B	(Meng et al. 2020)
	Phloretin	α-Glucosidase	0, 10,20,30,40,50, 60, 80, 100, 150, 200 μg/mL	Inhibiting α-glucosidase	(Han et al. 2017)
	Trilobatin	α-Glucosidase α-Amylase	2.5 mg/mL	Inhibiting α-glucosidase and α-amylase non-competitively	(Dong et al. 2012)
Cellular studies					
	Phloretin	Human retinal pigmented epithelial cells	0-25 μM	Improving cell viability Decreasing the activity of aldose reductase	(Sampath, Sang, and Ahmedna 2016)
		L6 myoblast cell line	100 μM	Increasing the expression of Akt, PI3K, IRS-1, and GLUT4 Improving GLUT4 translocation	(Shen et al. 2017)
		Mouse 3T3L1 fibroblast cells	5, 10 and 20 μM	Increasing insulin sensitivity by up-regulating the expression of related genes Increasing glucose uptake Suppressing Cdk5 activation and p-PPARγ (ser273)	(Kumar et al. 2019)
		High glucose-induced cardiac H9C2 cells	1.25, 2.5, 5, 10, 20, 40, 80 μM	Alleviating cardiomyocyte inflammation injury Decreasing fibrosis Increasing the expression of SIRT1	(Ying et al. 2019)
		L6 myoblast cell line BRL-3A rat liver cells	100 μM	Increasing glucose consumption	(Shen et al. 2020)
		Glucose-induced HUVECs	50 and 100 nM	Restoring the expression of KLF2 and eNOS	(Xia et al. 2020)
	Phlorizin	Mouse 3T3L1 fibroblast cells	5, 10 and 20 μM	Increasing insulin sensitivity by up-regulating the expression of related genes Increasing glucose uptake Suppressing Cdk5 activation and p-PPARγ (ser273)	(Kumar et al. 2019)
Animal studies					
Lithocarpus polystachyus Rehd. leaves	Extract	Double high diet-fed and STZ-induced T2DM mice	0.8 g/kg/d intragastric administration (i.g) for 4 weeks	Decreasing blood glucose Promoting glucose uptake and liver glycogen synthesis Reducing liver gluconeogenesis Increasing the expression of glucokinase, GLUT2, IRIRS Decreasing the expression G-6-P	(Wang, Huang, et al. 2016)
Lithocarpus polystachyus Rehd. leaves	Flavonoid-rich fraction	STZ-induced T1DM rats	0.3 g/kg/d fed orally for 3 weeks	Decreasing fasting blood glucose, total cholesterol, triglyceride, urea nitrogen, and creatinine Suppressing the descend in insulin level	(Hou et al. 2011)
		HCD and STZ-induced T2DM rats	0.3 and 1.5 g/kg/d fed orally for 4 weeks	Regulating blood glucose, glycosylated serum protein Decreasing fasting serum insulin and C-	

(*continued*)

Table 1. Continued.

Product	Extracts/Compounds	Subjects/Cell lines	Treatments	Main effects and related mechanisms	Ref.
				peptide level Improving insulin resistance	
	Phloretin	HFD-fed male C57BL/6J mice	25 and 75 mg/kg/d for 16 weeks	Decreasing FBG and AGEs accumulation Decreasing the activity of aldose reductase	(Sampath, Sang, and Ahmedna 2016)
		STZ-induced male diabetic C57BL/6 mice	10 mg/kg/d i.g. for 8 weeks	Preventing cardiomyopathy Alleviating fibrosis, oxidative stress and pathological parameters by Keap1/Nrf2 pathway	(Ying et al. 2018)
		STZ-induced diabetic mice	20 mg/kg/d i.g. for 8 weeks	Alleviating cardiomyocyte inflammation injury Decreasing fibrosis Improving cardiac damage	(Ying et al. 2019)
		STZ-induced diabetic Sprague Dawley rats	100 mg/kg/d i.g. for 4 weeks	Decreasing FBG Improving glucose resistance and insulin sensitivity combined with metformin Increasing the expression of p-Akt, PI3K, IRS-1 and GLUT4 in skeletal muscle and liver	(Shen et al. 2020)
		STZ-induced diabetic C57BL6 Apoe$^{-/-}$ mice	20 mg/kg/d i.g. for 10 weeks	Improving diabetic atherosclerosis Maintaining endothelial function by activating KLF2-eNOS	(Xia et al. 2020)
	Phlorizin	Male hyperglycemic Goto-Kakizaki T2DM rats	0.4 g/kg/d injected for 12 days	Inducing normoglycemic regulation Partially restoring the insulin response to glucose Partially recovering the abnormal expression of pancreatic islet exocytotic SNARE	(Gaisano et al. 2002)
		Diabetic BB/Wor T1DM rats	0.5 g/kg subcutaneous bolus	Moderating the glucagon response to hypoglycemia combined with AICAR and insulin Improving the defect in glucagon secretion	(McCrimmon et al. 2002)
		Zucker T2DM fatty rats	50 mg/kg/d hypodermic injection (i.h.) for 13 weeks	Suppressing the descend in insulin level	(Janssen et al. 2003)
		Male diabetic Fischer rats	First day: 200 mg/kg i.h. twice; Then 400 mg/kg i.h. twice daily for 6 days	Inhibiting proteinuria, hyperfiltration and kidney hypertrophy	(Malatiali, Francis, and Barac-Nieto 2008)
		STZ-induced diabetic rats		Decreasing hyperglycemia Reducing SGLT2 activity in BBMV	(Osorio et al. 2010)
		STZ-induced T1DM rats	51,02,040 mg/kg/d orally for 21 days	Reducing the level of blood glucose Decreasing urine output and water consumption	(Najafian et al. 2012)
		Male C57BLKS/J *db/db* mice	20 mg/kg/d i.g. for 10 weeks	Decreasing the serum concentration of FBG, AGEs, and MDA Increasing the serum SOD activity Alleviating the aorta damage	(Shen et al. 2012)
		Male C57BLKS/J *db/db* mice	20 mg/kg/d i.g. for 10 weeks	Improving diabetic hepatopathy Regulating carbohydrate metabolism Regulating the biosynthesis of fatty acid, β-oxidation, and cholesterol Influencing the expression of related proteins	(Lu et al. 2012)
		STZ-induced diabetic mice	400 mg/kg i.h. twice	Decreasing uptake of STZ in the kidney by inhibiting SGLTs	(Brouwers et al. 2013)
			20 mg/kg/d i.g. for 10 weeks		(Cai et al. 2013)

		Male diabetic *db/db* mice		Decreasing the serum concentration of FBG, TG, TC, and AGEs Regulating the expression of key proteins related to the cardiac lipid metabolism, mitochondrial function, and cardiomyopathy	
		Male C57BLKS/J *db/db* mice	20 mg/kg/d i.g. for 10 weeks	Decreasing the levels of FBG and AGEs Inhibiting the expression of GFAP Suppressing retina cell apoptosis Changing 60 proteins in the retinas	(Zhang et al. 2013)
		Male C57BLKS/J *db/db* mice	20 mg/kg/d i.g. for 10 weeks	Decreasing FBG, AGEs, blood urea nitrogen, creatinine, and 24-h urine albumin Alleviating renal damage Increasing the expression of caveolin 1, PECAM1, and ATP6V0C et al. and down-regulating SERPINA1 et al. Decreasing toxic free radicals	(Pei et al. 2014)
		Glucose infusion-induced male cynomolgus monkeys	133, 1,333, or 13,333 ng/mL infusion for 6 month	Nonselectively inhibiting SGLT1 and SGLT2 Increasing urinary glucose excretion by extending splay	(Nagata et al. 2014)
		SDT T2DM fatty rats	100 mg/kg/day i.h. for 23 weeks	Improving the delay of sciatic nerve conduction velocity Preventing the decrease of intraepidermal nerve fiber density Controlling the level of plasma glucose Alleviating diabetic complications Decreasing urinary albumin excretion Improving glomerulosclerosis and tubulopathy Preventing retinal dysfunction Improving histopathological abnormalities of the eye (retinal folding and cataracts)	(Katsuda et al. 2015)
		Male *db/db* (BKS.Cg-*Dock*^{7m}+/+*Lep*^{db}/J) mice	20 mg/kg/d i.g. for 10 weeks	Reducing serum lipopolysaccharide and insulin resistance Increasing the level of fecal SCFAs Alleviating hyperglycemia by regulating gut microbiota Promoting the growth of *Akkermansia muciniphila* and *Prevotella*	(Mei et al. 2016)
		Double high diet-fed and STZ-induced T2DM mice	80 mg/kg i.g. for 4 weeks	Promoting liver glycogen synthesis Increasing expression of glucokinase, GLUT2, and PEPCK	(Wang, Huang, et al. 2016)
		STZ-induced diabetic rats		Decreasing the amplitude of shortening and the amplitude of intracellular Ca^{2+} in ventricular myocytes	(Hamouda et al. 2016)
		STZ-induced diabetic Wistar rats	25 and 50 mg/kg/d orally for 4 weeks	Improving the antioxidant state of sciatic nerve tissue Improving issue histopathological changes	(Balaha, Kandeel, and Kabel 2018)
Lithocarpus polystachyus Rehd. leaves	Trilobatin	Double high diet-fed and STZ-induced T2DM mice	80 mg/kg i.g. for 4 weeks	Promoting liver glycogen synthesis Increasing expression of glucokinase, IRS and PEPCK	(Wang, Huang, et al. 2016)

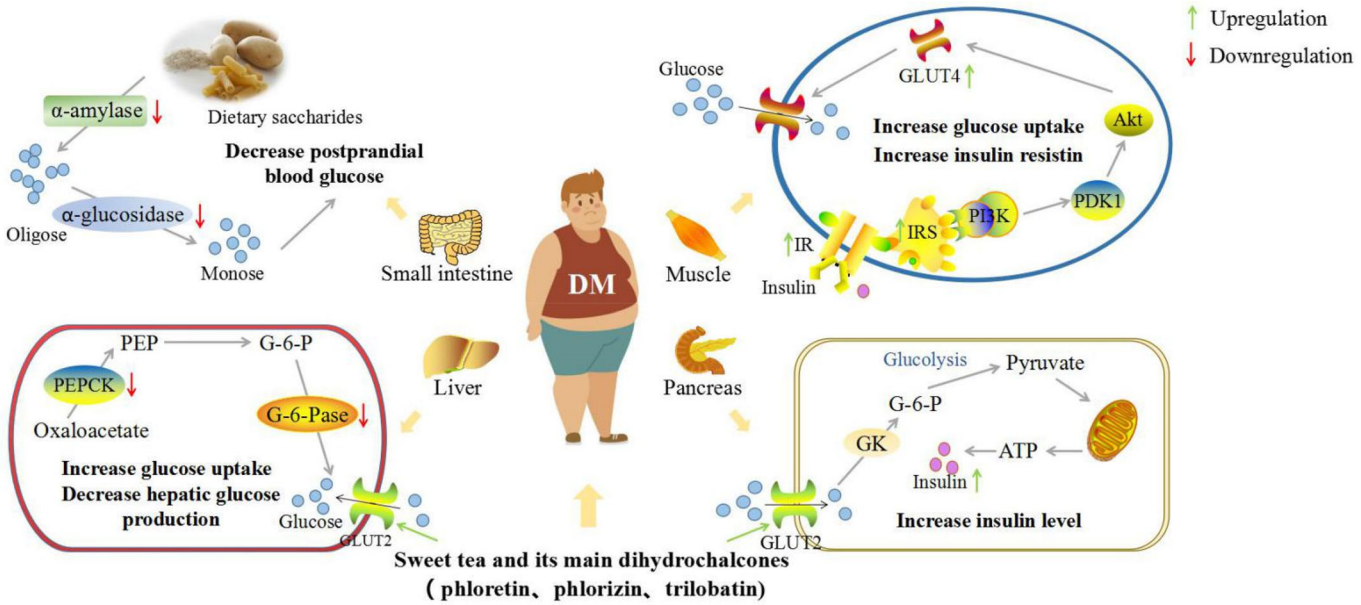

Figure 3. The antidiabetic mechanisms of sweet tea and its dihydrochalcones phloretin, phlorizin, and trilobatin. The antidiabetic effect of sweet tea and its dihydrochalcones mainly target the small intestine, liver, muscle, and pancreas. (a) In the small intestine, sweet tea and its ingredients inhibit the activity of α-amylase and α-glucosidase, and suppress the decomposition of dietary polysaccharides into easily absorbed oligose and monose, thus reducing postprandial blood glucose. (b) In the liver, they promote glucose uptake by activating the expression of GLUT2. On the other hand, they down-regulate the expression of PEPCK and G-6-Pase to block oxaloacetate from being synthesized into glucose via the gluconeogenic pathway, thereby reducing the production of hepatic glucose. (c) In the muscle, they increase glucose uptake and insulin resistance by activating the expression of IR and GLUT4. (d) In the pancreas, they activate GLUT2, thereby increasing glucose uptake, which is converted by GK into G-6-P to form pyruvate, and then promote ATP production through citric acid cycle in the mitochondria, thus prompting the insulin secretion. Abbreviations: Akt, protein kinase B; ATP, adenosine triphosphate; DM, diabetes mellitus; GLUT, glucose transporter; IR, insulin receptor; IRS, insulin receptor substrate; PDK1, phosphoinositide-dependent protein kinase-1; PEP, phosphoenolpyruvate; PEPCK, phosphoenolpyruvate carboxykinase; PI3K, phosphoinositide-3-kinase; GK, glucokinase; G-6-P, glucose-6-phosphate; G-6-Pase, glucose-6-phosphatas.

induce the apoptosis of A549 lung cancer cells, involving the activation of p38 MAPK, ERK1/2, and JNK1/2 signal pathways (Min et al. 2015). It can also induce apoptosis in B16 melanoma 4A5 cells by inhibiting glucose transmembrane transport, and induce apoptosis in HL60 human leukemia cells in a different way of suppressing the activity of protein kinase C (Kobori et al. 1999; Kobori et al. 1997).

In addition, phloretin can effectively inhibit cancer cell migration and invasion in vitro. It is reported to restrict invasion and migration of AGS gastric cancer cells, accompanied with downregulating the expression of p-JNK and p-38 MAPKs (Xu et al. 2018). In A549 lung cancer cells, it can inhibit the migration and invasion of cancer cells, mainly through regulating the matrix metalloproteinases (MMPs) signaling (Ma et al. 2016).

Besides, phloretin can help overcome anticancer drug resistance. In hepatocellular carcinoma cells, it is reported to sensitize the anticancer drug sorafenib by activating Src homology 2-containing phosphatase-1 (SHP-1) and inhibiting signal transducers and activators of transcription 3 (STAT3) and Akt/vascular endothelial growth factor receptor 2 (VEGFR2) pathways (Saraswati et al. 2019). Additionally, it can assist cisplatin, a chemotherapeutic drug, to fight against non-small cell lung cancer cells by inhibiting cell proliferation, invasion, and migration (Ma et al. 2016).

Moreover, phloretin can regulate cancer immunity. In SW-1116 colon cancer cells, it can activate the Wnt signaling pathway and increase the production of IFN-γ, thereby promoting the growth of $\gamma\delta$ T cells and enhancing its cytotoxic activity (Zhu et al. 2013), suggesting that phloretin may be beneficial for the immunotherapy against colon cancer.

On the other hand, few studies have reported that sweet tea and phloretin also exert the anticancer effect in animal models. In a study, sweet tea extract is found to inhibit the growth of human breast cancer in BALB/c nude mice (Lin et al. 2014). In addition, phloretin is confirmed to inhibit tumor growth in HepG2 xenograft model mice (Wu et al. 2009).

To sum up, sweet tea is a potential anticancer natural product, and its dihydrochalcone compound phloretin may play a vital role. Phloretin has a positive influence on the prevention and management of several cancers in vitro and in vivo, such as gastric, colon, liver, lung, glioblastoma, oral, cervical, and esophageal cancers, as shown in Table 2. Its anticancer mechanisms include inhibition of cancer cell growth, block of the cell cycle, promotion of cell apoptosis, suppression of metastasis and angiogenesis by at least partly targeting the Akt, p38 MAPK, ERK1/2, and JNK signaling pathways. In addition, phloretin can assist chemotherapy drugs by targeting SHP-1, STAT3, and VEGFR2. These findings open up the possibility that sweet tea and phloretin can be used in the prevention and management of different cancers.

Cardioprotective effect

Cardiovascular disease is one of the major threats to human health. Hypertension, hyperlipidemia, hyperuricemia, and atherosclerosis are the main risk factors for cardiovascular diseases (Abeles 2015; Frostegard 2013; Inoue 2014; Tang

Table 2. Effects of sweet tea and its dihydrochalcones on cancers.

Product	Extracts/ Compounds	Subjects/Cell lines	Treatments	Main effects and related mechanisms	Ref.
Cellular studies					
Lithocarpus polystachyus Rehd leaves	Aqueous extract	MCF-7 human breast cancer cells	50, 100, 200, 300, and 400 μg/mL	Inducing cytotoxic and apoptotic of cancer cells Increasing the expressions of PPARγ, Bax, and caspase-3 Decreasing the expressions of Cyclin D1 and Bcl-2	(Lin et al. 2014)
	Phloretin	B16 mouse melanoma 4A5 cells	0.1 mM	Inducing cancer cell apoptosis Suppressing glucose transmembrane transport Suppressing activity of protein kinase C	(Kobori et al. 1997)
		B16 mouse melanoma 4A5 cells	0.1, 0.15, 0.2 mM	Inducing cancer cell apoptosis Up-regulating the expression of Bax	(Kobori et al. 1999)
		HL60 human leukemia cells	0.1, 0.2, 0.3 mM	Inducing cancer cell apoptosis Down-regulating the level of caspase 3 Suppressing activity of protein kinase C	
		HT-29 human colon cancer cells	25,50,75,100 μM	Inducing cancer cell apoptosis Up-regulating the expression of Bax Promoting cleavage of caspase-8, −9, −7, and −3 and PARP Up-regulating the expression of cytochrome C and Smac/Diablo	(Park et al. 2007)
		SMMC-7721 human hepatoma cells		Inhibiting the cancer cell proliferation Inducing cancer cell apoptosis Inducing G_1 phase cell circle arrest Decreasing mitochondrial transmembrane potential Interfering with intracellular calcium homeostasis	(Wang et al. 2012)
		SW-1116 human colon cancer cells	0, 2.35, 4.70, 18.75, 37.50, 75.00 μg/mL	Enhancing the cytotoxic activity of $\gamma\delta$ T cells on cancer cells Promoting the growth of $\gamma\delta$ T cells Activating the Wnt signaling pathway Increasing the production of IFN-γ Up-regulating the Granzyme B and perforin	(Zhu et al. 2013)
		A549 non-small cell lung carcinoma cells	2,55,01,00,200 μM	Inhibiting the cancer cell migration Up-regulating the expression of Bax Promoting cleavage of caspase-3 and −9 Activating P38 MAPK, ERK1/2, and JNK1/2 pathways	(Min et al. 2015)
		BGC823 human gastric cancer cells	1,02,030 μM	Inhibiting cancer cell proliferation Inhibiting the growth of cancer cells Promoting cleavage of anti-PARP Decreasing the expression of Bcl-2	(Lu et al. 2015)
		B16 mouse melanoma cells K-562 human erythroblasts	20 μM	Increasing the permeability of HSP70 to the cells	(Abkin et al. 2016)
		Human glioblastoma cells	10,01,50,20,02,50,300 μM	Inhibiting cancer cell proliferation and apoptosis Inducing G_0/G_1 phase cell circle arrest Down-regulating the expression of Cdk2, Cdk4, Cdk6, Cyclin D and E Inhibiting PI3K/AKT/mTOR signaling pathway Increasing the expression of Bax, Bak, and c-PARP Decreasing the expression of Bcl-2	(Liu et al. 2016)
		Non-small cell lung carcinoma cell lines (A549, Calu-1, H838, and H520)	2,55,075 μg/mL	Inducing cancer cell apoptosis Inhibiting the invasion and migration of cancer cells Promoting the anti-cancer effect of cisplatin Down-regulating the expression of Bcl-2 Promoting cleavage of caspase-3 and −9 Deregulating the expression of MMP-2 and −9	(Ma et al. 2016)

(*continued*)

Table 2. Continued.

Product	Extracts/ Compounds	Subjects/Cell lines	Treatments	Main effects and related mechanisms	Ref.
		EC-109 human esophageal cancer cells	60, 70 and 80 μg/mL	Inducing cancer cell apoptosis Decreasing the expression of Bcl-2	(Duan et al. 2017)
		Human gastric cancer cell lines	0, 4, 8, and 16 μM	Inducing cancer cell apoptosis Inducing G_2/M phase cell cycle arrest Inhibiting cancer cell invasion Decreasing the expressions of p-JNK and p38	(Xu et al. 2018)
		SW620 and HCT116 human colon cancer cells	100 μM	Inducing cancer cell apoptosis Inducing G_2/M phase cell cycle arrest Decreasing the expression of cyclin B and activation of Cdc2 combined with atorvastatin	(Zhou et al., 2017)
		SiHa human cervical cancer cells	2,04,060 μM	Inhibiting cancer cell invasion Down-regulating the expression of MMP-2	(Hsiao et al. 2019)
	Phloretin loaded chitosan nanoparticles	Human oral cancer cell lines	10-50 μg/mL	Inducing mitochondrial-mediated cancer cell apoptosis Inducing cell circle arrest	(Mariadoss et al. 2019)
		Hepatocellular carcinoma cell lines	50 μM	Inducing cancer cell apoptosis Increasing the expression of SHP-1 Decreasing the expression of STAT3 SHP-1-mediated inhibition of STAT3 and Akt/VEGFR2 pathway	(Saraswati et al. 2019)
Animal studies					
Lithocarpus polystachyus Rehd leaves	Aqueous extract	Nude mice xenograft model of MCF-7 cells	0.1, 0.2, 0.4% drink for 4 weeks	Inhibiting the growth of tumor	(Lin et al. 2014)
	Phloretin	SCID mice xenograft model of HepG2 cells	10 mg/kg three times per week for 6 weeks	Inhibiting the growth of tumor Inhibiting glucose uptake	(Wu et al. 2009)
		TPA-induced female ICR and HR-1 hairless mice	1 and 5 μmol applied topically twice a week for 18 weeks	Suppressing the tumor promotion Suppressing the expression of NF-κB and COX-2 Regulating the ERK signaling pathway	(Shin, Kundu, and Surh 2012)
		Nude mice xenograft model of A549 cells	10, 20 mg/kg i.p. every two days for 3 weeks	Inhibiting the growth of tumor	(Min et al. 2015)
		C57BL/6 mice xenograft model of B16 mouse melanoma cells		Promoting the anti-cancer effect of HSP70 Decreasing the tumor weight Extending the life span	(Abkin et al. 2016)
		Immunodeficient nude mice xenograft model of SiHa cells	20 mg/kg/d i.g. for 6 weeks	Inhibiting the growth of tumor Inhibiting metastasis and angiogenesis	(Hsiao et al. 2019)
		Sorafenib-sensitive and -resistant xenografts model of $HepG2^{SR}$ and $Huh7^{SR}$	Treat with clear hydrogel every two days	Inhibiting the growth of tumor Inhibiting the cancer cell proliferation Inducing apoptosis Inhibiting STAT3 and Akt/VEGFR2 mediated by SHP-1	(Saraswati et al. 2019)

Table 3. Effects of sweet tea and its dihydrochalcones on other diseases.

Product	Extracts/Compounds	Subjects/Cell lines	Treatments	Main effects and related mechanisms	Ref.
Cellular studies					
Lithocarpus polystachyus Rehd. leaves	Phenols	Hyaluronidase		Inhibiting hyaluronidase in vitro	(Li et al. 2000)
	Aqueous extract	Human SH-SY5Y neuroblastoma cells	25, 50 and 75 μg/mL	Protecting against hydrogen peroxide-induced oxidative stress injury Decreasing reactive oxygen species accumulation in cell and mitochondria	(Gao, Xu, et al. 2018)
	Phloretin	Differentiated 3T3-L1 cells RAW 264.7 macrophages	3–100 μM	Increasing lipolysis Up-regulating ATGL and HSL Inhibiting inflammatory response	(Huang et al. 2013)
		Rat basophilic leukemia RBL-2H3 cells	0, 6.25, 12.5, 25, 50, 100, 200 μM	Suppressing production of intracellular reactive oxygen species Alleviating IgE-mediated pro-inflammatory cytokines production	(Chung et al. 2013)
	Phlorizin	Differentiated 3T3-L1 cells	3-100 μM	Increasing lipolysis Inhibiting inflammatory response	(Huang et al. 2013)
	Trilobatin	Neuron-like highly differentiated rat pheochromocytoma PC12 cells	15, 30 and 60 μM	Protecting against oxidative stress injury Regulating mitochondrial reactive oxygen species homeostasis Regulating the AMPK/Nrf2/Sirt3 signaling pathway	(Gao, Liu, et al. 2018)
Animal studies					
Lithocarpus polystachyus Rehd leaves	Extract	Diet-induced obese Sprague-Dawley rats	7,51,50,300 mg/kg/d i.g. for 8 weeks	Decreasing body weight Alleviating leptin resistance	(Zhou et al. 2013)
	Phlorizin	Male Swiss mice	3.0–300.0 mg/kg inject	Enhancing memory storage	(Boccia, Kopf, and Baratti 1999)
		Diet-induced obese C57BL/6 mice	60 mg/kg/d for 14 weeks	Decreasing body weight and fat mass Increasing activity of brown adipose tissue Increasing thermogenesis	(Yuan et al. 2016)
		Diet-induced obese C57BL/6 mice	0.02% *w/w* dietary treatment for 16 weeks	Decreasing weights of visceral and white adipose tissue Improving hepatic steatosis and inflammation	(Shin et al. 2016)
		Aβ-induced Alzheimer's disease rats	0.02% *w/w* dietary treatment for 10 weeks	Alleviating oxidative stress Improving neuro-inflammation of brain	(Tian et al. 2018)

Abbreviations: Akt, protein kinase B; AGEs, advanced glycation end products; AICAR, 5-aminoimidazole-4-carboxamide; AMPK, adenosine 5′ -monophosphate-activated protein kinase; ATGL, adipose triglyceride lipase; BBMV, brush border membrane vesicles; Bak, Bcl-2 homologous antagonist killer; Bax, Bcl-2 associated X; Bcl-2, B cell lymphoma-2; Cdk, cyclin-dependent kinase; COX-2, cyclooxygenase-2; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; FBG, fasting blood glucose; GFAP, glial fibrillary acidic protein; GLUT, glucose transporter; G-6-P, glucose-6-phosphatase; HCD, high-cholesterol diet; HFD, high-fat diet; HSL, hormone-sensitive lipase; HSP70, heat-shock protein 70 kDa; HUVECs, human umbilical vascular endothelial cells; IAPP, islet amyloid polypeptide; i.g., intragastric administration; IR, insulin receptor; IRS, insulin receptor substrate; Keap1, Kelch-like ECH-associated protein 1; KLF2, kruppel-like factor 2; MDA, malondialdehyde; MMP, matrix metalloproteinases; mTOR, mammalian target of rapamycin; Nrf2, nuclear factor E2-related factor 2; PARP, poly (ADP-ribose) polymerase; PECAM1, platelet/endothelial cell adhesion molecule 1; PEPCK, phosphoenolpyruvate carboxykinase; PI3K, phosphoinositide-3-kinase; PPARγ, peroxisome proliferator-activated receptor γ; SCFAs, short chain fatty acids; SCID, severe combined immune deficiency; SDT, spontaneously diabetic torii; SERPINA1, serpin peptidase inhibitor; SGLT2, sodium/glucose cotransporter 2; SHP-1, Src homology region 2 domain-containing phosphatase-1; SIRT1, silent information regulator 2 homolog 1; SNARE, soluble N-ethylmaleimide-sensitive factor attachment protein receptor; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; STZ, streptozotocin; TPA, 12-O-tetradecanoylphorbol 13-acetate; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; VEGFR2, vascular endothelial growth factor receptor 2.

et al. 2017; Zhao et al. 2017). Two main dihydrochalcones in sweet tea, phloretin and phloridzin, have been reported to have beneficial effects on cardiovascular protection.

Phloretin and phlorizin can regulate blood pressure, blood uric acid, and atherosclerosis in vitro. As an inhibitor of SGLT1 and SGLT2, phlorizin can improve palmitic acid-induced endothelial dysfunction through inhibiting the expression of SGLT1 and SGLT2, activating the PI3K/Akt/endothelial nitric oxide synthase (eNOS) signaling pathway, followed by increasing the release of nitric oxide (NO) in human umbilical vein endothelial cells (HUVECs) (Li, Wang, et al. 2018). NO is a kind of vasodilator, and has the function of regulating vascular tension and resisting atherosclerosis (Ohta et al. 2005), contributing to the blood pressure-lowering effect of phloridzin.

Uric acid is the metabolic end product of purine, and its abnormally high concentration in the blood, known as hyperuricemia, is closely associated with cardiovascular diseases (Puddu et al. 2012). Uric acid can reduce the cell viability and tube formation of HUVECs, and increase the inflammatory response and monocyte adhesion. Phloretin can mitigate the hyperuricemia-induced endothelial injury by reducing inflammation, inhibiting the activation of the ERK/NF-κB signaling pathway, and reducing the uptake of uric acid via downregulating GLUT9 in HUVECs (Liu et al. 2017).

The progression of atherosclerosis is complicated, in which the cell adhesion factor-mediated inflammatory cell transendothelial migration and recruitment are important participants. The platelet aggregation promotes thrombosis and the occurrence and development of atherosclerosis, and thrombin plays an important role (Brass 2003; Kim et al. 2014). It is reported that phloretin can destroy the thrombin-induced stable adhesion of monocytes and platelets to the endothelium, revealing its potential for preventing thrombosis and atherosclerosis (Kim et al. 2014). Stangl et al. also find the suppressive effect of phloretin on platelet aggregation, probably by inhibiting the elevation of vascular cell adhesion molecule (VCAM)-1, intercellular adhesion molecule (ICAM)-1, and E-selectin induced by TNF-α or IL-1β in HUVECs (Stangl et al. 2005). During the process of leukocyte-endothelial cell interaction, the expression of adhesion molecules, including selectins, ICAMs, VCAMs, and integrins is activated (Blankenberg, Barbaux, and Tiret 2003). The vascular smooth muscle cell is another main component of the blood vessel wall, and their abnormal proliferation and migration are crucial for cardiovascular diseases. Phloretin is observed to inhibit the proliferation and migration of rat aortic smooth muscle cells induced by platelet-derived growth factor homodimer (Wang et al. 2015).

In addition, the cardioprotective effects of sweet tea and its compounds have also been demonstrated in animal models. The flavonoid fraction of sweet tea is reported to effectively reduce the blood pressure in spontaneously hypertensive rats (SHRs), while it does not affect normal rats (Hou et al. 2012). The same study also finds that the hypotensive activity may involve the regulation of the renin-angiotensin-aldosterone system, the antioxidant system, and the skin microcirculation. Moreover, phlorizin can improve the dyslipidemia of diabetic rats and can be used as an antihyperlipidemic agent (Najafian et al. 2012), with the possible mechanisms including the promotion of lipid hydrolysis and the inhibition of cholesterol biosynthesis by acting on 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase, suggesting that phlorizin has an effect on moderating hyperlipidemia, which may be helpful for the treatment of cardiovascular diseases. Besides, phlorizin can prevent ventricular tachyarrhythmia by improving impulse conduction slowing during ischemia in guinea-pig hearts (Hirose et al. 2014). Another major dihydrochalcone phloretin in sweet tea is reported to reduce the formation of neointima after carotid artery injury in rats, indicating that it has the potential to relieve atherosclerosis and restenosis after the vascular damage (Wang et al. 2015).

Sweet tea dihydrochalcones, therefore, can improve cardiovascular risk factors, such as high blood pressure, high blood lipid, high uric acid, and atherosclerosis, with no significant side effects.

Hepatoprotective activity

Sweet tea and its dihydrochalcones have hepatoprotective activities in vitro. Geohagen et al. report that the pharmacophores 2′,4′,6′-trihydroxyacetophenone (THA) and phloroglucinol of phloretin have a protective effect on acetaminophen (APAP)-induced hepatotoxicity in hepatocytes (Geohagen et al. 2016). The protective mechanism of THA is related to the resistance to oxidative stress.

Sweet tea and its dihydrochalcones also exhibit hepatoprotective activities in vivo. The total flavonoids of sweet tea show the ability to protect the liver against tetrachloromethane-induced injury in rats, probably due to its antioxidant activity (Li et al. 2013). One of the main dihydrochalcones in sweet tea, phloretin, is reported to alleviate liver histopathological lesion, and downregulate the elevation of liver damage indicators, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (γ-GT), alkaline phosphatase (ALP), and total bilirubin (TB) in mice with D-Galactosamine (D-GalN)-induced acute hepatic injury (Zuo et al. 2014). In addition, phloretin can also alleviate high choline diet-induced hepatotoxicity in mice, and regulate the oxidative stress indicators of the liver, such as malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) (Ren et al. 2016). Further, phlorizin has also been observed to reduce CCl_4-induced lipid peroxidation, protect hepatocyte membranes, and ameliorate hepatic fibrosis in rats (Deng et al. 2012).

In general, sweet tea and its dihydrochalcones, mainly phloretin and phlorizin, can improve the liver injury induced by D-GalN, APAP, and CCl_4, accompanied with the improvement of the liver histopathological lesion and liver function indexes.

Antimicrobial activity

The main dihydrochalcone of sweet tea, phloretin, has been reported to possess antimicrobial activities in vitro. It has been reported to suppress the growth of *Streptococcus*

pyogenes, *Pseudomonas fluorescens*, *and Photobacterium fischeri* (Adil, Baig, and Rupasinghe 2019; Wang, Gao, Wang, Wang, et al. 2019). It can also inhibit *Staphylococcus aureus* by directly targeting its pathogenic agent sortase B (SrtB), leading to the loss of SrtB activity (Wang, Gao, Wang, Wang, et al. 2019). In addition, it can prevent the formation of biofilm in *Escherichia coli* O157:H7 (Park et al. 2012). Similarly, it can inhibit the formation of *Salmonella typhimurium* biofilm by regulating pathogenic genes, and decrease the adhesion and invasion of *S. typhimurium* to IEC-6 cells (Wu et al. 2016).

On the other hand, phloretin also shows antimicrobial effects in vivo. It is reported to inhibit Zika virus infection by blocking glucose uptake (Lin et al. 2019). In addition, it can reduce the bacterial load in the cecum of the *Salmonella typhimurium*-infected mice (Wu et al. 2016). Moreover, by targeting and inhibiting SrtA and listeriolysin O, two virulence factors of *Listeria monocytogenes*, it can decrease the bacterial burden of infected mice (Wang et al. 2017).

In general, phloretin shows broad antimicrobial spectra, and it can not only inhibit the growth of bacteria, but also suppress virulence factors of bacteria, such as biofilms. Therefore, phloretin has the potential to be used as a natural food preservative, due to its antibacterial and antioxidant effects. However, whether other dihydrochalcones in sweet tea exhibit antimicrobial activity needs further investigation.

Other health benefits

Sweet tea and its dihydrochalcones also have other health benefits in vitro (Table 3). Sweet tea has a protective effect on human neuroblastoma neuronal cell damage induced by H_2O_2 (Gao, Liu, et al. 2018). As one of the main dihydrochalcones in sweet tea, trilobatin can protect neuronal PC12 cells from oxidative injury (Gao, Liu, et al. 2018). In addition, phloretin and phlorizin exhibit the activity of promoting lipolysis in cellular experiments (Huang et al. 2013).

Sweet tea and its dihydrochalcones also exhibit other health benefits in vivo. Sweet tea extract can reduce serum lipid levels and decrease body weight gain in diet-induced obese rats (Zhou et al. 2013). Phlorizin can ameliorate obesity in diet-induced obese animal models, and the mechanism of action includes improving the thermogenesis of brown adipose tissue and reducing insulin resistance (Shin et al. 2016; Yuan et al. 2016). Phlorizin has been shown to alleviate neuroinflammation and improve cognitive deficits in Alzheimer's disease rats, as well as enhancing memory storage in mice (Boccia, Kopf, and Baratti 1999; Tian et al. 2018).

The safety issue

The safety of sweet tea has also been investigated. Sweet tea flavonoids at 140 mg/kg/day cause no observed adverse effect, and its flavonoids at 560 mg/kg/d only causes minor side effects on the hematological and biochemical indexes in male SD rats, suggesting its overall safety in rodents (Liang et al. 2017). Hence, sweet tea is overall safe.

Conclusions

Sweet tea is herbal tea with pleasant sweetness widely used in the folk. It is rich in dihydrochalcones, mainly phlorizin, phloretin, and trilobatin. The health benefits of sweet tea and its main dihydrochalcones have been extensively investigated. Although some studies have investigated the potential molecular mechanisms of sweet tea extract and its main dihydrochalcones, such as the PI3K-Akt and MAPK signaling, potential molecular targets need to be further clarified. More importantly, there has been no report about the health benefits of sweet tea on human, especially its effect on diabetes, which should be further verified to support its folk usage to prevent and manage diabetes.

In addition, although the safe dose of sweet tea on rodents has been studied, the safe dose for humans has yet to be determined. Moreover, understanding the bioavailability, pharmacokinetics, and metabolic pathways of sweet tea dihydrochalcones in the body is the prerequisite for its further applications in human. In conclusion, sweet tea is a precious resource of natural dihydrochalcones. Due to its potential health benefits and sweet taste, sweet tea and its dihydrochalcones have the potential to be developed into functional foods or food additives with the applications in the food industry.

Disclosure statement

The authors declare no conflict of interest.

Funding

This study was supported by Local Financial Funds of National Agricultural Science and Technology Center, Chengdu (No. NASC2020KR02), the Central Public-interest Scientific Institution Basal Research Fund (No. Y2020XK05), and the National Key R&D Program of China (No. 2018YFC1604405).

ORCID

Hang-Yu Li http://orcid.org/0000-0003-2332-8554
Hua-Bin Li http://orcid.org/0000-0003-2332-8554
Ren-You Gan http://orcid.org/0000-0002-4162-1511

References

Abeles, A. M. 2015. Hyperuricemia, gout, and cardiovascular disease: An update. *Current Rheumatology Reports* 17 (3):13 doi: 10.1007/s11926-015-0495-2.

Abkin, S. V., O. S. Ostroumova, E. Y. Komarova, D. A. Meshalkina, M. A. Shevtsov, B. A. Margulis, and I. V. Guzhova. 2016. Phloretin increases the anti-tumor efficacy of intratumorally delivered heat-shock protein 70 kDa (HSP70) in a murine model of melanoma. *Cancer Immunology, Immunotherapy : CII* 65 (1):83–92. doi: 10.1007/s00262-015-1778-1.

Adil, M., M. H. Baig, and H. P. V. Rupasinghe. 2019. Impact of citral and phloretin, alone and in combination, on major virulence traits of *Streptococcus pyogenes*. *Molecules* 24 (23):4237. doi: 10.3390/molecules24234237.

Aliomrani, M., M. R. Sepand, H. R. Mirzaei, A. R. Kazemi, S. Nekonam, and O. Sabzevari. 2016. Effects of phloretin on oxidative

and inflammatory reaction in rat model of cecal ligation and puncture induced sepsis. *Daru Journal of Faculty of Pharmacy, Tehran University of Medical Sciences* 24 (1):15 doi: 10.1186/s40199-016-0154-9.

Amessou, M., S. Bortoli, V. Liemans, M. Collinet, B. Desbuquois, S. Brichard, and J. Girard. 1999. Treatment of streptozotocin-induced diabetic rats with vanadate and phlorizin prevents the over-expression of the liver insulin receptor gene. *European Journal of Endocrinology* 140 (1):79–86. doi: 10.1530/eje.0.1400079.

Balaha, M., S. Kandeel, and A. Kabel. 2018. Phloretin either alone or in combination with duloxetine alleviates the STZ-induced diabetic neuropathy in rats. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 101:821–32. doi: 10.1016/j.biopha.2018.02.135.

Blankenberg, S., S. Barbaux, and L. Tiret. 2003. Adhesion molecules and atherosclerosis. *Atherosclerosis* 170 (2):191–203. doi: 10.1016/S0021-9150(03)00097-2.

Boccia, M. M., S. R. Kopf, and C. M. Baratti. 1999. Phlorizin, a competitive inhibitor of glucose transport, facilitates memory storage in mice. *Neurobiology of Learning and Memory* 71 (1):104–12. doi: 10.1006/nlme.1998.3856.

Brass, L. F. 2003. Thrombin and platelet activation. *Chest* 124 (3 Suppl):18S–25S. doi: 10.1378/chest.124.3_suppl.18S.

Brouwers, B.,. V. Pruniau, E. J. G. Cauwelier, F. Schuit, E. Lerut, N. Ectors, J. Declercq, and J. W. M. Creemers. 2013. Phlorizin pretreatment reduces acute renal toxicity in a mouse model for diabetic nephropathy. *The Journal of Biological Chemistry* 288 (38):27200–7. doi: 10.1074/jbc.M113.469486.

Cai, Q., B. Y. Li, F. Yu, W. D. Lu, Z. Zhang, M. Yin, and H. Q. Gao. 2013. Investigation of the protective effects of phlorizin on diabetic cardiomyopathy in db/db mice by quantitative proteomics. *Journal of Diabetes Research* 2013:263845 doi: 10.1155/2013/263845.

Chang, W. T., W. C. Huang, and C. J. Liou. 2012. Evaluation of the anti-inflammatory effects of phloretin and phlorizin in lipopolysaccharide-stimulated mouse macrophages. *Food Chemistry* 134 (2):972–9. doi: 10.1016/j.foodchem.2012.03.002.

Cheon, D., J. Kim, D. Jeon, H. C. Shin, and Y. Kim. 2019. Target proteins of phloretin for its anti-inflammatory and antibacterial activities against *Propionibacterium acnes*-induced skin infection. *Molecules* 24 (7):1319. doi: 10.3390/molecules24071319.

Chung, M. J., J. K. Sohng, D. J. Choi, and Y. I. Park. 2013. Inhibitory effect of phloretin and biochanin A on IgE-mediated allergic responses in rat basophilic leukemia RBL-2H3 cells. *Life Sciences* 93 (9-11):401–8. doi: 10.1016/j.lfs.2013.07.019.

Deng, G. G., J. Z. Wang, Q. Y. Zhang, H. B. He, F. F. Wu, T. Y. Feng, J. G. Zhou, K. Zou, and M. Hattori. 2012. Hepatoprotective effects of phloridzin on hepatic fibrosis induced by carbon tetrachloride against oxidative stress-triggered damage and fibrosis in rats. *Biological & Pharmaceutical Bulletin* 35 (7):1118–25. doi: 10.1248/bpb.b12-00057.

Dong, H. Q., M. Li, F. Zhu, F. L. Liu, and J. B. Huang. 2012. Inhibitory potential of trilobatin from *Lithocarpus polystachyus Rehd* against alpha-glucosidase and alpha-amylase linked to type 2 diabetes. *Food Chemistry* 130 (2):261–6. doi: 10.1016/j.foodchem.2011.07.030.

Du, C. G., M. Bhatia, S. C. W. Tang, M. Z. Zhang, and T. Steiner. 2015. Mediators of inflammation: Inflammation in cancer, chronic diseases, and wound healing. *Mediators of Inflammation* 2015:570653 doi: 10.1155/2015/570653.

Duan, H. T., R. X. Wang, X. L. Yan, H. G. Liu, Y. Zhang, D. G. Mu, J. Han, and X. F. Li. 2017. Phloretin induces apoptosis of human esophageal cancer via a mitochondria-dependent pathway. *Oncology Letters* 14 (6):6763–8. doi: 10.3892/ol.2017.7037.

Ehrenkranz, J. R. L., N. G. Lewis, C. R. Kahn, and J. Roth. 2005. Phlorizin: A review. Diabetes Metab. Res. Rev 21 (1):31–8. doi: 10.1002/dmrr.532.

Fan, X. L., Y. H. Zhang, H. Q. Dong, B. Y. Wang, H. Q. Ji, and X. Liu. 2015. Trilobatin attenuates the LPS-mediated inflammatory response by suppressing the NF-κB signaling pathway . *Food Chemistry* 166:609–15. doi: 10.1016/j.foodchem.2014.06.022.

Frostegard, J. 2013. Immunity, atherosclerosis and cardiovascular disease. *BMC Medicine* 11 (117). doi: 10.1186/1741-7015-11-117.

Gaisano, H. Y., C. G. Ostenson, L. Sheu, M. B. Wheeler, and S. Efendic. 2002. Abnormal expression of pancreatic islet exocytotic soluble N-ethylmaleimide-sensitive factor attachment protein receptors in Goto-Kakizaki rats is partially restored by phlorizin treatment and accentuated by high glucose treatment. *Endocrinology* 143 (11):4218–26. doi: 10.1210/en.2002-220237.

Gao, J. M., S. Liu, F. Xu, Y. G. Liu, C. Lv, Y. Deng, J. S. Shi, and Q. H. Gong. 2018. Trilobatin protects against oxidative injury in neuronal PC12 cells through regulating mitochondrial ros homeostasis mediated by AMPK/Nrf2/Sirt3 signaling pathway. *Frontiers in Molecular Neuroscience* 11:267 doi: 10.3389/fnmol.2018.00267.

Gao, J. M., Y. S. Xu, J. Y. Zhang, J. S. Shi, and Q. H. Gong. 2018. Lithocarpus polystachyus Rehd. leaves aqueous extract protects against hydrogen peroxide- induced SH-SY5Y cells injury through activation of Sirt3 signaling pathway. *International Journal of Molecular Medicine* 42 (6):3485–94. doi: 10.3892/ijmm.2018.3916.

Geohagen, B. C., A. Vydyanathan, B. Kosharskyy, N. Shaparin, T. Gavin, and R. M. LoPachin. 2016. Enolate-forming phloretin pharmacophores: Hepatoprotection in an experimental model of drug-induced toxicity. *The Journal of Pharmacology and Experimental Therapeutics* 357 (3):476–86. doi: 10.1124/jpet.115.231001.

Gutierrez, B. L., G. Y. Zhong, and S. K. Brown. 2018. Increased phloridzin content associated with russeting in apple (*Malus domestica*). *Genetic Resources and Crop Evolution* 65 (8):2135–49. doi: 10.1007/s10722-018-0679-5.

Hamouda, N. N., M. A. Qureshi, J. M. Alkaabi, M. Oz, and F. C. Howarth. 2016. Reduction in the amplitude of shortening and Ca(2+) transient by phlorizin and quercetin-3-O-glucoside in ventricular myocytes from streptozotocin-induced diabetic rats . *Physiological Research* 65 (2):239–50. doi: 10.33549/physiolres.933045.

Han, L., C. Fang, R. X. Zhu, Q. Peng, D. Li, and M. Wang. 2017. Inhibitory effect of phloretin on α-glucosidase: Kinetics, interaction mechanism and molecular docking. *International Journal of Biological Macromolecules* 95:520–7. doi: 10.1016/j.ijbiomac.2016.11.089.

He, J. H., L. X. Chen, and H. Li. 2019. Progress in the discovery of naturally occurring anti-diabetic drugs and in the identification of their molecular targets. *Fitoterapia* 134:270–89. doi: 10.1016/j.fitote.2019.02.033.

Hirose, M., T. Shibazaki, T. Nakada, T. Kashihara, S. Yano, Y. Okamoto, M. Isaji, N. Matsushita, E. Taira, and M. Yamada. 2014. Phlorizin prevents electrically-induced ventricular tachyarrhythmia during ischemia in langendorff-perfused guinea-pig hearts. *Biological & Pharmaceutical Bulletin* 37 (7):1168–76. doi: 10.1248/bpb.b14-00046.

Hou, S. Z., S. X. Chen, S. Huang, D. X. Jiang, C. J. Zhou, C. Q. Chen, Y. M. Liang, and X. P. Lai. 2011. The hypoglycemic activity of *Lithocarpus polystachyus* Rehd. leaves in the experimental hyperglycemic rats. *Journal of Ethnopharmacology* 138 (1):142–9. doi: 10.1016/j.jep.2011.08.067.

Hou, S. Z., S. J. Xu, D. X. Jiang, S. X. Chen, L. L. Wang, S. Huang, and X. P. Lai. 2012. Effect of the flavonoid fraction of *Lithocarpus polystachyus* Rehd. on spontaneously hypertensive and normotensive rats. *Journal of Ethnopharmacology* 143 (2):441–7. doi: 10.1016/j.jep.2012.06.016.

Hsiao, Y. H., M. J. Hsieh, S. F. Yang, S. P. Chen, W. C. Tsai, and P. N. Chen. 2019. Phloretin suppresses metastasis by targeting protease and inhibits cancer stemness and angiogenesis in human cervical cancer cells. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* 62:152964 doi: 10.1016/j.phymed.2019.152964.

Huang, W. C., W. T. Chang, S. J. Wu, P. Y. Xu, N. C. Ting, and C. J. Liou. 2013. Phloretin and phlorizin promote lipolysis and inhibit inflammation in mouse 3T3-L1 cells and in macrophage-adipocyte co-cultures. *Molecular Nutrition & Food Research* 57 (10):1803–13. doi: 10.1002/mnfr.201300001.

Huang, W. C., Y. W. Dai, H. L. Peng, C. W. Kang, C. Y. Kuo, and C. J. Liou. 2015a. Phloretin ameliorates chemokines and ICAM-1 expression via blocking of the NF-κB pathway in the TNF-α-induced HaCaT human keratinocytes . *International Immunopharmacology* 27 (1):32–7. doi: 10.1016/j.intimp.2015.04.024.

Huang, W. C., S. J. Wu, R. S. Tu, Y. R. Lai, and C. J. Liou. 2015b. Phloretin inhibits interleukin-1β-induced COX-2 and ICAM-1 expression through inhibition of MAPK, Akt, and NF-κB signaling in human lung epithelial cells . *Food & Function* 6 (6):1960–7. doi: 10.1039/c5fo00149h.

Inoue, N. 2014. Stress and atherosclerotic cardiovascular disease. *Journal of Atherosclerosis and Thrombosis* 21 (5):391–401. doi: 10.5551/jat.21709.

Janssen, S. W. J., G. J. M. Martens, C. G. J. Sweep, P. N. Span, A. A. J. Verhofstad, and A. Hermus. 2003. Phlorizin treatment prevents the decrease in plasma insulin levels but not the progressive histopathological changes in the pancreatic islets during aging of Zucker diabetic fatty rats. *Journal of Endocrinological Investigation* 26 (6): 508–15. doi: 10.1007/bf03345212.

Katsuda, Y., T. Sasase, H. Tadaki, Y. Mera, Y. Motohashi, Y. Kemmochi, K. Toyoda, K. Kakimoto, S. Kume, and T. Ohta. 2015. Contribution of hyperglycemia on diabetic complications in obese type 2 diabetic SDT fatty rats: Effects of SGLT inhibitor phlorizin. *Experimental Animals* 64 (2):161–9. doi: 10.1538/expanim.14-0084.

Kim, J., P. Durai, D. Jeon, I. D. Jung, S. J. Lee, Y. M. Park, and Y. Kim. 2018. Phloretin as a potent natural TLR2/1 inhibitor suppresses TLR2-induced inflammation. *Nutrients* 10 (7):868. doi: 10.3390/nu10070868.

Kim, M. S., S. H. Park, S. Y. Han, Y. H. Kim, E. J. Lee, J. H. Y. Park, and Y. H. Kang. 2014. Phloretin suppresses thrombin-mediated leukocyte-platelet-endothelial interactions. *Molecular Nutrition & Food Research* 58 (4):698–708. doi: 10.1002/mnfr.201300267.

Kobori, M., K. Iwashita, H. Shinmoto, and T. Tsushida. 1999. Phloretin-induced apoptosis in B16 melanoma 4A5 cells and HL60 human leukemia cells. *Bioscience, Biotechnology, and Biochemistry* 63 (4):719–25. doi: 10.1271/bbb.63.719.

Kobori, M., H. Shinmoto, T. Tsushida, and K. Shinohara. 1997. Phloretin-induced apoptosis in B16 melanoma 4A5 cells by inhibition of glucose transmembrane transport. *Cancer Letters* 119 (2): 207–12. doi: 10.1016/S0304-3835(97)00271-1.

Kumar, S., K. Sinha, R. Sharma, R. Purohit, and Y. Padwad. 2019. Phloretin and phloridzin improve insulin sensitivity and enhance glucose uptake by subverting PPARγ/Cdk5 interaction in differentiated adipocytes . *Experimental Cell Research* 383 (1):111480. doi: 10.1016/j.yexcr.2019.06.025.

Li, B. Y., X. Y. Xu, R. Y. Gan, Q. C. Sun, J. M. Meng, A. Shang, Q. Q. Mao, and H. B. Li. 2019. Targeting gut microbiota for the prevention and management of diabetes mellitus by dietary natural products. *Foods* 8 (10):440. doi: 10.3390/foods8100440.

Li, C. Y., L. X. Wang, S. S. Dong, Y. Hong, X. H. Zhou, W. W. Zheng, and C. Zheng. 2018. Phlorizin exerts direct protective effects on palmitic acid (PA)-induced endothelial dysfunction by activating the PI3K/AKT/eNOS signaling pathway and increasing the levels of nitric oxide (NO). *Medical Science Monitor Basic Research* 24:1–9. doi: 10.12659/msmbr.907775.

Li, S. H., J. Y. Zeng, J. Tan, J. Zhang, Q. F. Wu, L. P. Wang, and X. J. Wu. 2013. Antioxidant and hepatoprotective effects of *Lithocarpus polystachyus* against carbon tetrachloride-induced injuries in rat. *Bangladesh Journal of Pharmacology* 8 (4):420–7. doi: 10.3329/bjp.v8i3.16458.

Li, W. Y., Z. Er, X. S. Su, Y. S. Li, and Z. D. Chen. 2000. Studies on antiallergic activity of tea and Tiancha in Yunnan. *The Journal of Pharmaceutical Practice* 5:292–4.

Li, X. C., B. Chen, H. Xie, Y. H. He, D. W. Zhong, and D. F. Chen. 2018. Antioxidant structure-activity relationship analysis of five dihydrochalcones. *Molecules* 23 (5):1162. doi: 10.3390/molecules23051162.

Li, Y., S. Li, S. J. Lin, J. J. Zhang, C. N. Zhao, and H. B. Li. 2017. Microwave-assisted extraction of natural antioxidants from the exotic *Gordonia axillaris* fruit: Optimization and identification of phenolic compounds. *Molecules* 22 (9):1481. doi: 10.3390/molecules22091481.

Liang, J., S. X. Chen, S. Huang, Y. Y. Wu, C. J. Zhou, D. X. Jiang, C. Y. Liang, H. Q. Yuan, S. Z. Hou, and X. P. Lai. 2017. Evaluation of toxicity studies of flavonoid fraction of *Lithocarpus polystachyus* Rehd in rodents. *Regulatory Toxicology and Pharmacology* 88: 283–90. doi: 10.1016/j.yrtph.2017.07.006.

Lin, C. Y., L. Wang, H. Wang, S. T. Fang, Q. B. Zhang, L. Q. Yang, H. J. Guo, P. Lin, J. Zhang, and X. J. Wang. 2014. *Lithocarpus Polystachyus* Rehd leaf aqueous extract inhibits human breast cancer growth *in vitro* and *in vivo*. *Nutrition and Cancer* 66 (4):613–24. doi: 10.1080/01635581.2014.894094.

Lin, S. C., M. C. Chen, S. F. Liu, V. M. Callahan, N. R. Bracci, C. W. Lehman, B. Dahal, C. L. de la Fuente, C. C. Lin, T. T. Wang, et al. 2019. Phloretin inhibits Zika virus infection by interfering with cellular glucose utilisation. *International Journal of Antimicrobial Agents* 54 (1):80–4. doi: 10.1016/j.ijantimicag.2019.03.017.

Liu, S. Y., Y. J. Yuan, Y. J. Zhou, M. Zhao, Y. N. Chen, J. Q. Cheng, Y. R. Lu, and J. P. Liu. 2017. Phloretin attenuates hyperuricemia-induced endothelial dysfunction through co-inhibiting inflammation and GLUT9-mediated uric acid uptake. *Journal of Cellular and Molecular Medicine* 21 (10):2553–62. doi: 10.1111/jcmm.13176.

Liu, Y. Y., C. H. Fan, L. Pu, C. Wei, H. Q. Jin, Y. M. Teng, M. M. Zhao, A. C. H. Yu, F. Jiang, J. L. Shu, et al. 2016. Phloretin induces cell cycle arrest and apoptosis of human glioblastoma cells through the generation of reactive oxygen species. *Journal of Neuro-Oncology* 128 (2):217–23. doi: 10.1007/s11060-016-2107-z.

Lu, M. Q., Q. Z. Kong, X. H. Xu, H. D. Lu, Z. X. Lu, W. Yu, B. Zuo, J. Su, and R. Guo. 2015. Evaluation of apoptotic and growth inhibitory activity of phloretin in BGC823 gastric cancer cell. *Tropical Journal of Pharmaceutical Research* 14 (1):27–31. doi: 10.4314/tjpr.v14i1.5.

Lu, W. D., B. Y. Li, F. Yu, Q. Cai, Z. Zhang, M. Yin, and H. Q. Gao. 2012. Quantitative proteomics study on the protective mechanism of phlorizin on hepatic damage in diabetic *db*/*db* betic db/db mice. *Molecular Medicine Reports* 5 (5):1285–94. doi: 10.3892/mmr.2012.803.

Ma, L. J., R. X. Wang, Y. D. Nan, W. P. Li, Q. W. Wang, and F. G. Jin. 2016. Phloretin exhibits an anticancer effect and enhances the anticancer ability of cisplatin on non-small cell lung cancer cell lines by regulating expression of apoptotic pathways and matrix metalloproteinases. *International Journal of Oncology* 48 (2):843–53. doi: 10.3892/ijo.2015.3304.

Malatiali, S., I. Francis, and M. Barac-Nieto. 2008. Phlorizin prevents glomerular hyperfiltration but not hypertrophy in diabetic rats. *Experimental Diabetes Research* 2008:1–7. doi: 10.1155/2008/305403.

Mariadoss, A. V. A., R. Vinayagam, V. Senthilkumar, M. Paulpandi, K. Murugan, B. J. Xu, K. M. Gothandam, V. S. Kotakadi, and E. David. 2019. Phloretin loaded chitosan nanoparticles augments the pH-dependent mitochondrial-mediated intrinsic apoptosis in human oral cancer cells. *International Journal of Biological Macromolecules* 130:997–1008. doi: 10.1016/j.ijbiomac.2019.03.031.

McCrimmon, R. J., M. L. Evans, R. J. Jacob, X. Fan, Y. Zhu, G. I. Shulman, and R. S. Sherwin. 2002. AICAR and phlorizin reverse the hypoglycemia-specific defect in glucagon secretion in the diabetic BB rat. *American Journal of Physiology. Endocrinology and Metabolism* 283 (5):E1076–83. doi: 10.1152/ajpendo.00195.2002.

Mei, X. R., X. Y. Zhang, Z. G. Wang, Z. Y. Gao, G. Liu, H. L. Hu, L. Zou, and X. L. Li. 2016. Insulin sensitivity-enhancing activity of phlorizin is associated with lipopolysaccharide decrease and gut microbiota changes in obese and type 2 diabetes (*db*/*db*) mice. *Journal of Agricultural and Food Chemistry* 64 (40):7502–11. doi: 10.1021/acs.jafc.6b03474.

Meng, J. M., S. Y. Cao, X. L. Wei, R. Y. Gan, Y. F. Wang, S. X. Cai, X. Y. Xu, P. Z. Zhang, and H. B. Li. 2019. Effects and mechanisms of tea for the prevention and management of diabetes mellitus and diabetic complications: An updated review. *Antioxidants* 8 (6):170. doi: 10.3390/antiox8060170.

Meng, Y., L. Ding, Y. Wang, Q. T. Nie, Y. Y. Xing, and Q. Ren. 2020. Phytochemical identification of *Lithocarpus polystachyus* extracts by ultra-high-performance liquid chromatography-quadrupole time-of-

flight-MS and their protein tyrosine phosphatase 1B and α-glucosidase activities. *Biomedical Chromatography : BMC* 34 (1):e4705. doi: 10.1002/bmc.4705.

Min, J., X. Li, K. N. Huang, H. Tang, X. Y. Ding, C. Qi, X. Qin, and Z. F. Xu. 2015. Phloretin induces apoptosis of non-small cell lung carcinoma A549 cells via JNK1/2 and p38 MAPK pathways. *Oncology Reports* 34 (6):2871–9. doi: 10.3892/or.2015.4325.

Muceniece, R., J. Namniece, I. Nakurte, K. Jekabsons, U. Riekstina, and B. Jansone. 2016. Pharmacological research on natural substances in Latvia: Focus on lunasin, betulin, polyprenol and phlorizin. *Pharmacological Research* 113 (Pt B):760–70. doi: 10.1016/j.phrs.2016.03.040.

Nagata, T., M. Suzuki, M. Fukazawa, K. Honda, M. Yamane, A. Yoshida, H. Azabu, H. Kitamura, N. Toyota, Y. Suzuki, et al. 2014. Competitive inhibition of SGLT2 by tofogliflozin or phlorizin induces urinary glucose excretion through extending splay in cynomolgus monkeys. *American Journal of Physiology. Renal Physiology* 306 (12):F1520–33. doi: 10.1152/ajprenal.00076.2014.

Najafian, M., M. Z. Jahromi, M. J. Nowroznejhad, P. Khajeaian, M. M. Kargar, M. Sadeghi, and A. Arasteh. 2012. Phloridzin reduces blood glucose levels and improves lipids metabolism in streptozotocin-induced diabetic rats. *Molecular Biology Reports* 39 (5):5299–306. doi: 10.1007/s11033-011-1328-7.

Ohta, M., H. Nanri, Y. Matsushima, Y. Sato, and M. Ikeda. 2005. Blood pressure-lowering effects of lifestyle modification: Possible involvement of nitric oxide bioavailability. *Hypertension Research: Official Journal of the Japanese Society of Hypertension* 28 (10): 779–86. doi: 10.1291/hypres.28.779.

Osorio, H., R. Bautista, A. Rios, M. Franco, A. Arellano, H. Vargas-Robles, E. Romo, and B. Escalante. 2010. Effect of phlorizin on SGLT2 expression in the kidney of diabetic rats. *Journal of Nephrology* 23 (5):541–6.

Park, A., H. H. Jeong, J. Lee, and C. S. Lee. 2012. The inhibitory effect of phloretin on the formation of *Escherichia coli* O157:H7 biofilm in a microfluidic system. *BioChip Journal* 6 (3):299–305. doi: 10.1007/s13206-012-6313-2.

Park, S. Y., E. J. Kim, H. K. Shin, D. Y. Kwon, M. S. Kim, Y. J. Surh, and J. H. Y. Park. 2007. Induction of apoptosis in HT-29 colon cancer cells by phloretin. *Journal of Medicinal Food* 10 (4):581–6. doi: 10.1089/jmf.2007.116.

Pei, F., B. Y. Li, Z. Zhang, F. Yu, X. L. Li, W. D. Lu, Q. Cai, H. Q. Gao, and L. Shen. 2014. Beneficial effects of phlorizin on diabetic nephropathy in diabetic *db*/*db* mice. *Journal of Diabetes and Its Complications* 28 (5):596–603. doi: 10.1016/j.jdiacomp.2014.04.010.

Puddu, P.,. G. M. Puddu, E. Cravero, L. Vizioli, and A. Muscari. 2012. Relationships among hyperuricemia, endothelial dysfunction and cardiovascular disease: molecular mechanisms and clinical implications. *Journal of Cardiology* 59 (3):235–42. doi: 10.1016/j.jjcc.2012.01.013.

Rani, V., G. Deep, R. K. Singh, K. Palle, and U. C. S. Yadav. 2016. Oxidative stress and metabolic disorders: Pathogenesis and therapeutic strategies. *Life Sciences* 148:183–93. doi: 10.1016/j.lfs.2016.02.002.

Ren, D. Y., Y. F. Liu, Y. Zhao, and X. B. Yang. 2016. Hepatotoxicity and endothelial dysfunction induced by high choline diet and the protective effects of phloretin in mice. *Food and Chemical Toxicology* 94:203–12. doi: 10.1016/j.fct.2016.06.004.

Rezk, B. M., G. Haenen, W. J. F. van der Vijgh, and A. Bast. 2002. The antioxidant activity of phloretin: The disclosure of a new antioxidant pharmacophore in flavonoids. *Biochemical and Biophysical Research Communications* 295 (1):9–13. doi: 10.1016/S0006-291X(02)00618-6.

Rolo, A. P., and C. M. Palmeira. 2006. Diabetes and mitochondrial function: Role of hyperglycemia and oxidative stress. *Toxicology and Applied Pharmacology* 212 (2):167–78. doi: 10.1016/j.taap.2006.01.003.

Sampath, C., S. M. Sang, and M. Ahmedna. 2016. *In vitro* and *in vivo* inhibition of aldose reductase and advanced glycation end products by phloretin, epigallocatechin 3-gallate and [6]-gingerol. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 84:502–13. doi: 10.1016/j.biopha.2016.09.073.

Saraswati, S.,. A. Alhaider, A. M. Abdelgadir, P. Tanwer, and H. M. Korashy. 2019. Phloretin attenuates STAT-3 activity and overcomes sorafenib resistance targeting SHP-1-mediated inhibition of STAT3 and Akt/VEGFR2 pathway in hepatocellular carcinoma. *Cell Communication and Signaling: CCS* 17 (1):127 doi: 10.1186/s12964-019-0430-7.

Shang, A., S. Y. Cao, X. Y. Xu, R. Y. Gan, G. Y. Tang, H. Corke, V. Mavumengwana, and H. B. Li. 2019. Bioactive compounds and biological functions of garlic (Allium sativum L.). *Foods* 8 (7):246. doi: 10.3390/foods8070246.

Shen, L., B. A. You, H. Q. Gao, B. Y. Li, F. Yu, and F. Pei. 2012. Effects of phlorizin on vascular complications in diabetes *db*/*db* mice. *Chinese Medical Journal* 125 (20):3692–6. doi: 10.3760/cma.j.issn.0366-6999.2012.20.017.

Shen, X., L. B. Wang, N. Zhou, S. C. Gai, X. Y. Liu, and S. Y. Zhang. 2020. Beneficial effects of combination therapy of phloretin and metformin in streptozotocin-induced diabetic rats and improved insulin sensitivity *in vitro*. *Food & Function* 11 (1):392–403. doi: 10.1039/c9fo01326a.

Shen, X., N. Zhou, L. Mi, Z. S. Hu, L. B. Wang, X. Y. Liu, and S. Y. Zhang. 2017. Phloretin exerts hypoglycemic effect in streptozotocin-induced diabetic rats and improves insulin resistance *in vitro*. *Drug Design, Development and Therapy* 11:313–24. doi: 10.2147/DDDT.S127010.

Shin, J. W., J. K. Kundu, and Y. J. Surh. 2012. Phloretin inhibits phorbol ester-induced tumor promotion and expression of cyclooxygenase-2 in mouse skin: Extracellular signal-regulated kinase and nuclear factor-κB as potential targets . *Journal of Medicinal Food* 15 (3):253–7. doi: 10.1089/jmf.2011.1851.

Shin, S. K., S. J. Cho, U. J. Jung, R. Ryu, and M. S. Choi. 2016. Phlorizin supplementation attenuates obesity, inflammation, and hyperglycemia in diet-induced obese mice fed a high-fat diet. *Nutrients* 8 (2):92. doi: 10.3390/nu8020092.

Stangl, V., M. Lorenz, A. Ludwig, N. Grimbo, C. Guether, W. Sanad, S. Ziemer, P. Martus, G. Baumann, and K. Stangl. 2005. The flavonoid phloretin suppresses stimulated expression of endothelial adhesion molecules and reduces activation of human platelets. *The Journal of nutrition* 135 (2):172–8. doi: 10.1093/jn/135.2.172.

Stumvoll, M., B. J. Goldstein, and T. W. van Haeften. 2005. Type 2 diabetes: Principles of pathogenesis and therapy. *Lancet (London, England)* 365 (9467):1333–46. doi: 10.1016/S0140-6736(05)61032-X.

Sun, Y., Y. Y. Yu, and S. W. Cao. 2013. Antioxidant capacity of caffeic acid, phloretin and glutathione mixtures and formula optimization. *Asian Journal of Chemistry* 25 (7):3971–8. doi: 10.14233/ajchem.2013.13860.

Sun, Y. S., W. Li, and Z. B. Liu. 2015. Preparative isolation, quantification and antioxidant activity of dihydrochalcones from sweet tea (*Lithocarpus polystachyus* Rehd.). *Journal of Chromatography. B, Analytical Technologies in the Biomedical and Life Sciences* 1002: 372–8. doi: 10.1016/j.jchromb.2015.08.045.

Tang, G. Y., X. Meng, Y. Li, C. N. Zhao, Q. Liu, and H. B. Li. 2017. Effects of vegetables on cardiovascular diseases and related mechanisms. *Nutrients* 9 (8):857. doi: 10.3390/nu9080857.

Tian, Y., L. Gao, Y. Guo, and Y. C. Xu. 2017. Short-term phlorizin treatment attenuates adipose tissue inflammation without alerting obesity in high-fat diet fed mice. *Journal of Food Biochemistry* 41 (6):e12407. doi: 10.1111/jfbc.12407.

Tian, Y., W. B. Lu, H. H. Deng, F. Yang, Y. Guo, L. Gao, and Y. C. Xu. 2018. Phlorizin administration ameliorates cognitive deficits by reducing oxidative stress, tau hyper-phosphorylation, and neuroinflammation in a rat model of Alzheimer's disease. *Journal of Food Biochemistry* 42 (6):e12644. doi: 10.1111/jfbc.12644.

Wang, D., Q. J. Wang, G. L. Yan, Y. Qiao, and C. C. Tang. 2015. Phloretin inhibits platelet-derived growth factor-BB-induced rat aortic smooth muscle cell proliferation, migration, and neointimal formation after carotid injury. *Journal of Cardiovascular Pharmacology* 65 (5):444–55. doi: 10.1097/fjc.0000000000000213.

Wang, G. Z., Y. W. Gao, H. S. Wang, J. F. Wang, and X. D. Niu. 2019. Correction to: Phloretin reduces cell injury and inflammation mediated by Staphylococcus aureus via targeting sortase B and the

molecular mechanism. *Applied Microbiology and Biotechnology* 103 (14):5925–7. doi: 10.1007/s00253-019-09924-7.

Wang, H., D. J. Wang, Y. B. Pu, D. K. Pan, W. J. Guan, and Y. H. Ma. 2012. Phloretin induced apoptosis of human hepatoma cells SMMC-7721 and its correlative biological mechanisms. *African Journal of Pharmacy and Pharmacology* 6 (9):648–59. doi: 10.5897/ajpp11.869.

Wang, H., T. Yang, T. Wang, N. Y. Hao, Y. C. Shen, Y. Q. Wu, Z. C. Yuan, L. Chen, and F. Q. Wen. 2018. Phloretin attenuates mucus hypersecretion and airway inflammation induced by cigarette smoke. *International Immunopharmacology* 55:112–9. doi: 10.1016/j.intimp.2017.12.009.

Wang, J., J. Fang, L. N. Wei, Y. Zhang, H. Deng, Y. R. Guo, C. Y. Hu, and Y. H. Meng. 2019. Decrease of microbial community diversity, biogenic amines formation, and lipid oxidation by phloretin in Atlantic salmon fillets. *LWT-Food Science and Technology* 101: 419–26. doi: 10.1016/j.lwt.2018.11.039.

Wang, J. F., Y. M. Huang, K. X. Li, Y. Y. Chen, D. Vanegas, E. S. McLamore, and Y. B. Shen. 2016. Leaf extract from *Lithocarpus polystachyus* Rehd. promote glycogen synthesis in T2DM mice. *Plos One* 11 (11):e0166557. doi: 10.1371/journal.pone.0166557.

Wang, J. F., B. W. Liu, Z. H. Teng, X. Zhou, X. Y. Wang, B. Zhang, G. J. Lu, X. D. Niu, Y. J. Yang, and X. M. Deng. 2017. Phloretin attenuates *Listeria monocytogenes* virulence both *in vitro* and *in vivo* by simultaneously targeting listeriolysin O and sortase A. *Frontiers in Cellular and Infection Microbiology* 7:9. doi: 10.3389/fcimb.2017.00009.

Wang, S. P., S. C. Lin, S. M. Li, Y. H. Chao, G. Y. Hwang, and C. C. Lin. 2016. Potent Potent antiarthritic properties of phloretin in murine collagen-induced arthritis. *Evidence-Based Complementary and Alternative Medicine : eCAM* 2016:9831263. doi: 10.1155/2016/9831263.

Wang, Z. G., Z. Y. Gao, A. Q. Wang, L. Jia, X. Y. Zhang, M. Fang, K. Yi, Q. J. Li, and H. L. Hu. 2019. Comparative oral and intravenous pharmacokinetics of phlorizin in rats having type 2 diabetes and in normal rats based on phase II metabolism. *Food & Function* 10 (3): 1582–94. doi: 10.1039/c8fo02242a.

Wu, C. H., Y. S. Ho, C. Y. Tsai, Y. J. Wang, H. Tseng, P. L. Wei, C. H. Lee, R. S. Liu, and S. Y. Lin. 2009. *In vitro* and *in vivo* study of phloretin-induced apoptosis in human liver cancer cells involving inhibition of type II glucose transporter. *International Journal of Cancer* 124 (9):2210–9. doi: 10.1002/ijc.24189.

Wu, S. C., B. D. Fu, X. L. Chu, J. Q. Su, Y. X. Fu, Z. Q. Cui, D. X. Xu, and Z. M. Wu. 2016. Subinhibitory concentrations of phloretin repress the virulence of *Salmonella typhimurium* and protect against *Salmonella typhimurium* infection. *Antonie Van Leeuwenhoek International Journal of General and Molecular Microbiology* 109 (11):1503–12. doi: 10.1007/s10482-016-0752-z.

Xia, Y., H. Feng, Z. W. Li, K. X. Tang, H. Q. Gao, W. L. Wang, X. P. Cui, and X. L. Li. 2020. Low-dose phloretin alleviates diabetic atherosclerosis through endothelial KLF2 restoration. *Bioscience, Biotechnology, and Biochemistry* 84 (4):815–23. doi: 10.1080/09168451.2019.1699396.

Xiao, Z. C., Y. Y. Zhang, X. Chen, Y. L. Wang, W. F. Chen, Q. P. Xu, P. M. Li, and F. W. Ma. 2017. Extraction, identification, and antioxidant and anticancer tests of seven dihydrochalcones from *Malus* 'Red Splendor' fruit. *Food Chemistry* 231:324–31. doi: 10.1016/j.foodchem.2017.03.111.

Xu, M., W. G. Gu, Z. Shen, and F. Wang. 2018. Anticancer activity of phloretin against human gastric cancer cell lines involves apoptosis, cell cycle arrest, and inhibition of cell invasion and INK signalling pathway. *Medical Science Monitor* 24:6551–8. doi: 10.12659/MSM.910542.

Yang, D. J., Z. C. Zhong, and Z. Y. Xiao. 1991. Sweet tea chemical composition research I: Sweet ingredients. *Chinese Traditional and Herbal Drugs* 3:99–101.

Yang, J., Y. Y. Huang, Z. Yang, C. Zhou, and X. J. Hu. 2018. Identification and quantitative evaluation of major sweet ingredients in sweet tea (*Lithocarpus polystachyus* Rehd.) based upon location, harvesting time, leaf age. *Journal of the Chemical Society of Pakistan* 40 (1):158–64.

Yang, Q., L. Han, J. Li, H. Xu, X. F. Liu, X. Y. Wang, C. Y. Pan, C. Z. Lei, H. Chen, and X. Y. Lan. 2019. Activation of Nrf2 by phloretin attenuates palmitic acid-induced endothelial cell oxidative stress via AMPK-dependent signaling. *Journal of Agricultural and Food Chemistry* 67 (1):120–31. doi: 10.1021/acs.jafc.8b05025.

Yang, Y. C., C. K. Lii, A. H. Lin, Y. W. Yeh, H. T. Yao, C. C. Li, K. L. Liu, and H. W. Chen. 2011. Induction of glutathione synthesis and heme oxygenase 1 by the flavonoids butein and phloretin is mediated through the ERK/Nrf2 pathway and protects against oxidative stress. *Free Radical Biology & Medicine* 51 (11):2073–81. doi: 10.1016/j.freeradbiomed.2011.09.007.

Ying, Y.,. C. Jiang, M. L. Zhang, J. Y. Jin, S. Y. Ge, and X. D. Wang. 2019. Phloretin protects against cardiac damage and remodeling via restoring SIRT1 and anti-inflammatory effects in the streptozotocin-induced diabetic mouse model. *Aging* 11 (9):2822–35. doi: 10.18632/aging.101954.

Ying, Y.,. J. Y. Jin, L. Ye, P. P. Sun, H. Wang, and X. D. Wang. 2018. Phloretin prevents diabetic cardiomyopathy by dissociating Keap1/Nrf2 complex and inhibiting oxidative stress. *Frontiers in Endocrinology* 9:774. doi: 10.3389/fendo.2018.00774.

Yuan, X., Y. Y. Wu, J. Liang, H. Q. Yuan, X. J. Zhao, D. M. Zhu, H. Z. Liu, J. Z. Lin, S. Huang, X. P. Lai, et al. 2016. Phlorizin treatment attenuates obesity and related disorders through improving BAT thermogenesis. *Journal of Functional Foods* 27:429–38. doi: 10.1016/j.jff.2016.09.022.

Zhang, J. J., Y. Li, S. J. Lin, and H. B. Li. 2018. Green extraction of natural antioxidants from the *Sterculia nobilis* fruit waste and analysis of phenolic profile. *Molecules* 23 (5):1059. doi: 10.3390/molecules23051059.

Zhang, L. Q., X. W. Yang, Y. B. Zhang, Y. Y. Zhai, W. Xu, B. Zhao, D. L. Liu, and H. J. Yu. 2012. Biotransformation of phlorizin by human intestinal flora and inhibition of biotransformation products on tyrosinase activity. *Food Chemistry* 132 (2):936–42. doi: 10.1016/j.foodchem.2011.11.071.

Zhang, S. Y., B. Y. Li, X. L. Li, M. Cheng, Q. Cai, F. Yu, W. D. Wang, M. Tan, G. Yan, S. L. Hu, et al. 2013. Effects of phlorizin on diabetic retinopathy according to isobaric tags for relative and absolute quantification-based proteomics in *db*/*db* mice. *Molecular Vision* 19: 812–21.

Zhang, Y. T., L. M. Lin, Y. H. Long, H. Y. Guo, Z. Wang, M. H. Cui, J. Huang, and Z. B. Xing. 2019. Comprehensive transcriptome analysis revealed the effects of the light quality. Forests 10 (11):995. doi: 10.3390/f10110995.

Zhang, Y. Z., T. Wang, J. J. Zhu, X. Liu, F. C. Zhou, and Q. Wang. 2018. Content determination of phlorizin and trilobatin in *Lithocarpus litseifolius* by HPLC. *China Pharmaceuticals* 27 (18):5–8. doi: 10.3969/j.issn.1006-4931.

Zhang, Z. C., S. Li, H. Y. Cao, P. Shen, J. X. Liu, Y. H. Fu, Y. G. Cao, and N. S. Zhang. 2019. The protective role of phloretin against dextran sulfate sodium-induced ulcerative colitis in mice. *Food & Function* 10 (1):422–31. doi: 10.1039/c8fo01699b.

Zhao, C. N., X. Meng, Y. Li, S. Li, Q. Liu, G. Y. Tang, and H. B. Li. 2017. Fruits for prevention and treatment of cardiovascular diseases. *Nutrients* 9 (6):598. doi: 10.3390/nu9060598.

Zhao, Y., X. Li, X. Zeng, S. Huang, S. Z. Hou, and X. P. Lai. 2014. Characterization of phenolic constituents in *Lithocarpus polystachyus*. *Analytical Methods* 6 (5):1359–63. doi: 10.1039/c3ay41288a.

Zhou, C. J., S. Huang, J. Q. Liu, S. Q. Qiu, F. Y. Xie, H. P. Song, Y. S. Li, S. Z. Hou, and X. P. Lai. 2013. Sweet tea leaves extract improves leptin resistance in diet-induced obese rats. *Journal of Ethnopharmacology* 145 (1):386–92. doi: 10.1016/j.jep.2012.09.057.

Zhou, M., J. K. Zheng, J. F. Bi, X. Y. Wu, J. Lyu, and K. Gao. 2017. Synergistic inhibition of colon cancer cell growth by a combination of atorvastatin and phloretin. *Oncology Letters* 15 (2):1985–92. doi: 10.3892/ol.2017.7480.

Zhou, Y., X. Y. Xu, R. Y. Gan, J. Zheng, Y. Li, J. J. Zhang, D. P. Xu, and H. B. Li. 2019. Optimization of ultrasound-assisted extraction of antioxidant polyphenols from the seed coats of red sword bean (*Canavalia gladiate* (Jacq.) DC). *Antioxidants* 8 (7):200. doi: 10.3390/antiox8070200.

Zhu, S. P., G. Liu, X. T. Wu, F. X. Chen, J. Q. Liu, Z. H. Zhou, J. F. Zhang, and S. J. Fei. 2013. The effect of Phloretin on human gamma delta T cells killing colon cancer SW-1116 cells. *International Immunopharmacology* 15 (1):6–14. doi: 10.1016/j.intimp.2012.11.001.

Zuo, A. R., Y. Y. Yu, Q. L. Shu, L. X. Zheng, X. M. Wang, S. H. Peng, Y. F. Xie, and S. W. Cao. 2014. Hepatoprotective effects and antioxidant, antityrosinase activities of phloretin and phloretin isonicotinyl hydrazone. *Journal of the Chinese Medical Association: JCMA* 77 (6):290–301. doi: 10.1016/j.jcma.2014.01.007.