The Effect of Oleanolic Acid

Subjects: Cardiac & Cardiovascular Systems

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The natural product oleanolic acid (OA: 3b-hydroxyolean-12-en-28-oic acid) is a pentacyclic triterpenoid compound. It has been extracted from many species, including *Olea europaea*. Studies on biological activity have shown that OA has a liver-protective effect, and has been listed as a liver-protective drug in China. OA also has anti-inflammatory, anti-oxidant, anti-hyperglycemia, anti-hyperlipidemia, cardioprotective, anti-atherosclerotic, and some other pharmacological effects.

oleanolic acid | metabolic syndrome | cardiovascular diseases

1. Anti-Metabolic Syndromes' Effects

1.1. Anti-Obesity

Obesity is associated with numerous diseases and a shortened life expectancy [1]. Fat production is the maturation of fat cells by which preadipocytes become adipocytes, so they play an essential part in obesity [2]. In the process, CCAAT/enhancer-binding protein (C/EBP) and peroxisome proliferator-activated receptor γ (PPARγ) are thought to be the vital early regulatory proteins for lipogenesis. Adiponectin, sterol regulatory element-binding protein 1 (SREBP1), and fatty acid synthetase (FAS) are in charge of the production of mature fat cells [3]. OA could inhibit the expression of the visceral fat-specific adipokine and downregulate PPARγ and C/EBPα to reduce the intracellular accumulation of fat in adipocytes [4]. Furthermore, OA may reduce obesity via the suppression of the adipogenic factors PPARα, SREBP1, and FAS [5]. OA has been shown to reduce the synthesis of fat and accelerate the utilization of fat through the alteration of hepatic PPARα, recombinant carnitine palmitoyltransferase 1A (CPT1A), SREBP-1, the acetyl coenzyme A carboxylase, and coupled protein 1 (UCP1) [6]. In addition, OA can reduce blood glucose and lipid levels by promoting carbohydrate and fat metabolism [7]. Another piece of research showed that OA can be effective against postmenopausal obesity by inhibiting fat synthesis acetyl-CoA carboxylase (ACC) and upregulating essential genes for estrogen production, CYP11, CYP1, and CYP17A19 [8].

Inflammation is crucial in obesity [9]; chronic inflammation in adipose tissue is primarily driven by macrophages [10] that are classified into two types: M1-type macrophages and M2-type macrophages [11]. An increase in the ratio of M1/M2-type macrophages can enhance adipocyte growth, fat storage, and adipocyte differentiation [12]. Recent research has discovered that OA was able to reduce inflammation via the inhibition of macrophage infiltration, the M1/M2 ratio in adipose tissues, reactive oxygen species (ROS), and decreasing NACHT, LRR, and PYD structural domain protein 3 (NLRP3) [13].

Resistin is an adipocyte-specific secreted factor associated with adipocyte differentiation [14]. OA could reduce resistin synthesis in vivo by stimulating the cellular signaling transcriptional repressor three signaling and interfering with the tyrosine kinase 2-transcriptional signaling sensor activator [15]. Furthermore, glucose homeostasis and adipocyte differentiation are regulated by transcription factor hepatocyte nuclear factor 1b (HNF1b) [16]. The research showed that OA could relieve glucose/lipid metabolic dysfunction via HNF1b [17].

The causes of obesity are complex, the symptoms are diverse, and multiple organs are implicated, so OA in treating obesity is far from sufficient, especially in molecular mechanisms where it is even more insufficient. Therefore, more research is needed to demonstrate the role of OA in treating obesity.

1.2. Anti-Hyperlipidemia

Hyperlipidemia is defined as elevations of the fasting total cholesterol concentration, which could directly cause some severe diseases [18]. Numerous studies have suggested that OA is beneficial in the treatment of hyperlipidemia. OA could attenuate the triglycerides (TG) in rats by reducing the fat synthesis factor sterol regulatory element and activating transcription factor 1 [19]. OA also reduces total cholesterol (TC) formation by inhibiting cholesterol acyltransferase activity [20]. A high-fat diet will increase the level of peroxisome proliferator-activated receptor gamma coactivator 1β (PGC-1β) leading to lipogenesis and very-low-density lipoprotein secretion [21]; OA could decrease serum lipids in mice via the inhibition of PGC-1β expression [22]. Clinical investigations also have shown that OA decreased serum lipids in hyperlipidemic patients [23].

Hyperlipidemia is frequently one of the risk factors for various issues. Thus, improving blood lipids is critical for human health. Recent research demonstrated that OA can decrease low-density lipoprotein-cholesterol (LDL-c), TC, and TG in mice. The process is thought to be connected to essential targets of lipid synthesis and accumulation.

1.3. Anti-Hypertension

One of the cardiovascular risk factors is hypertension [24]. Research revealed that OA was helpful in hypertension [25][26]. OA could diminish vascular resistance by promoting nitric oxide (NO) and inhibiting COX levels in isolated rat vessels [27]. OA also prevented hypertension in rats via the suppression of NO catabolism [28]. Another study indicated that OA can improve high blood pressure by increasing the expression of eNOS [29]. Meanwhile, OA increased the vasodilator endothelium-derived hyperpolarizing factor (EDHF) and NO to maintain normal blood pressure [30].

The renin–angiotensin system and atrial natriuretic peptide (ANP) are crucial to blood pressure homeostasis [31]. It was found that OA can maintain the homeostasis of blood pressure by inhibiting the renin–angiotensin system and enhancing the fluid balance [32]. OA also could increase the expression of atrial ANP, thus enhancing vascular homeostasis [33]. In addition, the diuretic and nephroprotective properties of OA could reduce hypertension [34]. Furthermore, OA could improve hypertension via upregulating the anti-oxidative stress capacity and enhancing diuretic and natriuretic functions in hypertensive rats [35].

Hypertension is one of the most prevalent systemic metabolic disorders [36]; hypertensive patients also have substantially elevated levels of lipid metabolites [37]. Numerous studies have demonstrated that reducing lipids can improve hypertension. OA was found to reduce hypertension by downregulating the expression of pro-inflammatory factor-secreting phospholipase A2 and fat synthesis factor FAS and inhibiting lipid accumulation [38].

In conclusion, the incidence of hypertension has been rising steadily over the past decade, and the effective treatment of hypertension has a positive impact on middle-age and old-age patients. OA, a natural compound, can protect vascular endothelial cells, enhance body fluid balance, and promote glucose and lipid metabolism to reduce hypertension.

1.4. Anti-Nonalcoholic Fatty Liver

Non-alcoholic fatty liver is caused by hepatic steatosis in the liver [39]. Among the pathological mechanisms, the fat overloading in the liver triggered an inflammatory cascade response and subsequently developed into steatohepatitis [40]. Recent research indicated that OA could delay the development of a nonalcoholic fatty liver by reducing inflammation, steatosis, and fibrosis in rats [41]. Furthermore, the liver could be in danger from microbial disorders and increased intestinal permeability, which may exacerbate the inflammatory responses to the nonalcoholic fatty liver [42]; research has shown that OA could treat nonalcoholic fatty liver by ameliorating intestinal barrier dysfunction and the Toll-like receptor 4 (TLR4)-associated inflammatory responses [43].

Oxidative stress induced by a hepatic lipid overload exacerbates liver injury [44]. It was discovered that OA could substantially mitigate a nonalcoholic fatty liver by ameliorating hepatic oxidative stress and decreasing lipid synthesis factor SREBP1 [45].

Liver X receptors (LXR) are highly expressed in the liver and responsible for cholesterol metabolism and homeostasis [46]; LXR primarily activates the hepatic fat synthesis pathway by activating the promoter region of SREBP-1 [47]. Research demonstrated that OA was able to improve the abnormal accumulation of fat in the liver by reducing the expression of LXR and the activity of SREBP-1, as well as increasing the expression of reverse cholesterol transport (RCT)-related genes, including ATP-binding cassette transporter protein (ABC)A1 and ABCG1 [48]. Furthermore, OA could directly inhibit the expression of the SREBP-1 protein and decrease fatty acid accumulation in the body, thus ameliorating the progress of nonalcoholic fatty liver [49].

Briefly speaking, OA inhibits fat accumulation, accelerates cholesterol transport in the liver, and suppresses hepatic inflammation and oxidative stress in the treatment of nonalcoholic fatty liver.

1.5. Anti-Diabetes Mellitus

Diabetes mellitus is a metabolic disorder characterized by elevated blood sugar, mainly caused by an absolute or relative insulin deficiency and insulin resistance, classified as type 1 and type 2, with type 2 comprising nearly 95% of cases [50]. Insulin sensitivity can be affected by oxidative stress, inflammation, and metabolic disorders.

Inflammation is significant in diabetes mellitus [51]; an inordinate increase of inflammatory factors hinders insulin receptor signaling and leads to insulin resistance [52]. Research has shown that the expression of TLR4, TLR9, interleukin 6 (IL-6), IL-18, tumor necrosis factor α (TNF-α), TNF-1, and C-reactive protein (CRP) was reduced by OA in diabetic rats [53][54][55][56]. Furthermore, OA also could improve insulin resistance by inhibiting the activity of nuclear factor-κB (NF-κB) [57].

Oxidative stress is closely associated with diabetes and causes deleterious consequences of diabetes [58]. OA could improve the antioxidant capacity in diabetic rats by attenuating the levels of NO and malonaldehyde (MDA), as well as enhancing the level of catalase (CAT) and superoxide dismutase (SOD) [59][60]. In addition, OA was able to enhance the antioxidant function of mitochondria by increasing the expression of glutathione peroxidase 4 (Gpx4) and SOD [61]. Furthermore, OA was reported to improve the mitochondrial ultrastructure and function and antioxidant capacity by inhibiting MDA and ROS levels, as well as increasing CAT, SOD, and glutathione peroxidase (GSH-px) in diabetic rats [62][63][64].

Diabetes is associated with disorders of energy metabolism [65]. Lipid accumulation and the dysregulation of glucose homeostasis are significant causes of insulin resistance [66]. It was demonstrated that OA could improve diabetes by inhibiting the level of α-glucosidase and α-amylase [67]. Meanwhile, OA was able to improve diabetes in rats by stimulating insulin secretion [68] and decreasing blood glucose and blood lipid levels [69], increasing hepatic glycogen and muscle glycogen [70]. The research indicated that OA could prevent hyperglycemia by inhibiting glucose absorption and promoting the change of glucose to glycogen [71]. Elevated blood glucose and glycated hemoglobin (HbA1c) levels (referred to as the prediabetic condition) occurred before the transition from normal to diabetic [72] and OA could improve glucose homeostasis via the reduction of blood glucose and HbA1c levels [73]. It was verified that OA affects diabetes, which was related to increasing glucose transporter-5 (GLUT-5) and GLUT-4 expressions and decreasing FAS and ACC-1 expressions [74]. In addition, OA was observed to maintain glucose homeostasis in rats by decreasing the activity of hexokinase, the expression of glycogen phosphorylase (GP), and increasing the expression of glycogen synthase (GS) [75]. Another study indicated that OA could accelerate glucose and lipid metabolism via increasing the level of PPARγ/α and its related regulators, as well as GLUT-4 and fatty acid transport protein-1 (FATP-1) proteins [76]. Furthermore, takeda G protein-coupled receptor 5 (TGR5) belongs to the g-protein-coupled receptors involved in various cellular physiological effects [77]. By activating the expression of TGR5, OA was able to decrease the blood glucose levels [78]. Based on the accumulated evidence, the imbalance of the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) signaling pathway could cause the development of diabetes mellitus [79]. OA was verified to inhibit gluconeogenesis by reducing the level of Akt, forkhead box O1 (FoxO1), and glucose-6-phosphatase (G6Pase) [80]. It also exhibited that OA was able to accelerate glucose transport by increasing p-Akt levels and GS levels, as well as decreasing GP levels [81][82]. Furthermore, OA has positive effects on diabetes via increasing PI3K/Akt and AMPK phosphorylation, phosphoenolpyruvate carboxykinase (PEPCK), and G6Pase levels, as well as decreasing the level of the mammalian target of rapamycin (mTOR) [83]. It was discovered that OA could improve insulin resistance through the activation of the level of the insulin receptor substrate (IRS-1) and PI3K/Akt [84]. Moreover, OA may normalize insulin, high-density lipoprotein (HDL), IRS1, GLUT2, GLUT4, and Akt levels, and decrease TC, TG, and low-density lipoprotein (LDL) levels [85]. Furthermore, OA could decrease insulin resistance by improving β-cells [86].

High-glucose environments have been found to cause endothelial cell dysfunction [87]. Research has shown that OA attenuated human umbilical vein endothelial cells (HUVECs) function damage via activating PPARδ, increasing the phosphorylation of Akt and eNOS [88]. Furthermore, persistent hyperglycemia will change blood composition, such as erythrocyte morphology [89], and increase the production of erythropoietin (EPO) [90]. OA could improve diabetes by reducing plasma glucose, HbA1c, and EPO levels and increasing the antioxidant capacity of erythrocytes [91].

Complications caused by diabetes are also a leading cause of harm to human health, such as diabetic nephropathy [92]. Research reported that OA could protect rats against diabetic nephropathy by restoring plasma aldosterone and renal injury molecule-1 [93]. In addition, advanced glycosylation end products, such as renal N-(carboxymethyl) lysine, HbA1c, and glycosylated albumin, are also related to the development of diabetic nephropathy [94]. OA was able to inhibit diabetic nephropathy via a reduction of the level of renal N-(carboxymethyl) lysine, HbA1c, urinary albumin, and urine glycated albumin, as well as increasing the level of plasma insulin and renal creatinine clearance [95]. Furthermore, OA could also restore the damaged renal structure by increasing insulin secretion, renal units, and endothelial-selective adhesion molecules, and decreasing urinary albumin/creatinine levels [96].

There is accumulating evidence that OA cures diabetes by decreasing inflammation, reducing oxidative stress, and protecting endothelial cell function. Furthermore, OA could enhance the glucose–lipid metabolism in diabetic rats, restore blood components damaged by high glucose levels, and alleviate diabetic nephropathy problems. To summarize, OA in the treatment of diabetes mellitus has shown tremendous potential and is supported by numerous pieces of research; however, this research may require additional clinical trials to confirm. The detailed pharmacological effects of OA on metabolic syndrome are shown in **Table 1**.

Table 1. Pharmacological Effects of OA in the Treatment of MetS.

Experimental Models	Dose of OA	Signaling Pathways	Pharmacologic Action	Refs.
Obesity				
3T3-L1 cells	1 to 25 μM/L OA for 6 days	↓PPARγ, ↓C/EBPα, ↓adiponectin	↓Lipid accumulation	[4]
Female C57BL/6J mice induced by high-fat diet (HFD)	OA in water feeders at 0.005% for 16 weeks	↑↑CD36, ↑PPARα, ↑↑SREBP1, ↓↓FAS	↓↓Adipose tissue weights, ↓↓↓TG	[5]
HFD-induced C57BL6/J male mice	300 mg/kg OA for 10 weeks	↓PPARα, ↓↓CPT1A, ↓SERBP1, ↑↑UCP1	↓↓TC, ↓↓LDL, ↑↑HDL, ↓VLDL	[6]

Experimental Models	Dose of OA	Signaling Pathways	Pharmacologic Action	Refs.
HFD-induced male Swiss mice	5, 10, or 20 mg/kg OA for 7 days	↑Blood glucose tolerance	↓Plasma lipids, ↓blood glucose	[7]
3T3-L1 cells	3 μg/mL OA for 16 days	↓ACC, ↑CYP11A1, ↑↑CYP17, ↑↑CYP19, ↓↓CYP1A1	↓↓Fat production, ↑estrogen homeostasis	[8]
C57BL/6J mice were fed with HFD	25 and 50 mg/kg OA for 4 weeks	↓↓↓ROS, ↓NLRP3	↓↓↓Adipose tissue hypertrophy	[13]
3T3-L1 cells	1 to 25 μM OA for 2 days	↓STAT1/3, ↓Tyk2, ↑SOCS3, ↓resistin	↓Adipogenesis	[15]
Polychlorinated biphenyls-induced male C57B6/J mice	50 mg/kg OA for 10 weeks	↑HNF1b, ↓ROS, ↓NOX4, ↑SOD1/2, ↑GPx1	↓TG, ↓TC, ↓FFAs, ↓adipocyte size	[17]
Hyperlipidemia				
HFD-male Sprague-Dawley (SD) rats	50 mg/kg OA for 4 weeks	↓↓Levels of acetyl-CoA carboxylase, ↓↓glycerol-3-phosphate acyltransferase, ↓↓Srebf1	↓TG, ↓TC, ↓phospholipid	[19]
Human colorectal adenocarcinoma cells and typical western-diet-induced male Lakeview Golden Syrian hamsters	50 μg OA in vitro; 0.01% OA for 4 weeks in vivo	↓Enzyme cholesterol acyltransferase activity	↓VLDL, ↓LDL, ↓TC	[20]
Male C57BL/6 mice were fed HFD	20 mg/kg for 4 weeks	↓↓PGC-1β	↓↓TG, ↓↓TC, ↓↓LDL-c	[22]
Patients with hyperlipidemia	OA 4 tablets once, three times a day for 4 weeks	↑↑↑CACNA1B, ↓FCN, ↑STEAP3, ↑AMPH, ↑NR6A1	↓TC, ↓TG, ↓HDL-c	[23]
Hypertension				

Experimental Models	Dose of OA	Signaling Pathways	Pharmacologic Action	Refs.
Male spontaneously hypertensive rats (SHR)	10^{-7} to 10^{-4} M OA	↑NO	↑↑↑Vasorelaxation	[25]
Male Wistar and Dahl salt-sensitive rats induced by a high-salt Na diet^{+}	160 μM OA	↑NO, ↓COX	↑↑↑Relaxation in aortic rings	[27]
Dexamethasone-induced male Wistar rats	60 mg/kg for 5 days	↑Plasma nitrate/nitrite, ↑NO	↓↓Systolic pressure	[28]
HFD-induced Wistar Kyoto rats and SHR	800 parts per million OA for 12 weeks	↑eNOS	↑↑↑Relaxation aorta	[29]
Male Wistar Kyoto rats, and HFD-induced SHR	800 parts per million OA for 12 weeks	↑NO/EDHF	↓↓Endothelial dysfunction	[30]
Male SD rats induced by two-kidney, one-clip hypertensive	20 and 30 mg/kg/day OA for 7 days	↓↓Renin activity, ↓↓angiotensin II type-1/2 receptor, ↓aldosterone, ↑↑↑ANP	↑↑↑Glomerular filtration rate, ↑↑↑electrolyte excretion, ↑↑↑urinary volume, ↓↓↓arterial blood pressure	[32]
Isoproterenol-induced male SD rats	10, 20, or 30 mg/kg/day OA for 2 weeks	↑↑↑ANP	↓Atrial pressure, ↓pulse pressure	[33]
Glucocorticoid-induced male Wistar rats	60 mg/kg/day OA for 4 weeks	↑↑Urine volume, ↑↑urine sodium, ↑potassium	↓↓↓Blood pressure	[34]
Dahl salt-sensitive genetically hypertensive rats and normotensive Dahl salt-resistant rats	60 mg/kg OA for 6 weeks	↑GPx, ↑SOD	↑Systolic and diastolic blood pressure	[35]
SHR and Wistar Kyoto rats	1.08 mg/kg OA for 4 weeks	↓FAS, ↓sPLA2	↓↓TG, ↓LDL-c, ↓↓systolic blood pressure and diastolic blood pressure	[38]
Nonalcoholic fatty liver				
Fructose-induced male and female SD rats	60 mg/kg for 7 days	↓Inflammation, ↓steatosis and fibrosis	↓↓Body mass, ↓liver mass, ↓hepatic lipid storage	[41]

Experimental Models	Dose of OA	Signaling Pathways	Pharmacologic Action	Refs.
HFD with 60 kcal% fat-induced rats	25, 50, or 100 mg/kg for 8 weeks	↓↓IL-6, ↓↓TLR4, ↓↓IL-1β, ↓↓TNF-α	↓↓↓Body weight, ↓↓↓fatty liver score, ↓↓fasting blood glucose, ↓↓TG, ↓↓TC, ↓ALT, ↓AST	[43]
Male SD rats induced by a high-fat high-carbohydrate diet	80 mg/kg for 12 weeks	↓SREBP1, ↓MDA, ↑GPX, ↑SOD	↓Body/liver weight ratio, ↓TG, ↓VLDL, ↑total bilirubin, ↓ALT, ↓AST	[45]
HepG2 cells	5, 10, or 20 μM OA	↓↓↓LXR, ↓↓↓SREBP-1c, ↑↑↑ABCA1, ↑↑↑ABCG1	↓↓↓Lipogenesis	[48]
Liquid fructose-induced male SD rats	5 or 25 mg/kg OA for 10 weeks	↓SREBP-1	↓TG, ↓lipid accumulation	[49]
Diabetes mellitus				
Male SD rats induced by Streptozotocin (STZ)	5 mg/kg OA for 21 days	↓↓↓TLR9, ↓↓↓NF-κB, ↓IL-18, ↓↓↓MDA	↓↓Glucose	[53]
High-fructose diet in male SD rats and pups	60 mg/kg OA for 14 days	↓↓↓TNF-α, ↓↓↓IL-6, ↑↑↑MAPK, ↑↑↑adiponectin	↓Diabetes	[54]
Male SD rats induced by STZ and a high-fat diet	25 or 100 mg/kg OA for 8 weeks	↓↓TLR4, ↓↓NF-κB	↓↓Fasting blood glucose	[55]
Male SD rats induced by high-fat and high-carbohydrate diet	80 mg/kg OA for 12 weeks	↓TNF-α, ↓IL-1β, ↓CRP	↓Diabetes, ↓immune cell counts	[56]
HepG2 cells induced by free fatty acids	5, 10, or 25 μM/L OA for 24 h	↓↓NF-κB, ↓↓IL-6, ↑↑IRS1, ↑GLUT4, ↓↓TNF-α	↓Insulin resistance, ↓blood glucose	[57]

Experimental Models	Dose of OA	Signaling Pathways	Pharmacologic Action	Refs.
Male SD rats induced by high-fat and -fructose (HFF) diet	25 mg/kg OA for 6 weeks	↓MDA, ↓NO, ↑SOD, ↑CAT	↓Body weights, ↓serum insulin	[59]
STZ and high sugar and fat-induced female SD rats	25 mg/kg OA for 6 weeks	↓↓↓MDA, ↓↓↓NO, ↑↑↑SOD, ↑↑↑CAT	↓↓↓Weight gain, ↓↓↓fasting blood glucose levels, ↑↑↑insulin sensitivity index	[60]
STZ-induced male SD rats	100 mg/kg OA for 4 weeks	↑GPx, ↑SOD	↓Blood glucose, ↑body weight	[61]
HFD-induced Wistar rats	60 or 100 mg/kg OA for 40 days	↓↓MDA, ↑SOD, ↑↑GSH-px	↓↓Blood glucose	[63]
C57BL/KsJ-Lepdb (db/db) mice and wild mice	20 mg/kg/day OA for 2 weeks	↓ROS, ↑Nrf2	↓Fasting blood glucose	[62]
STZ-induced male SD rats	20, 40, or 60 mg/kg/day OA for 8 weeks	↑CAT, ↑↑↑SOD, ↑GSH	↓Diabetes	[64]
Bioactive compound(s)	Not mentioned	↓α-glycosidase, ↓α-amylase activities	↓Diabetes	[67]
Glucose-pancreatic β-cells, rat islets	30 or 50 μM OA	↑↑Insulin secretion	↓Blood glucose	[68]
STZ-induced male Wistar rats	100 or 200 mg/kg OA for 40 days	↑↑Insulin	↓↓Blood glucose, ↓↓blood lipids	[69]
STZ-induced male SD rats	40, 80, or 120 mg/kg OA for 5 weeks	↑Hepatic glycogen, ↑muscle glycogen	↓Blood glucose, ↑insulin sensitivity	[70]
STZ-induced male Wistar rats	80 mg/kg OA for 18 h	↓Glucose uptake	↓Blood glucose	[71]
Male SD rats induced by a high-fat high-carbohydrate diet	80 mg/kg OA for 12 weeks	↓HbA1c	↓Caloric intake, ↓body weight, ↓blood glucose	[73]
High-fructose-diet-induced SD rats	60 mg/kg OA for 7 days	↑↑Nrf-1, ↓Acc-1, ↑↑GLUT-4,	↓↓↓Body mass, ↓visceral fat	[74]

Experimental Models	Dose of OA	Signaling Pathways	Pharmacologic Action	Refs.
		↓FAS, ↑GLUT-5		
STZ-induced male SD rats	80 mg/kg OA for 14 days	↓GP, ↓GS, ↓hexokinase activity	↑Glycogen homeostasis	[75]
C2C12 muscle cells and 3T3-L1 cells	1 to 50 μM OA	↑PPARγ/α, ↑GLUT4, ↑FATP1	↑Lipid homeostasis	[76]
HFD-induced male C57BL/6J mice	100 mg/kg/day OA for 7 days	↑TGR5	↓Serum glucose, ↓insulin levels	[78]
STZ-induced male C57BL/6J mice were fed HFD	100 mg/kg/day OA for 2 weeks	↑p-Akt, ↑↑p-FoxO1, ↓G6Pase	↓↓Urine glucose, ↓↓gluconeogenesis	[80]
STZ-induced male SD rats	100 mg/kg OA for 14 days	↑p-Akt, ↑GS, ↓GP	↓Blood glucose	[81]
Male C57BL/KsJ-Lepdb (db/db) mice	250 mg/kg OA for 4 weeks	↑Akt, ↑PI3K, ↑AMPK, ↓↓↓G6Pase, ↓mTOR, ↓↓↓PEPCK, ↓GP	↓↓↓Blood glucose, ↑gluconeogenesis	[83]
High-fructose-induced male SD rats	25 mg/kg/day OA for 10 weeks	↑IRS-1, ↑PI3K, ↑p-Akt	↓Plasma glucose	[84]
STZ-induced male Institute of Cancer Research mice	25, 50, or 75 mg/kg OA for 15 days	↑↑IRS1, ↑↑GLUT2, ↑↑GLUT4, ↑↑Akt	↓TC, ↓↓TG, ↓↓LDL, ↑↑HDL, ↓↓blood glucose	[85]
Fructose-induced male and female SD rats [98]	60 mg/kg OA for 7 days	↓β-cell dysfunction [97]	↓Insulin resistance	[86]
High-glucose-induced human vascular endothelial cells	0.1 to 50 μM OA for 24 h [100]	↑PPARβ/δ, ↑eNOS, ↑p-eNOS, ↑p-Akt	↓Endothelial dysfunction [99]	[88]
STZ-induced male SD rats	80 mg/kg OA for 5 weeks	↓HbA1c, ↓EPO, ↓MDA, [101]	↓Diabetes	[91]

ress, and neuronal damage asing the oxidative OD, GSH-Px, mitochondrial membrane potential (MMP), and succinate dehydrogenase (SDH), and decreased MDA and LDH levels [102]. Meanwhile, OA also could restrain the blood–brain barrier indicator occludin, matrix metalloproteinase 9 (MMP9), and Evans blue leakage, and inhibit oxidative indicator dihydroethidium fluorescence and MDA

Experimental Models	Dose of OA	Signaling Pathways	Pharmacologic Action	Refs.
[103]		↑SOD, ↑GPx	[104]	[105]
High-fat-high-carbo-hydrate-diet-induced male SD rats	80 mg/kg OA for 12 weeks	↓Aldosterone, ↓KIM-1	↓Blood and urine electrolytes, ↓estimated glomerular filtration rate, ↓albumin/creatinine ratio	[93]
STZ-induced male Balb/cA mice	0.05, 0.1, or 0.2% OA for 10 weeks	↓HbA1c, ↓fructose,↓renal N^{ε}-(carboxymethyl)lysine	↓Plasma glucose, ↑plasma insulin	[95]
Otsuka Long-Evans Tokushima fatty rats [108]	100 mg/kg OA for 20 weeks	↓Urinary albumin/creatinine levels	↑Blood [106] insulin secretion, ↓ER stress, ↓damaged kidney structures	[96]

The number of arrows indicates different statistical significance: ↓/↑: $p < 0.05$; ↓↓/↑↑: $p < 0.01$; ↓↓↓/↑↑↑: $p < 0.001$. PPAR: peroxisome proliferator-activated receptor; C/EBPα: CCAAT/enhancer-binding protein α; CD36: cluster of differentiation 36; SREBP1: sterol regulatory element-binding protein 1; FAS: fatty acid synthetase; CPT1A: carnitine palmitoyltransferase 1A; UCP1: coupled protein 1;TC: total cholesterol; TG: triglycerides; LDL-c: low-sensitivity lipoprotein-cholesterol; HDL-c: high-density lipoprotein-cholesterol; VLDL: very-low-density lipoprotein; ACC: acetyl-CoA carboxylase; ROS: reactive oxygen species; NLRP3: NACHT, LRR, and PYD structural domain protein 3; STAT: signal transducers and activators of transcription; Tyk2: tyrosine kinase 2; SOCS3: suppressor of cytokine signaling 3; HNF1b: hepatocyte nuclear factor 1b; Nox4: nicotinamide adenine dinucleotide phosphate oxidase 4; SOD: superoxide dismutase; Gpx1: glutathioneperoxidase; FFA: free fatty acid; PGC-1β: peroxisome proliferator-activated receptor gamma coactivator 1β; NO: nitric oxide; COX: cyclooxygenase; eNOS: endothelial nitric oxide synthase; EDHF: endothelium-derived hyperpolarizing factor; ANP: atrialnatriureticpeptide; sPLA2: secretory phospholipase A2; IL-6: interleukin 6; TLR4: toll-like receptor 4; IL-1β: interleukin 1β; TNF-α: tumor necrosis factor α; MDA: malonaldehyde; LXR: Liver X receptors; ABCA/ABCG1: ATP-binding cassette transporter A1/G1; NF-κB: nuclear factor κB; CRP: C-reactive protein; IRS1: insulin receptor substrate 1; GLUT4: glucose transporter 4; CAT: catalase; GSH-px: glutathione peroxidase; Nrf2: nuclear factor erythroid-2-related factor 2; HbA1c: glycated hemoglobin; GP: glycogen phosphorylase; GS: glycogen synthase; FATP1: fatty acid transport protein 1; TGR5: takeda G protein-coupled receptor 5; PI3K: phosphatidylinositol-3-kinase; Akt: protein kinase B; FoxO1: forkhead box O1; G6Pase: glucose-6-phosphatase; mTOR: mammalian target of rapamycin; PERCK: phosphoenolpyruvate carboxykinase; KIM-1: kidney injury molecule 1; ER: endoplasmic reticulum; ALT: alanine aminotransferase; AST: aspartate transaminase.

HO-1/Nrf2 to increase SOD and GS, as well as decrease MDA and GP [109]. Meanwhile, OA was verified to prevent CVDs by improving the inflammatory reaction, MDA, SOD, GPx, as well as heart weight in rats [110]. In addition, OA could improve myocardial apoptosis by increasing the antioxidant capacity and decreasing apoptosis signaling caspase-3 and BAX activity, increasing Bcl-2 activity [111][112]. Endothelin 1 (ET-1) aggravates the development of CVDS [113], and OA could inhibit cardiomyocyte injury through the regulation of the expression of ET-1 [114]. Furthermore, ET-1 and NF-κB modulate the fibrotic process in the heart, as well as promote the expression of fibronectin in cardiac tissues [115]. OA could improve fibrotic hearts in rats by reducing the activation of NF-κB and ET-1 [116]. Moreover, the Akt/mTOR exacerbates the pathological process of myocardial remodeling [117]; OA performed cardiac protection with the inhibition of vascular remodeling by decreasing the levels of Akt and mTOR [118]. In addition, OA possessed the ability to suppress the platelet aggregation mediated by phospholipase C, thereby aiding in the prevention of cardiovascular thrombosis [119]. Therefore, current research demonstrates that OA could treat a variety of heart diseases, as well as prevent cardiac fibrosis and the cardiac remodeling process. The mechanism includes the inhibition of inflammation, oxidative stress, and the improvement of the expression of vasoconstrictive factors.

2.3. Anti-Atherosclerosis

Atherosclerosis (AS) is the underlying pathology of CVDs [120]. OA could prevent AS by inhibiting many pathological developments, such as oxidative stress, endothelial dysfunction, and lipid deposition. Oxidative stress was deemed the critical mechanism in AS [121]. Research demonstrated that OA may safeguard HUVECs damage by inhibiting the levels of lipoprotein receptor 1 (LOX-1), ROS, as well as hypoxia-inducible factor 1 α (HIF-1α) [122]. Moreover, OA has been confirmed to alleviate HUVECs damage via the reduction in the level of ROS and LOX-1, as well as enhancing the level of Nrf2/HO-1 [123].

PPARγ is considered a ligand-activated transcription factor that regulates the glycolipid metabolism, and adiponectin promotes fatty acid biosynthesis and inhibits hepatic gluconeogenesis [124]. OA could reduce lipids and enhance high-density lipoprotein cholesterol (HDL-c) by increasing PPARγ and adiponectin Receptor 1 (AdipoR1) Levels, decreasing AdopoR2 levels [125].

Farnesoid-X-receptor (FXR) is associated with the bile metabolism [126], and angiotensin1-7 (Ang1-7) has been implicated as an AS protector [127]. OA was found to decrease the levels of lipids in rats via the regulation of the expression of FXR and Ang1-7 [128]. In addition, OA inhibited the expression of iNOS, thereby delaying the progression of aortic stenosis [129].

In conclusion, OA can reduce the area of vascular lipid plaque and treat AS by protecting HUVECs, reducing inflammatory factors and the accumulation of lipids. The detailed pharmacological effects of OA on metabolic syndrome-related cardiovascular diseases are shown in **Table 2**.

Table 2. Pharmacological effects of OA in the treatment of CVDs.

Experimental Models	Dose of OA	Signaling Pathways	Pharmacologic Action	Refs.
Stroke				
Ischemia reperfusion experiment-induced female SD rats	0.6 or 1.2 mM/kg OA for 3 days	↓LDH, ↑GSH, ↑α-TOC	↓Brain injury	[101]
Male Institute of Cancer Research mice and male SD rats injured by bilateral common carotid artery ligation	25 or 50 mg/kg OA for 4 days	↑SOD, ↑↑GSH-Px, ↓↓MDA, ↓↓LDH, ↑MMP, ↑↑SDH	↑↑Survival time, ↓cerebral infarction area	[102]
Male Institute of Cancer Research mice	6 mg/kg/day OA for 3 days	↓Evans blue leakage, ↓MMP9, ↓occludin, ↓dihydroethidium fluorescence, ↓MDA	↓Infarct volumes, ↑locomotor activity, ↑memory ability	[103]
SH-SY5Y Cells and rats	10, 20, or 40 μM OA for 12 h in vitro; 10 or 20 mg/kg OA for 3 days in vivo	↑↑GSK-3β, ↑↑HO-1, ↓↓ROS	↓↓Infarct volume in the brain, ↓↓apoptosis	[105]
Heart protection				
Isoproterenol-induced adult male albino rats of the Wistar strain	20, 40, or 60 mg/kg OA for 7 days	↓ALT, ↓AST,	↑Heart protection	[108]

Experimental Models	Dose of OA	Signaling Pathways	Pharmacologic Action	Refs.
		↓CPK, ↓LDH, ↓TBARS		
STZ-induced male SD rats	80 mg/kg OA for 14 days	↓↓↓GS, ↓↓↓GP, ↑↑↑HO-1, ↑↑↑Nrf2	↓↓↓Diabetic cardiomyopathy	[109]
SD rats to high-fat high-carbohydrate diet	Not mentioned	↓CRP, ↓IL-6, ↓TNF-α, ↓MDA, ↑SOD, ↑GPx	↓Mean arterial pressure, ↓heart weights, ↓TG, ↓TC, ↓LDL-c, ↓HDL-c	[110]
H9c2 cells	5 or 10 μM OA	↓ROS, ↓GSSG, ↓IL-6, ↓TNF-α, ↑GSH, ↑GPX, ↑GR, ↑CAT, ↑NF-κB, ↑caspase-3, ↓bcl-2	↑Cell viability, ↓plasma membrane damage, ↓apoptosis	[114]
High-glucose-induced H9c2 cells	20 or 50 μM OA for 6 and 20 h	↓↓↓Caspase-3, ↑↑SOD, ↓ROS	↓↓↓Apoptosis, ↑↑↑heart protection	[112]
High-glucose-induced injury in neonatal rat ventricular cardiomyocytes	10 μM OA for 24 h	↓↓↓BNP, ↓↓ET-1, ↓↓MMP	↓↓Cardiomyocyte damage	[114]
Male Zucker Diabetic fatty rats and lipopolysaccharide-induced RAW264.7	Not mentioned exactly in vivo; 10 to 300 mM OA for 24 h in vitro	↓↓ET-1, ↓ETA, ↓IκBβ, ↑↑IκBα	↓↓Cardiac fibrosis	[116]
C57BL/6J male mice and H9c2 cells	25 or 100 mg/kg/day OA for 8 weeks	↓Akt, ↓mTOR, ↓GSK-3β, ↓FoxO3a	↓Cardiac hypertrophy, ↓tissue fibrosis	[118]
The platelets	25, 50, 100, or 200 μM OA	↑↑Phospholipase C	↓↓Platelets aggregation	[119]

Experimental Models	Dose of OA	Signaling Pathways	Pharmacologic Action	Refs.
Atherosclerosis				
HUVECs induced by Ox-LDL	1, 5, or 10 μM OA	↓LOX-1, ↓ROS, ↓HIF-1α	↓Apoptosis	[122]
High-fat-diet-induced male quails and HUVECs induced by Ox-LDL	25, 50, or 100 mg/kg OA for 10 weeks in vivo; 5, 10, or 20 μM OA for 24 h in vitro	↓NADPH, ↓ROS, ↑Nrf2, ↑HO-1, ↓LOX-1	↓TG, ↓TC, ↓LDL, ↑HDL	[123]
New Zealand rabbits and C57BL/6J mice and Apoe-/- mice fed with an atherogenic diet	25 mg/kg OA for 5 weeks	↑PPARγ, ↑↑AdipoR1, ↓↓AdipoR2	↓↓TG, ↓TC, ↓↓LDL-c,↓intimal thickening of the artery	[125]
Atherogenic diet (1% cholesterol and 5% lard oil)-induced male New Zealand White rabbits and Ox-LDL-induced HUVECs	50 mg/kg/day OA for 28 days in vivo; 40 μM OA for 24 h in vitro	↑↑↑Ang1-7, ↑↑↑NO, ↑↑↑eNOS, ↑FXR	↓↓↓TC, ↓↓↓TG, ↓LDL-C, ↓↓HDL-C, ↓↓↓cell apoptosis, ↓intimal thickening of the artery	[128]
ApoE-/- mice were fed a high-cholesterol Western-type diet	100 mg/kg/day OA for 8 weeks	↓iNOS	↓Plaque area, ↓↓TC, ↓↓plaque area	[129]

The number of arrows indicates different statistical significance: ↓/↑: $p < 0.05$; ↓↓/↑↑: $p < 0.01$; ↓↓↓/↑↑↑: $p < 0.001$. LDH: lactate dehydrogenase; GSH: glutathione; eTEC: cuboidal; SOD: superoxide dismutase; GSH-px: glutathione peroxidase; MDA: malondialdehyde; MMP-1: matrix metalloproteinase 9; GSK-3β: glycogen synthase kinase-3β; HO-1: heme oxygenase-1; ROS: reactive oxygen species; ALT: alanine aminotransferase; AST: aspartate transaminase; CPK: creatine phosphokinase; TBARS: thiobarbituric acid reactive substances; Nrf2: nuclear factor erythroid-2-related factor 2; CRP: C-reactive protein; IL-6: interleukin 6; TNF-α: tumor necrosis factor α; Gpx: glutathione peroxidase; TG: triglycerides; TC: total cholesterol; LDL-C: low-density lipoprotein-cholesterol; HDL-C: high-density lipoprotein-cholesterol; GSSG: oxidized glutathione; GR: glutathione reductase; CAT: catalase; NF-κB: Nuclear factor-κB; Bcl-2: B-cell lymphoma-2; BNP: natriuretic peptide B; ET-1: endothelin 1; MMP: mitochondrial membrane potential; ETA: endothelin receptors; IκBβ/α: inhibitory protein β/α; Akt: protein kinase B; mTOR: mammalian target of rapamycin; GSK-3β: glycogen synthase kinase-3β; FoxO3a: forkhead box class O3a; LOX-1: lipoprotein receptor 1; HIF-1α: hypoxia-inducible factor 1 α; NADPH: nicotinamide adenine dinucleotide phosphate; PPAR: peroxisome proliferator-activated receptor; AdiPoR1/2: adiponectin Receptor 1/2; Ang1-7: angiotensin 1-7; NO: nitric oxide; eNOS: endothelial nitric oxide synthase; FXR: farnesoid-X-receptor; iNOS: inducible nitric oxide synthase.

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