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REVIEW

Hesperidin: A Therapeutic Agent For Obesity

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Abstract: Obesity is a chronic metabolic disease caused by multiple factors and is considered to be a risk factor for type 2 diabetes, cardiovascular disease, hypertension, stroke and various cancers. Hesperidin, a flavanone glycoside, is a natural phenolic compound with a wide range of biological effects. Mounting evidence has demonstrated that hesperidin possesses inhibitory effect against obesity diseases. Our review discusses mechanisms of hesperidin in the treatment of obesity. Hesperidin regulates lipid metabolism and glucose metabolism by mediating AMPK and PPAR signaling pathways, directly regulates antioxidant index and anti-apoptosis, and indirectly mediates NF-κB signaling pathway to regulate inflammation to play a role in the treatment of obesity. In addition, hesperidin-enriched dietary supplements can significantly improve symptoms such as postprandial hyperglycemia and hyperlipidemia. Further clinical trials are also required for confirming lipid-lowering efficacy of this natural flavonoid and evaluating its safety profile.

Keywords: citrus flavonoids, lipid metabolism, glucose metabolism, anti-oxidation, anti-inflammatory

Introduction

Obesity refers to the pathological state in which the intake of energy is greater than the consumption,[1] causing excessive body fat[2] and making the body weight more than 20% of the standard body weight.[3] Obesity is a metabolic syndrome[4] that is prevalent in today's society,[5] and its prevalence is increasing worldwide.[6] According to research, the global obese or overweight population has more than 30% of the global population,[7] and it has reached epidemic proportions globally.[8] Obesity has become a major public health problem worldwide.[9]

The prevalence of obesity continues to rise throughout the world, mainly due to lifestyle changes,[10] urbanization[11] and genetic factors,[12] such as eating habits and lack of exercise.[13] Food is one of the main environmental factors inducing obesity,[14] excessive consumption of dietary fat leads to an increase in the number of fat cells (hyperplasia) and size (hypertrophy).[15] The increase in fat cell size and the inability to store triglycerides under excessive feeding are critical for metabolic dysfunction and are characterized by activation of the inflammatory and apoptotic pathways and secretion of pro-inflammatory adipokines.[16] Obesity promotes the infiltration of inflammatory cells into various tissues, leading to the development of substantial and stromal cell interactions as well as cellular and organ dysfunction.[17] In addition, oxidative stress and injury are involved in the pathophysiology of obesity and its metabolic complications.[18] Insulin(INS) resistance is a pathological condition in which insulin target tissues (muscle, liver, adipose tissue, and hypothalamus) are insufficiently sensitive to normal levels of insulin.[19] Excessive accumulation of visceral fat is the main cause of inflammation[20] and insulin resistance,[9]

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and is closely related to the occurrence of cardiovascular,[21,22] cerebrovascular diseases, hypertension,[23] type 2 diabetes,[24,25] hyperlipidemia, sleep apnea syndrome[26] and other diseases.[27] It has also increased non-alcoholic fatty liver disease,[9] cancer[28] and other diseases, which seriously affect the health of patients and even endanger their lives.[7] Therefore, prevention and treatment of obesity[29] is the key to reducing the increasing morbidity and mortality of humans.[6]

Flavonoids are a class of phenolic compounds widely distributed in plants. Currently, a large number of these compounds are evaluated in the form of free state and glycoside,[30] and have some biological properties including antioxidant,[31,32] anticancer and anti-inflammatory[33] effects.[34] The adipose tissue is the primary regulator of energy balance and nutrient homeostasis. White adipose tissue(WAT)[35] is the main site of excess energy storage in the form of triglycerides, while brown adipose tissue(BAT)[36] with multi-room fat cells contains large amounts of mitochondria. Under some stimulations such as high-fat diets, the content of mitochondria in WATs increases dramatically, a process called "browning". Thus, it can prevent obesity and lipid accumulation through induction of brown-like adipocyte formation.[9,37] Citrus flavonoids have been proven to induce browning of white adipocytes,[38] reduce plasma lipid levels, improve glucose tolerance, and reduce obesity,[39] and can also be used to prevent postprandial hyperglycemia.[40] Studies have shown that feeding a high-fat, high-cholesterol diet for 12 weeks affects atherosclerosis, PPARs, lipoprotein receptors, and apolipoprotein-related genes in monocyte chemoattractant protein-3 mice.[41] During the differentiation of adipocytes, several transcription factors, including CCAAT/enhancer binding protein(C/EBPs) and peroxisome proliferator-activated receptor gamma(PPAR-γ), activate lipogenesis.[42] Extracts of citrus flavonoids inhibit intracellular triglyceride and fat accumulation and reduce the expression of PPAR-γ 2[43] Citrus flavonoids inhibit oleic acid-induced expression of miR-122 and miR-33, and their target mRNAs fatty acid synthase(FAS) and carnitine palmitoyltransferase 1α(TNF-α) are likely to be the main mechanisms leading to decreased lipid accumulation in HepG 2 cells.[44] It has been reported that the chemical structure of flavanones is the most effective in inhibiting adipogenesis because flavonoids such as hesperidin induce a significant decrease in triacylglycerol content in preadipocytes.[45] Recent studies have shown that citrus flavonoids play an important role in the treatment of dyslipidemia, insulin resistance, hepatic steatosis, obesity and atherosclerosis. Citrus flavonoids, including naringenin, hesperidin, nobiletin and hesperetin, have become promising therapeutic agents for the treatment of metabolic disorders.[46]

Hesperidin($C_{28}H_{34}O_{15}$) is a flavonoid glycoside[47] which was first isolated from citrus peel by the French chemist Lebreton.[48] The presence of this compound has also been proven in the genus Rutaceae, the bergamot fruit,[49] the banana fruit, the lemon fruit, the lemon peel, etc.[50] It may also be present in the aerial part of the genus Rubiaceae and the Cruciferous plant leeks, with roots and whole grasses. Hesperidin has an aglycon (hesperetin or methyl eriodictyol) bonded to rutinose [6-O-(α-l-Rhamnopyranosyl)-D-glucopyranose] and/or [6-O-(α-l-Rhamnosyl)-D-glucose], as a disaccharide, in its structure[47] (Figure 1).

Mechanisms Of Hesperidin In The Treatment Of Obesity

Hesperidin has anti-inflammatory, anti-oxidative and anti-cancer activities, can lower cholesterol levels and blood pressure,[28] and has anti-obesity activity.[43] Hesperetin and hesperidin can stimulate the release of cholecystokinin (CCK), an appetite-regulating hormone, in enteroendocrine STC-1 cells, which is ultimately used to treat obesity by suppressing appetite.[51] Dietary bioflavonoid hesperidin can reduce cholesterol and triglyceride levels in broiler serum and pectoral muscle, and positively improve fatty acid and lipid metabolism in broiler breasts in a dose-dependent manner.[52] The main types of HPD metabolism in rats are mainly hydrolysis, demethoxylation, dehydration, dehydrogenation, demethylation, glucuronide binding, sulfate binding and N-acetylcysteine binding.[53] HPD can significantly increase

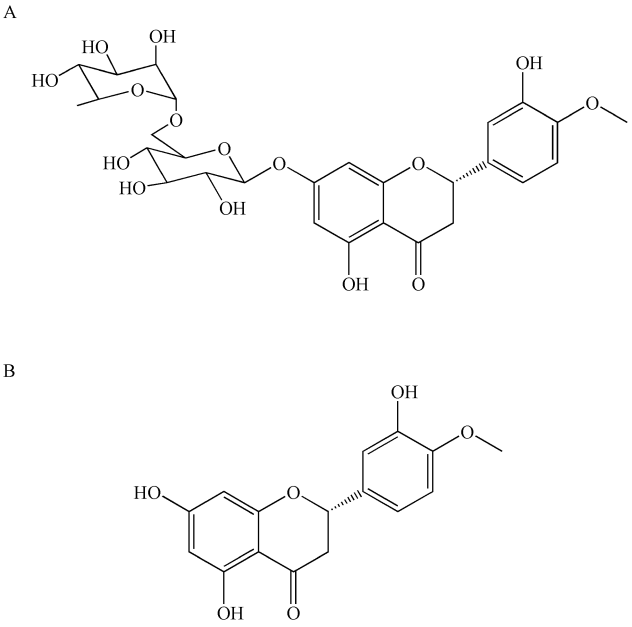

Figure 1 Chemical structures of hesperidin (**A**) and hesperetin (**B**).

the level of α-KL in serum, liver and kidney tissues of diabetic rats, and significantly reduce the levels of aspartate aminotransferase(AST), alanine aminotransferase(ALT), blood urea nitrogen(BUN) and creatinine in fibroblast growth factor-23(FGF-23) in kidney tissues and serum samples.[54] High-dose hesperidin up-regulates adenosine 5′-monophosphate (AMP)-activated protein kinase(AMPK) mRNA expression in mice with glycolipid metabolism disorder induced by high-fat diet, affecting insulin signaling pathway (insulin receptor (INSR), insulin receptor substrate 1(IRS-1), GLUT2/4) and lipid metabolism-related genes (sterol regulatory element-binding protein 1c(SREBP1c) and FAS and acetyl-CoA carboxylase(ACC)) gene expression also activates PPAR-α mRNA expression.[55] In addition, HPD enhances the expression of genes encoding LDL receptors, which are some of the possible mechanisms by which HPD reduces blood lipids.[56]

The details on weight loss effect of hesperidin are shown in Table 1.

The Effect Of Hesperidin On Lipid Metabolism

Changes in body fat content beyond a certain limit can cause obesity,[73] so obesity is closely related to fat metabolism. Hesperidin can improve lipid metabolism[74] (Figure 2). Adipose tissue stores lipids in the form of triglycerides, which secrete and regulate a variety of adipokines and cytokines. During obesity, in order to compensate for excessive lipid load, adipose tissue rapidly expands.[46] Hesperidin (0.08%) reduces hepatic steatosis, adipose tissue and liver weight, and decreases serum total cholesterol and retinol binding protein(RBP) 4 concentrations in high-fat diets.[60] Heart fatty acid–binding protein(H-FABP)and cutaneous fatty acid–binding protein(C-FABP) are thought to play key roles in fatty acid metabolism, such as fatty acid storage and transport.[62] Hesperidin may improve hypercholesterolemia and fatty liver by inhibiting cholesterol synthesis and absorption, regulating RBP, C-FABP and H-FABP mRNA expression.[60] HPD reduced systolic blood pressure(SBP),[75] plasma total cholesterol and TG levels in obese hypertensive rats, attenuated plasma fatty acid synthase(FFA) through its anti-lipolytic activity, significantly increased high density lipoprotein-cholesterol(HDL-C), and decreased plasma low density lipoprotein-cholesterol(LDL-C) and very low density lipoprotein-cholesterol(VLDL-C).[63]

Hesperidin inhibits genes involved in the three stages of adipogenesis, C/EBPβSREBP1c, PPAR-γ and perilipin.[68] Hesperidin-treated animals showed decreased expression levels of three key adipogenesis-related genes, SREBP1, FAS[68] and stearoyl-CoA desaturase(SCD),[32] and normalization of PKLR gene expression.[8] Hesperidin showed specific inhibitory activity on 3T3-L1 preadipocytes in the intermediate stage of differentiation.[32] HPD increases the expression of messenger RNA by hormone-sensitive lipases and stimulates the breakdown of mature adipocytes.[76] Hesperidin significantly down-regulates the expression of stearoyl-CoA desaturase, fatty-acid desaturase(FAT-6 and FAT-7), and reduces the expression of other genes involved in lipid metabolism, including acetyl-CoA carboxylase-2(POD-2), mediator subunit-15(MDT-15), acyl-CoA synthetase-2(ACS-2) and 3-ketoacyl-CoA thiolase-1 (KAT-1), thereby reducing fat accumulation.[72] Dietary bioflavonoid hesperidin can positively improve fatty acid and lipid metabolism in broiler breasts in a dose-dependent manner.[52] Therefore, hesperidin can treat obesity to a certain extent by regulating adipokines, cytokines, genes, and the like in lipid metabolism.

The Effect Of Hesperidin On Glucose Metabolism

Obesity has a certain degree of impaired glucose tolerance[77] and insulin dysfunction.[78] Impaired glucose metabolism-related genetic variants likely interact with obesity-modifiable factors in response to glucose intolerance.[79] Glucose provides most of the carbon used to construct the essential molecules of daughter cells, such as amino acids, fatty acids and nucleotides.[80] Hesperidin shows moderate and selective alpha-glucosidase inhibitory activity,[81] and it can inhibit the digestion of amylose and amylopectin and significantly reduce glucose-6-phosphatase activity in HepG2 cells.[40] Docking simulations showed that hesperetin and hesperidin block enzyme entry into the channel, preventing the production of pyruvate, alpha-ketoglutarate and oxaloacetate, inhibiting hepatic gluconeogenesis, thereby impeding the progression of diabetes.[58] In addition, hesperidin stimulates glycogenolysis and glycolysis in isolated perfused rat liver[57] and reduces glucose levels induced in porcine streptozotocin-induced diabetic and diabetic rat models.[82] The postprandial glycemic response of orange juice can be adjusted by partially inhibiting the intestinal glucose transporter according to the concentration of sugar and hesperidin,[83] indicating that hesperidin can be used to prevent postprandial hyperglycemia.[40]

PPAR-c is a nuclear protein transcription factor that regulates lipid and glucose metabolism, and hesperidin maintains glucose metabolism by regulating PPAR-c activation

Table 1 Studies Demonstrating The Weight Loss Effect Of Hesperidin

Model	Dose And Treat Time	Described Effect	Weight Loss Mechanism	Ref
Sisolated perfused male wistar rats, ad libitum with a standard laboratory diet	300μM; 0–70min	Glycogenolysis and glycolysis in the liver↑; glucose phosphorylation catalysed by GK↓	G-6-Pase↓	57
Rats	1mL; 24h	Enzyme activities↓; production of pyruvate↓; hepatic gluconeogenes↓; α-ketoglutarate and the oxaloacetate↓	Liver ALT↓; liver AST↓	58
HIGH fat fed/streptozotocin-induced type 2 diabetic rats	50mg/kg; 4w	Serum glucose and glycosylated hemoglobin↓; vitamin C and vitamin E↑	NO↓; IL-6↓; TNF-α↓; serum INS↑; GSH↑; liver MDA↓; liver antioxidant enzymes↑	59
Male wistar rats, high-cholesterol diet	25g/d; 12w	Hepatic steatosis, adipose tissue and liver weights↓; serum TC ↓	RBP, H-FABP, C-FABP in liver and adipose tissue↓	60
Male wistar rats, high-fat/sucrose (western) diet	100mg/kg; 8w	Blood lipid profle↑; hepatic lipid accumulation↓; non-alcoholic steatohepatitis↓	SREBP1↓; PPAR-γ↓; SCD↓; FAS↓	8
Type 2 diabetic rats, high fat diet	50mg/kg; 4w	White blood cell count↓; neutrophils↓; monocytes↓; basophils↓	IL-6↓; adipose tissue ACDC↑	61
Streptozotocin-induced marginal type 1 diabetic rats	10g/kg; 4w	Blood glucose↓; TC↓	Serum ACDC↑; TG↓; G-6-Pase↓; GK↑; LDL-C↓; VLDL-C↓; HDL-C↑; serum INS↑;	56
Rats, high-cholesterol diet	8mg/d; 6–12w	Body and liverand adipose tissue weights↓; cholesterol synthesis and absorption↓	Lipid-related factors (RBP4, H-FABP and C-FABP)↓; ICAM-1↓; inflammatory-related factors (MCP1, CCR2 and TNF-α)↓	62
Goto-Kakizaki weanling rats with type 2 diabetes	0.01g/; 4w	Lipids in the serum and liver↓; blood glucose↓; HDL-C/TC↑	The genes coding for PPARs↑; HMG-CoA reductase↓; the expression of genes encoding LDL receptor↑; serum ACDC↑; TG↓; INS↑	15
Rats with diabetes induced by streptozotocin	100mg/kg; 2w	Strong positive effects on diabetic toxicity in the liver and kidneys	Liver, kidney and serum α-KL ↑; FGF-23↓; MDA↓	20
Rats subjected to isoproterenol- induced cardiotoxicity	200mg/kg; 7d	TC↓	LDL-C↓; TG↓; VLDL-C↓; FFA↓; plasma PL↓; HDL-C↑; PL in the heart and liver↑	63
Rats, high-cholesterol diet	100mg/kg; 5d	TC↓; HDL-C/TC↑; serum triglyceride levels↓	GSH in the liver↑; serum and liver MDA↓	64
Streptozotocin-induced hyperglycemic mice	200mg/kg; 14d	Blood glucose↓; lipid peroxidation and total nitrate/nitrite↓	Bad/Bcl-2↑; Bad/Bcl-XL↑; SOD↑; GSH↑	65
C57BL/6J mice, high-fat diet	100mg/kg/d; 4w	Serum total antioxidant capacity↑; liver TBARS levels↓; spleen mass↓; fat accumulation↓; liver damage↓	IL-6↓; MCP-1↓; hs-CRP↓; LDL-C↓	66
C57 mice, high-fat diet	100,200,400mg/kg/d; 16w	Body weight↓; body fat deposition↓; serum glucose↓; serum lipid↓; HOMA-IR index↓	mRNA of AMPK↑; serum INS↑; impact on signaling pathway genes↑ (INSR, IRS-1, GLUT2/4) and lipid metabolism pathway genes (SREBP1↓, FAS↓, ACC↓,PPAR-α↑)	55
Mice, high-fat diet	0.07mg/100g; 9w	Body weight and liver and adipose tissue weight↓	PPAR-γ↑	67
C2C12 cells	0.07mg/100g; 6h	Stimulated glucose↑	PPAR-γ↑	

(*Continued*)

Table 1 (Continued).

Model	Dose And Treat Time	Described Effect	Weight Loss Mechanism	Ref
Pre-adipocytes of mesenchymal stem cells	1,10,25μM; 48h-8d	Anti-adipogenic and delipidating	C/EBPβ↓; SREBP1↓; perilipin↓;PPAR-γ↓	68
Mature adipocytes from mesenchymal stem cells	1,10,25μM; 48h-8d	Anti-adipogenic effect and delipidating	mRNA of ATGL↑; FAS↓;TG accumulation↓	
3T3-L1 pre-adipocytes	1,10,25μM; 0-60h-8d	Lipid accumulation↓; riacylglycerol content in pre-adipocytes↓	SREBP1↓	45
3T3-L1 adipocytes	20μM; 8d	Lipid accumulation↓	ROS↓; PPAR-γ↓; C/EBPα↓; FABP4↓	28
3T3-L1 cells	0.5mg/mL; 24h	Induction of adipolytic activity↓; key adipogenic transcription factors↓	C/EBPα↓; PPAR-γ↓; SREBP1↓	42
3T3-L1 cells	10, 50, 100μM; 8d	Anti-lipogenic capacity↑	Binding affinity for the PPAR-γ rceptor↓; SCD↓; LPL↓	69
RAW264.7 and 3T3-L1 cells	1.8–8.3μM; 24h	Anti-inflammatory activity↑	ACDC↑; IL-6↓; TNF-α↓; NO↓	70
Enteroendocrine STC-1 cells	0.1,0.5,1.0μM; 60min	Appetite-regulating hormones↑; cholecystokinin release↑	Intracellular Ca(2+) concentrations↑	51
Retinal ganglial cells −5	12.5,25,50μmol/L; 6h	High glucose-mediated cell loss↓; mitochondrial function↑; Cell apoptosis↓	ROS, MDA and protein carbonyl↓; SOD↑; CAT↑; GSH↑; caspase-9, caspase-3 and Bax/Bcl-2↓	71
HepG2 cells	100ug/mL; 48h	Lipid accumulation↓	miR-122 and miR-33 expression↓; CPT1α↑; FAS↓	44
HepG-2 cells	50μM; 1min	Digestive enzyme activities↓; glycogen↑	GK activity↑; G-6-Pase↓	40
Porcine pancreas	100μM; 1min	Glucose consumption↑; glycogen↑; glucokinase activity↑	α-amylase activity↓; α-glucosidase activity↓	
Caenorhaditis elegans	50μM,100μM; 0–35d	Fat accumulation↓; the ratio of oleic acid/stearic acid↓	SCD↓; FAT-6↓; FAT-7↓; POD-2↓; MDT-15↓; ACS-2↓; KAT-1↓	72
Broilers	20mg/kg; 42d	Plasma antioxidant parameters↑; TC↓; total antioxidant capacity↑	Total SOD↑; MDA↓; TG↓	52

Note: ↓indicates inhibition/reduction while ↑indicates increase/promotion.

Abbreviations: ACDC, adiponectin; hs-CRP, High-sensitivity C-reactive protein; INSR, Insulin receptor; IRS-1, Insulin receptor substrate 1; ATGL, adipose triacylglyceride lipase; PL, phospholipids; FFA, free fatty acids; TG, triglycerides; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; VLDL-C, very low density lipoprotein-cholesterol; MDA, malondialdehyde; GSH, glutathione; G-6-Pase, glucose-6-phosphatase; HMG-CoA,3-hydroxy-3-methyl-glutatyl coenzyme A; α-KL, α-Klotho; FGF-23, fibroblast growth factor-23; RBP4,retinol-binding protein 4; CCR2, C-C chemokine receptor type 2; MCP1, monocyte chemoattractant protein-1; TNF-α, tumor necrosis factor alpha; TBARS, thiobarbituric acid reactive substances; ROS, reactive oxygen species; CAT, catalase; GK, glucokinase; C/EBPβ, CCAAT/enhancer-binding protein beta; PPAR-γ, peroxisome proliferator-activated receptor gamma; SREBP1, sterol regulatory element-binding protein 1; RBP, lipid metabolism–related proteins; H-FABP, heart fatty acid–binding protein; C-FABP, cutaneous fatty acid–binding protein; IL-6,interleukin-6; NF-κB, nuclear factor kappa B; SCD, stearoyl-CoA desaturase; TC, Total cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPT1α, carnitine palmitoyltransferase 1α; FAS, fatty acid synthase; LPL, lipoprotein lipase; FAT-6/7, Fatty-acid desaturase 6/7; ACS-2, acyl-CoA synthetase-2; KAT-1, ketoacyl-CoA thiolase-1; POD-2, acetyl-CoA carboxylase-2; MDT-15, mediator subunit-15.

and inhibiting fat accumulation.[67] It has been demonstrated in weaned Goto-Kakizaki rats that hesperidin and cyclodextrin-clathrated hesperetin normalize blood glucose levels by altering the activity of glucose-regulating enzymes and lowering serum and liver lipid levels. These hypoglycemic and hypolipidemic effects in type 2 diabetic rats are partially altered by altering the expression of genes encoding PPAR, 3-hydroxy-3-methyl-glutatyl coenzyme A(HMG-CoA) reductase and LDL receptors.[15] RBP4 has been identified as an adipokines involved in the regulation of glucose metabolism.[62] The activation of GLUT4 enhances glucose uptake and increases the amount of intracellular glucose available for metabolic conversion, thereby promoting enhanced cell proliferation.[80] Hesperidin can reduce the expression of RBP4 and affect GLUT4[60] Insulin can promote the synthesis of fatty acids in the liver, promote the entry of

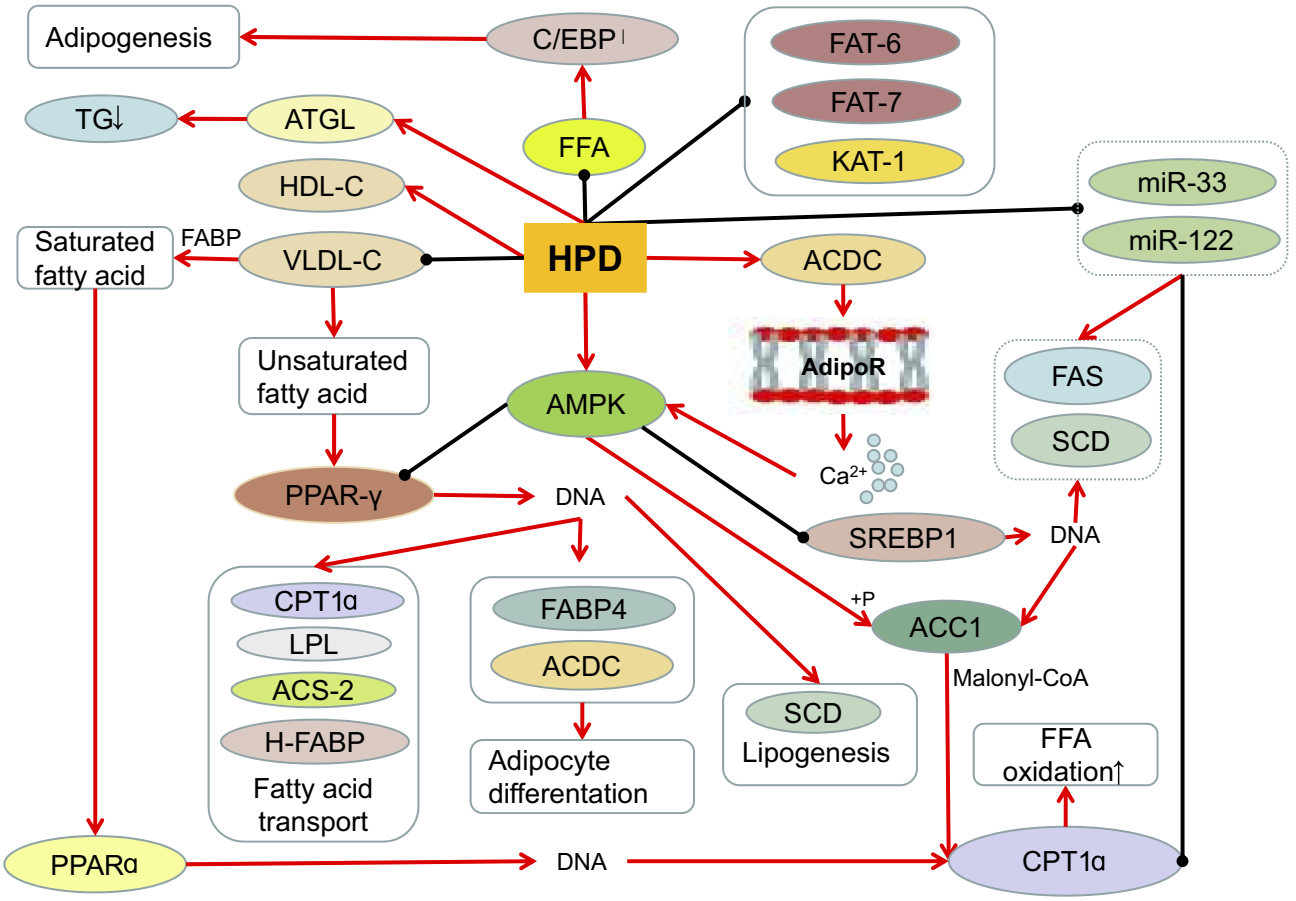

Figure 2 The effect of hesperidin on lipid metabolism.
Note: ⊣ indicate inhibition/reduction while → indicate increase/promotion.

glucose into fat cells and convert it into triacylglycerol for storage, while inhibiting the activity of lipase and reducing the decomposition of fat.[84] Insulin resistance caused by obesity inhibits insulin absorption of glucose and fat in muscle and muscle tissue.[19] Hesperidin indirectly affects insulin resistance and stimulates intestinal microbial growth to increase the production of short-chain fatty acid(SCFA), thereby regulating adipose tissue, skeletal muscle and liver tissue function, and improving glucose homeostasis and insulin sensitivity.[85] Hesperidin directly or indirectly regulates the metabolism of glucose and insulin (Figure 3) to improve the interaction between obesity and glucose metabolism disorders (such as hyperglycemia, diabetes, etc.), which is one of the effective ways to treat obesity.

The Effect Of Hesperidin On Oxidation And Inflammation

The serum oxidative index of young obese subjects increased significantly, and the antioxidant index decreased significantly, suggesting that accumulation of oxidative products in serum may be one of the causes of obesity.[86,87] Hesperidin decreases the contents of glucose, glycosylated hemoglobin(HbA1c%), MDA and NO in diabetic rats, and increases levels of serum insulin, GSH, vitamin C and vitamin E. It has a protective effect on oxidative damage induced by hyperglycemia.[59] The combination of hesperidin and alpha amylase has low antioxidant activity.[88] Hesperidin can prevent the increase of reactive oxygen species(ROS) production in rats by exhaustive exercise, and avoid the decrease of SOD and catalase activity in thymus and spleen,-[89] which can effectively inhibit the formation of superoxide and oxygen.[90] Hesperidin reduces ROS, MDA, caspase-9, caspase-3 and Bax/Bcl-2 levels and inhibits apoptosis, thereby protecting RGC-5 cells from high glucose-induced oxidative stress.[71] Dietary application of different levels of hesperidin has a significant effect on the antioxidant capacity of mutton during cold storage,[91] and can also increase plasma antioxidant parameters of broilers, including total antioxidant

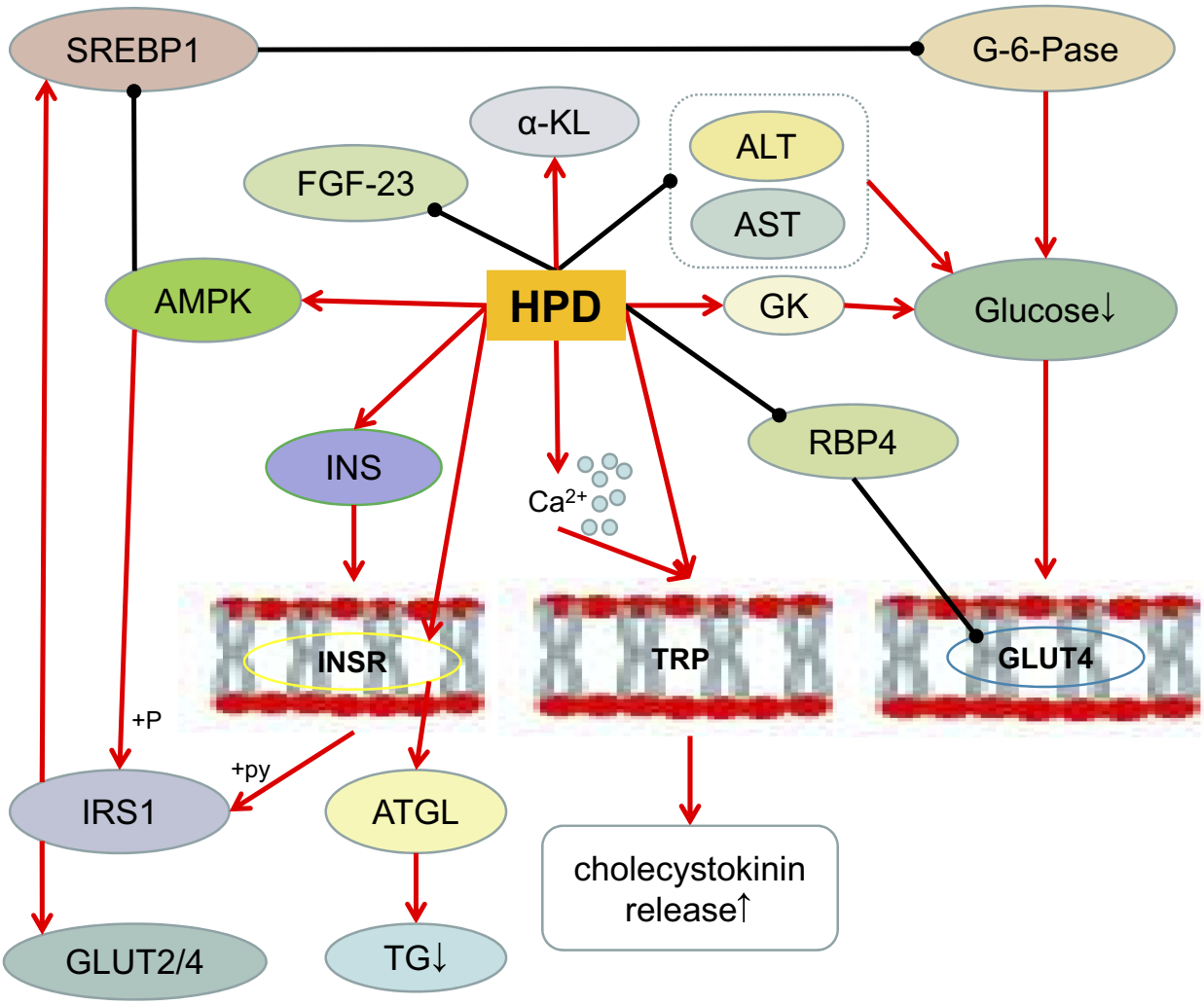

Figure 3 The effect of hesperidin on glucose metabolism.
Note: —● indicate inhibition/reduction while → indicate increase/promotion.

capacity, malondialdehyde(MDA) production, and total superoxide dismutase(SOD) activity.[52] Medium doses of hesperidin(100 mg/kg) and high doses of hesperidin(200 mg/kg) improved and increased the level of endogenous antioxidant enzyme glutathione(GSH) in the liver of hyperlipidemic rats.[64] Hesperidin can alter the oxidative state in hepatocytes by affecting parameters related to hepatic fatty acid oxidation, namely oxygen uptake, citrate cycling activity and ketone production.[92] The bioflavonoid mixture of curcumin, hesperidin and rutin improves hepatic oxidative stress caused by streptozotocin- induced hyperglycemia, thereby improving liver function and glucose regulation.[65]

Obesity is a systemic low-level chronic persistent inflammatory state.[93] It is currently believed that the pathophysiological basis of obesity is the early inflammatory changes in adipose tissue.[94] PPAR-γ is a nuclear transcription factor involved in the inhibition of nuclear factor kappa B(NF-κB) activation and IL-6 production, which can be induced by adiponectin, while adiponectin pretreatment of porcine macrophages inhibits NF-κB activation and inhibits TNF-α secreted by LPS-stimulated macrophages.[70] Injection of hesperidin can increase the content of adiponectin, thereby reducing lipid accumulation.[56] Oral administration of 50 mg/kg hesperidin daily in type 2 diabetic rats for 4 weeks significantly improved red blood cells, white blood cells and their functional indicators, and significantly improved adiponectin expression downregulation and IL-6 down-regulation in adipose tissue Relationship. Hesperidin protects diabetes-related anemia by affecting adipose tissue.[61] In addition, hesperidin can increase the serum total antioxidant capacity of mice with high-fat diet, inhibit IL-6, macrophage chemoattractant protein 1(MCP-1) and C-reactive protein(hs-

CRP) to reduce liver thiobarba Bilobate-reactive substance (TBARS) levels and spleen mass, and prevent mouse inflammation and oxidative stress caused by a high-fat diet, thereby preventing metabolic changes associated with cardiovascular disease development in other animals.[66] Hesperidin improves the degree of inflammation and oxidative damage caused by hyperglycemia and hyperlipidemia by directly affecting oxidation- related index and inflammatory factors (Figure 4), which indirectly plays a therapeutic role in the treatment of obesity- related diseases.

Conclusions

Obesity is an abnormality in energy metabolism caused by a variety of factors,[84] which in turn affects various metabolisms in the body, so the way to lose weight is also diverse. In this review, the most relevant articles were evaluated to reveal how hesperidin is effective in obesity through multi-target ways. As a cellular energy sensor, AMP activates protein kinase(AMPK), which not only restores energy balance between activities, but also plays an important role in lipid metabolism.[95] PPARs are nuclear receptor proteomes, transcription factors that play important roles in lipid metabolism and glucose homeostasis.[67] Hesperidin mainly regulates lipid metabolism and glucose metabolism by affecting AMPK and PPAR signaling pathways, thereby exerting a lipid-lowering effect. In addition, obesity is a systemic low-level chronic persistent inflammatory state.[93]Hesperidin has a therapeutic effect on obesity by mediating AMPK and PPAR pathways to regulate NF-κB inflammatory signaling pathways and reducing inflammation and apoptosis. Hesperidin can also directly regulate the oxidation index, inhibit apoptosis, thereby protecting against damage caused by oxidative stress, and improving lipid peroxidation.

Furthermore, the above-mentioned lipid-lowering effect of hesperidin can be extended to other similar flavonoids. Naturally occurring extracts and biotransformed extracts from citrus fruits can be used for the treatment of obesity, natural extracts can be used to reduce new fat cell synthesis and lipid accumulation, and biotransformation extracts can be used to induce lipolysis of adipose tissue.[96] For example, citrus peel extract has potential antioxidant and lipid peroxidation and lipoxygenase inhibition.[97] *Citri Reticulatae Pericarpium* has been investigated with a health promoting properties,[98,99] which can remove moisture and protect the spleen,[100] while reducing NO levels,[101] exerting antioxidant effects,[38,102] and lowering the liver lipid content.[103] Its extract has anti-lipase activity,[104] which can directly or indirectly treat obesity. Moreover, given the various biological

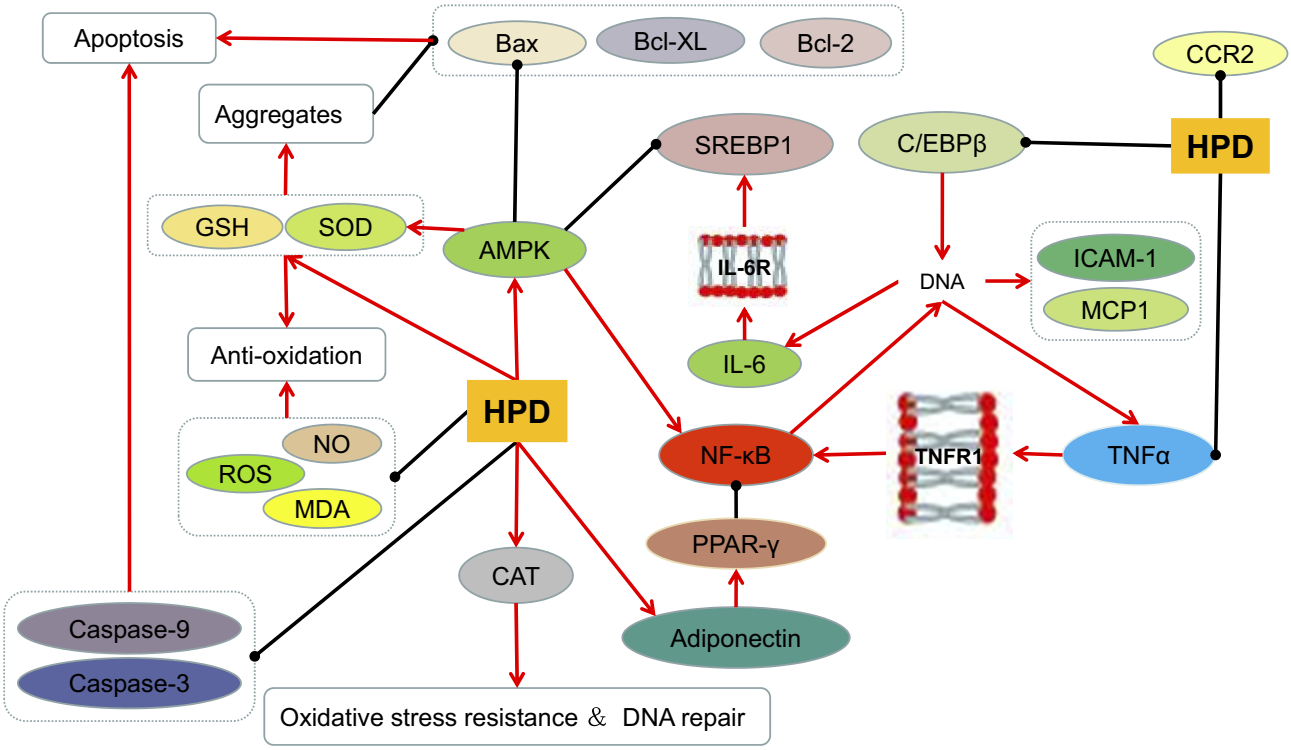

Figure 4 The effect of hesperidin on oxidation and inflammation.
Note: ⟶● indicate inhibition/reduction while ⟶ indicate increase/promotion.

properties of hesperidin, this phytochemical may have a wider range of biological applications in the future. Therefore, research on natural drugs or foods containing hesperidin can help expand the range of weight loss and reduce the rate of obesity in the body. Further studies on flavonoids similar to hesperidin can better reveal the preventive and therapeutic effects of hesperidin on obesity.

Although the hypoglycemic and lipid-lowering activities of hesperidin have been studied in some animals (such as rats) or cells, the lack of clinical trials on the therapeutic effect of hesperidin is a significant limitation that deserves further study. Furthermore, little is known about the clinical aspects of this compound, such as bioavailability, the appropriate dose, tolerance and efficacy of hesperidin and its metabolites for human disease.[15] More investigations should be needed before hesperidin treatment is extended to humans, especially reliable clinical trials, including large-scale, rigorously controlled, and multicenter randomized controlled clinical trials are needed to assess its long-term safety.

Consent For Publication

All authors have provided consent for publication.

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Author Contributions

Haijun Xiong and Jin Wang are first authors and responsible for collecting materials and writing the paper. Qian Ran, Guanhua Lou, Chengyi Peng, Qingxia Gan, Ju Hu, Jilin Sun and Renchuan Yao helped with organizing the information and edited in the article pictures. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

Jilin Sun is the general manager of Sichuan Fuzheng Pharmaceutical Co. Ltd. The authors report no other conflicts of interest in this work.

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