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# The structures and regulatory roles of natural products in lipid metabolism: focus on medicinal and edible plants

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ABSTRACT

Lipids are essential for normal life activities and biological functions of the human body, and disorders of lipid metabolism produce a lipotoxic environment, endoplasmic reticulum (ER) stress, inflammation, and cell death, which can lead to a variety of diseases in the body. It has been found that lipid metabolism disorders are closely associated with brain injury disease, cancer, metabolic disease, cardiovascular disease (CVD), respiratory disease and infectious disease. In recent years, many medicinal and edible plants such as *Pueraria lobata*, *Gardenia jasminoides*, *Curcuma longa*, citrus fruits, peanuts, etc. have shown great potential in regulating lipid metabolism and some of the hidden active components showed innovative mechanisms. AMPK, PPARγ, SIRT1, Foxp3, NLRP3, and Keap1 are increasingly recognized as therapeutic targets in the field of regulating lipid metabolism. This study aims to provide a comprehensive review of natural lipid-regulating modulators in medicinal and edible plants and their mechanism of actions, which offer valuable references for the discovery of natural lipid metabolism modulators and a therapeutic strategy for treatment of lipid metabolism-related diseases.



## 1. Introduction

Lipids are one of the important nutrients in the human body, which play a crucial role in regulating various biological processes, including energy conversion, material transportation, information recognition and transmission, cell development and differentiation, and apoptosis[1]. The human body needs a variety of lipids to maintain the health of the organism, but abnormal lipid levels can lead to fat deposition on the arterial walls, which can lead to intravascular complications, and excessive lipids can easily adhere to the nerve walls of the blood circulation, leading to atherosclerotic disease[2]. It has been shown that disorders of lipid metabolism play an important role in the development and progression of cancer, as they lead to the abnormal expression of various genes and proteins, as well as the dysregulation of cytokines and signaling pathways[3]. Excess body fat and metabolic disorders often lead to obesity, which increases the risk of other diseases and health problems, such as heart disease, diabetes, high blood pressure, and Alzheimer's disease (AD)[2].

Currently, the treatment of lipid metabolism disorders mainly involves lifestyle changes and the use of various types of lipid metabolism regulators, such as statins, cholesterol absorption inhibitors, bile acid sequestrants, etc. Although these drugs are commonly used in clinical practice for the treatment of lipid metabolism, the adverse effects should not be ignored. For example, statins can cause myopathy, and cholesterol absorption inhibitors could cause gastrointestinal discomfort. Thereby, it is urgent to innovate and develop efficient and low-toxicity therapeutic leads.

The concept of food medicine homology has a long history in China, and there is a close relationship between medicine and food.

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Some foods not only satisfy satiety, but also have the function of promoting health and preventing disease[4]. Chinese medicine believes that all edible materials contain certain nutrients that can help maintain good health, and nowadays the shift from "drug supplementation" to "food therapy" is becoming more pronounced[5]. There are numerous studies disclosed more and more natural products have great potential in regulating disorders of lipid metabolism, especially those hidden in medicinal and edible plants. Sesamin is a potent spleen tyrosine kinase (SYK) inhibitor and may be a potential strategy for the treatment of allergic diseases[6]. In addition, ingested phenolic natural products may enhance health when interacting with proteins[7]. Puerarin in *Pueraria lobata* significantly reduced lipid accumulation as well as total cholesterol and triglyceride levels in zebrafish larvae[8]. Curcumin in *Curcuma longa*, a widely accepted dietary polyphenol, reduces lipid accumulation in nonalcoholic fatty liver disease (NAFLD)[9]. Broccoli, a natural food that regulates key genes involved in lipolysis and promotes lipolysis to reduce hepatic lipid accumulation. These plant-derived natural products offer promising avenues for future therapeutic interventions targeting lipid metabolism-related diseases.

## 2. Lipid classification systems and lipid metabolism processes

Lipids are important nutrients needed by the body. Classically, lipids are mainly classified into 2 types: lipoid (e.g. phospholipids, glycolipids and sterols, etc.) and fat, such as triglycerides (TG), and sterols also include cholesterol, sex hormones and vitamin D, etc.[3]. There are numerous lipid species, and in order to advance the lipidomics, the International Lipid Classification and Nomenclature Committee (ILCNC) has developed a "Comprehensive Lipid Classification System", which comprehensively and unambiguously categorizes lipids into 8 classes (Table 1)[10]. Lipid metabolism includes lipid synthesis and catabolism. Synthesis requires the glycolytic intermediate dihydroxyacetone phosphate and the TCA cycle intermediate citric acid to produce 3-phosphoglycerol and acetyl-CoA, respectively. Fatty acid synthase (FASN) converts acetyl-CoA to palmitate, which together with 3-phosphoglycerol forms lipids, and acetyl-CoA is used to produce cholesterol. After lipid synthesis, it is broken down into fatty acids, which can be used by the mitochondria and undergo $\beta$-oxidation to produce ATP, and finally is supplied to the organism as energy[11]. Hence, lipid metabolism holds paramount importance for the organism's vital activities and biological functions.

**Table 1**
Comprehensive classification system for lipids.

| No. | Classification | Abbreviation |
|---|---|---|
| 1 | Fatty acyls | FA |
| 2 | Glycerolipids | GL |
| 3 | Glycerophospholipids | GP |
| 4 | Sphingolipids | SP |
| 5 | Sterol lipids | ST |
| 6 | Prenol lipids | PR |
| 7 | Saccharolipids | SL |
| 8 | Polyketides | PK |

## 3. Diseases associated with disorders of lipid metabolism

Dysfunctions in lipid metabolism intricately intertwine with a spectrum of ailments, spanning metabolic diseases, cardiovascular disease (CVD), nervous system diseases, cancer, and infectious diseases, etc.

### *3.1 Metabolic diseases*

Excessive accumulation of lipids in the liver leads to lipid metabolism disorders, which in turn leads to steatosis and a lipotoxic environment. The lipotoxic environment causes endoplasmic reticulum (ER) stress, mitochondrial dysfunction, lysosomal dysfunction and impaired autophagy, extracellular vesicle, tissue hypoxia, etc., which ultimately leads to cell death and inflammation, and thus contributes to the development of NAFLD[12]. Type 2 diabetes mellitus (T2DM) is a common metabolic disorder characterized by a pathology of overnutrition and insulin resistance (IR)[13]. Free fatty acid (FFA) promotes the activation of nuclear factor kappa B (NF-κB), which induces ER stress, leading to the production of reactive oxygen species (ROS), triggering a pro-inflammatory response that contributes to the development of T2DM[14]. Obesity is also a common metabolic disorder that results in an increase in body weight and adipose tissue due to the body's energy intake exceeding energy expenditure[15]. Obesity can cause hypertension, coronary artery disease, diabetes, nephropathy and many other diseases.

### *3.2 Cardiovascular diseases*

Numerous CVDs are linked to disorders of lipid metabolism, resulting in the excessive deposition of lipids within the vessel wall. It has been found that higher levels of lipid accumulation products are significantly correlated with increased CVD mortality[15]. Intracranial aneurysm is a common intracranial vascular lesion that develops mainly as a result of lipid deposition and blood flow, which exacerbates local inflammation and progressively weakens blood vessels, which in turn facilitates aneurysm development[16]. Atherosclerosis is a chronic inflammatory disease characterized by lipid deposition and plaque formation, which is a multifactorial vascular disease caused by lipid metabolism disorder. Dyslipidemia causes low-density lipoprotein (LDL) and cholesterol to continuously accumulate in the lining of blood vessels, forming plaques and causing atherosclerotic lesions.

### *3.3 Nervous system diseases*

Nervous system diseases including AD and Parkinson's disease (PD) etc. AD is a destructive neurodegenerative disease and a leading cause of dementia in the elderly population[16]. It has been shown that soluble β-amyloid oligomers (Aβ oligomers) formed early in the pathogenesis of AD trigger multiple vicious cycles that decrease synaptic transmission, damage mitochondria, and increase oxidative stress, ultimately leading to chronic ER stress and autophagy dysfunction[16]. Whereas the pathogenesis of AD may be related to altered lipid status, adequate lipid membrane content protects neurons from Aβ oligomer-induced neurodegeneration[17]. PD is another neurodegenerative disorder characterized by the degeneration of dopaminergic neurons[18].

Oxidized polyunsaturated fatty acids interact with α-synuclein in an aberrant manner, leading to loss of mitochondrial function, which in turn leads to the death of dopaminergic neurons and ultimately to PD[19].

### 3.4 Cancer

Lipid metabolism is closely related to tumor cell survival and proliferation. In a wide range of cancers, fat uptake, storage and fat production are up-regulated, which in turn promotes the rapid growth, invasion, and migration of tumors[20]. The dysregulation of lipid metabolism in cancer involves multiple aspects, including increased lipid uptake, fatty acid oxidation and cholesterol accumulation, which facilitate tumor growth and progression[21]. As a result of further research into the relationship between lipids and cancer, numerous lipid regulators have been utilized in anti-tumor therapy[21].

### 3.5 Others

It has been shown that excess circulating non-esterified fatty acids (NEFA) promote systemic inflammation through innate immune activation of inflammatory factors, which in turn exacerbate respiratory disease[22]. It has also been found that disorders of lipid metabolism contribute to intervertebral disc degeneration by activating inflammatory responses, ER stress and oxidative stress, and inhibiting autophagy[23].

Given the correlation between disorders in lipid metabolism and a variety of diseases (Fig. 1), it is imperative to regulate the equilibrium of lipid metabolism and develop dietary supplements (DSs) that can effectively manage these disorders and finally to prevent and assist in the treatment of these diseases.

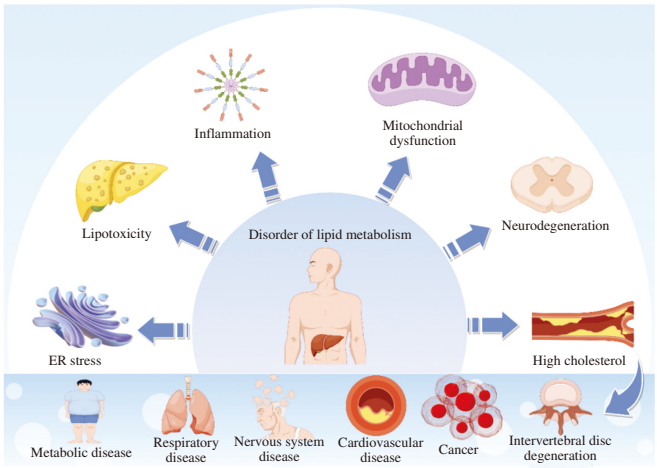


**Fig. 1** Diseases associated with disorders of lipid metabolism. Materials provided by figdraw (www.figdraw.com).

## 4. Treatment of disorders of lipid metabolism

Currently, management strategies for lipid metabolism disorders primarily entail dietary modifications, exercise regimens, and pharmacological interventions. In cases of severe conditions, pharmacotherapy becomes imperative, typically involving lipid metabolism regulators. These regulators modulate the body's processes of lipid production, metabolism, and storage. Notable drug categories utilized for regulating lipid metabolism disorders encompass statins, cholesterol absorption inhibitors, bile acid sequestrants, nicotinic acid, fibrates, proprotein convertase subtilisin/Kexin type 9 (PCSK9) inhibitors, among others (Table 2)[23]. However, most of the current lipid regulators produce adverse effects such as poor compliance and specificity. Acute and short-term toxicity, chronic toxicity, and reproductive toxicity have been reported following the use of certain lipid regulators[24]. Hence, there is an urgent need to develop a novel lipid-regulating medication that possesses low toxicity, high efficacy, and enhanced safety.

Natural products from medicinal and edible plants have become a potential direction of wide interest due to their green and healthy sources and obvious pharmacological effects. Quercetin is a flavonoid natural product that alleviates a wide range of diseases such as diabetes, CVD and obesity[25]. Genistein, a natural product from soybeans, significantly inhibits the proliferation and invasion of tumor cells[26]. Several studies have demonstrated the presence of natural products in medicinal and edible plants that are capable of modulating disorders in lipid metabolism[27-28]. For instance, berberine found in *Coptis chinensis*, curcumin abundant in *C. longa* and resveratrol sourced from grapes. Many medicinal plants in traditional Chinese medicine, as well as vegetables and fruits in daily diet, have the effect of regulating lipid metabolism, as shown in Fig. 2. These medicinal and edible plants show remarkable characteristics of safety, accessibility and remarkable therapeutic potential in treating diseases. Under the Dietary Supplement Health and Education Act (DSHEA), the nomenclature of any plant and natural concentrate and extract ingredient is now referred to as a dietary supplement[29]. Preclinical and clinical studies provide evidence that food-based bioactive compounds are beneficial for liver diseases such as NAFLD and improve steatosis[30]. In a recent analysis, through a meta-analysis of 17 256 subjects with an average age between 26–28 years old, the results of the study found that berberine supplementation was effective in improving lipid profiles[31]. Another study conducted a randomized, double-blind, controlled trial of 71 individuals diagnosed with dyslipidemia and randomized to receive either resveratrol (100 mg/day) or sucrose (0.5 g/day) for 2 months found significant reductions in total cholesterol and triacylglycerol in the resveratrol group, suggesting that supplementation with resveratrol may improve patients' lipid profile[32]. This evidence suggests that natural products from medicinal and edible plants have great potential in the treatment of disorders of lipid metabolism.

Lovastatin is an U.S. Food and Drug Administration (FDA)-approved lipid-lowering drug that belongs to the statin class and is used to treat hypercholesterolemia and minimize the risk of CVD, while its natural sources include red yeast rice (a traditional Chinese medicine and food)[33]. Guggul tree is a small thorny herb having remarkable hypocholesterolaemic properties, and guggul is a gum-resin portion obtained from the bark of the guggul tree[34]. Guggul is used for the treatment of lipid metabolism disorders in Ayurvedic medicine. Following regulatory sanction in India in 1987, guggulsterone, the bioactive constituent derived from guggul, has garnered extensive employment in the management of hyperlipidemia, alongside lovastatin, it stands as a stalwart clinical agent, entrenched in the therapeutic armamentarium for various manifestations of dyslipidemia[33]. Currently, berberine in *C. chinensis* and silymarin in *Silybum marianum* have been approved by the U.S. FDA for entry into clinical phase IV studies[35].

**Table 2**
Representative drugs of the lipid-modulating class and their therapeutic effects, and adverse effects.

| Categorization | Representative medicines | Therapeutic effects | Adverse reactions |
|---|---|---|---|
| Statins | Atorvastatin, lovastatin | Lowering cholesterol levels, improving CVD, reducing inflammation, and alleviating atherosclerosis, etc. | Rhabdomyolysis, hepatotoxicity |
| Cholesterol absorption inhibitors | Ezetimibe | Lowering LDL-C levels | Myopathy, gastrointestinal upset |
| Bile acid sequestrants | Cholestyramine, cholestipol | Lowering LDL-C levels, improving CVD | Gastrointestinal effects |
| Nicotinic acid | Niacin | Lowering LDL-C levels and triglyceride levels and increasing HDL-C levels | Flushing, hepatic toxicity |
| Fibrates | Gemfibrozil, clofibrate | Reducing triglyceride levels, increasing HDL-C levels, decreasing LDL-C levels, and alleviating atherosclerosis | LDL-lowering is very modest |
| PCSK9 inhibitors | Alirocumab, evolocumab | Lowering LDL-C levels, improving CVD | Gastrointestinal effects |
| CETP inhibitors | Dalcetrapib, evacetrapib | Lowering cholesterol levels | Off-target effects |

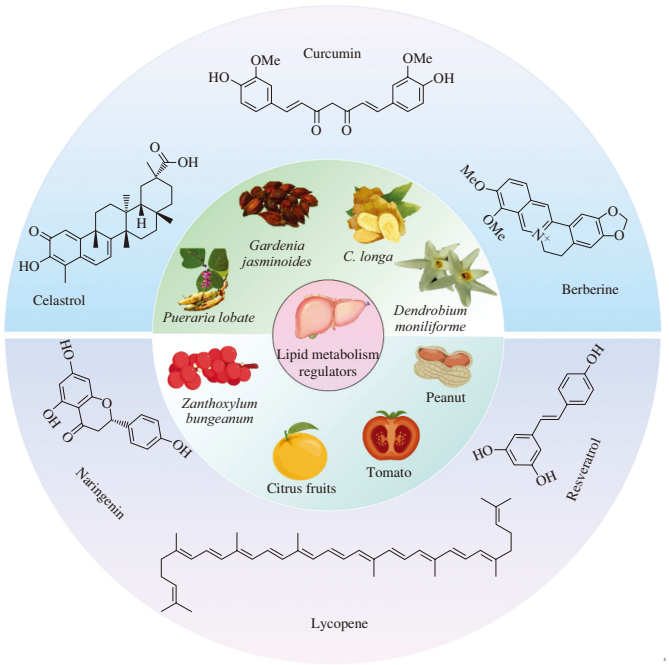


**Fig. 2** Medicinal and edible plants associated with lipid regulation. Materials provided by figdraw (www.figdraw.com).

## 5. Bioactive compounds and associated targets for the regulation of lipid metabolism

Natural products are one of the important sources for the development of DSs. Among them, bioactive compounds derived from medicinal and edible plants stand out for their immense potential in modulating lipid metabolism, and these compounds are predominantly classified into various categories, including glycosides, terpenoids, polyphenols (non-flavonoids), flavonoids, alkaloids and others.

### *5.1 Glucosides*

Glycosidic are one of the most important sources of natural lipid metabolism regulators. Within the category of glycosides, numerous active molecules have been experimentally proven to possess the potential to regulate lipid metabolism.

*P. lobata* is a medicinal herb with a variety of pharmacological activities. Puerarin is an isoflavone glycoside compound that has been isolated from *P. lobata*. It has a wide range of applications in the treatment of CVDs, diabetes, and cancer. Recent research findings indicate that puerarin may suppress the NF-κB signaling pathway through inhibiting matrix metalloproteinase-8 (MMP8) to inhibit liver lipid accumulation and inflammation[36]. It has been reported that puerarin attenuated atherosclerotic lesion progression in high-fat diet (HFD) apolipoprotein E-deficient mice (*ApoE*$^{-/-}$ mice), and its protective effect required phosphorylation of xtracellular signal-regulated kinase 5 (ERK5) and upregulation of kruppel-like factor 2 (KLF2)[37]. Furthermore, puerarin can target the PH domain of AKT serine/threonine kinase 1 (AKT1), activate AKT1, and increase the phosphorylation or activity of downstream proteins, thus improving insulin resistance and assisting in the regulation of disorders of glucose and lipid metabolism[38]. Therefore, puerarin can regulate lipid metabolism by regulating MMP8, ERK5/KLF2, AKT1, etc., and then improve lipid accumulation, inflammation and atherosclerosis, and realize the regulation of lipid metabolism.

Geniposide is the main active ingredient in *Gardenia jasminoides*, a water-soluble cyclic enol ether glycoside. It has been reported that geniposide accelerates reverse cholesterol transport in C57BL/6 and *ApoE*$^{-/-}$ mice, transferring more cholesterol from the plasma circulation to the liver and realizing lipid-lowering pharmacological effects, and also attenuates lipid accumulation in the mouse liver, and the above lipid-lowering effects may be mediated by inactivating the farnesoid X receptor (FXR)-mediated negative feedback regulation of bile acids[39]. In addition, several studies have shown that geniposide ameliorates atherosclerosis by modulating macrophage polarization through enhancing the expression of human CXC chemokine ligand 14 (CXCL14)[40].

We summarized here the current research on glycosidic bioactive components identified from medicinal and edible plants in the regulation of lipid metabolism. Their structures and therapeutic effects are shown in Table 3 and Fig. 3, respectively.

### *5.2 Terpenoids*

Terpenoids consisting of isoprene as the basic unit, which are widely found in nature and are an important part of various of herbal medicines. According to their chemical skeleton, they can be categorized into monoterpenoids, sesquiterpenoids, diterpenoids, sesterterpenes, triterpenoids and polyterpenoids, which have anti-inflammatory, anticancer and antiviral activities[62]. Here, we summarized a series of terpenoids with potential in regulating lipid metabolism, including sesquiterpenoids, diterpenoids, triterpenoids, tetraterpenoids, sesterterpenes.

**Table 3**
List of bioactive glycosidic compounds and their potential targets and therapeutic effects for regulating lipid metabolism.

| No. | Name | Source | Target | Therapeutic effects | Model | | Dose and duration | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | *In vitro* | *In vivo* | *In vitro* | *In vivo* | |
| 1 | Puerarin | *P. lobata* | ERK5/KLF2 | Alleviating atherosclerosis | HUVEC, human THP-1 monocytes | HFD-induced *ApoE*$^{-/-}$ mice | 10, 50 μmol/L for 24 h | 50, 100 mg/kg·day for 12 weeks | [37] |
| | | | MMP8 | Inhibiting lipid accumulation and inflammation | Ethanol (EtOH)-induced AML-12 cell; | NIAAA model | 6.25, 12.5, 25, 50 μmol/L for 24 h | 5, 25, 50, 100 mg/kg | [36] |
| | | | AKT1 | Regulating glucose and lipid metabolism | HepG2 cells | – | $10^{-6}$, $10^{-5}$, $10^{-4}$ mol/L | – | [38] |
| | | | Foxp3 | Alleviating atherosclerosis | – | HCD-induced *ApoE*$^{-/-}$mice | – | 100 mg/kg·day BW for 16 weeks | [41] |
| 2 | Geniposide | *G. jasminoides* | CXCL14 | Alleviating atherosclerosis | 3T3-L1 cells | Male *ApoE*$^{-/-}$ mice | 80 μmol/L for 24 h | 50 mg/kg·day for 12 weeks | [40] |
| | | | FOS/MAPK | Alleviating atherosclerosis | – | Male New Zealand rabbits fed HFD | – | 1.5 mg/kg·day for 4 weeks | [42] |
| | | | FXR | Reducing cholesterol accumulation | Human HepG2 cells and Caco2 cells | C57BL/6 and *ApoE*$^{-/-}$ mice | 100 μmol/L | 50 mg/kg·day for 4 weeks and 50 mg/kg·day for 13 weeks | [39] |
| 3 | Icariin | *Epimedium* Linn. | AMPK, PPARγ, C/EBPα, SREBP-1c | Inhibiting lipogenesis | 3T3-L1 cells | – | 100 μmol/L | – | [43-44] |
| | | | miR-205-5p/ERBB4/AKT | Alleviating atherosclerosis | AS cell model | *ApoE*$^{-/-}$ AS mice | 10 μmol/L for 30 min | 40 mg/kg·day for 12 weeks | [45] |
| 4 | Verbascoside | Mullein | LCAT, PLA2, LPCAT | Regulating glycerophospholipid metabolism, reducing lipid deposition | – | *ApoE*$^{-/-}$ mice | – | 60 mg/kg·day for 12 weeks | [46] |
| 5 | Phillyrin | *Forsythia suspensa* | PPARβ/δ-ANGPTL 4 | Reducing fat content | – | C57BL/6J mice | – | 15 or 45 mg/kg·day for 12 weeks | [47] |
| 6 | Cyanidin-3-*O*-*β*-glucoside (C3G) | *Lonicera caerulea* | AMPK, PPARγ, SREBP-1c | Inhibiting lipogenesis | – | Male C57BL/6J mice（fed HFHS） | – | 200 mg C3G equivalent/g dry weight for 17 weeks | [48] |
| 7 | Luteolin-7-*O*-glucoside | *Commelina communis* | GLUT4 | Inhibiting lipid accumulation | 3T3-L1 cells | Mice C57BL/6J mice | 0, 1, 5, 10, 50 μmol/L for 6 days | – | [49] |
| 8 | Phlorizin | Apple, pear, cherry | PPARγ, C/EBPα, CD36, FABP4 | Reducing inflammatory stress, attenuate adipose and hepatic insulin resistance | – | Male C57BL/6J mice (Induction of T2DM) | – | 100 mg/kg·day for 120 days | [50-51] |
| 9 | Isoquercitrin (IQ) | *Bidens pilosa* | Galectin-3 | Improving inflammation and lipid accumulation | IR-HepG2 cells | Male C57BL/6J mice (14–16 g) | 5, 15.8, 50, 158 μmol/L | 50, 100, 200 mg/kg·day BW | [52] |
| | | | AMPK | Regulating hepatic lipid accumulation | – | Male Sprague-Dawley (SD) rats | – | 10, 17.5, 25 mg/kg·day for 5 weeks | [53] |
| 10 | Stevioside | *Stevia rebaudiana* | AMPK, PI3K/Akt | Increasing glucose uptake and improving metabolism | – | IR induced male Wistar rats | – | 500 or 2 500 mg/kg body weight (BW) for 5 weeks | [54] |
| | | | PPARα | Regulating lipid accumulation | Rat BRL hepatocytes | Prague-Dawley rats were fed with HFD | 100, 200, 400 μmol/L for 36 h | 70, 150 mg/kg for 6 weeks | [55] |
| 11 | Rebaudioside A (RA) | | PPARγ | Improving metabolism | – | IR induced male Wistar rats | – | 500 or 2 500 mg/kg BW for 5 weeks | [54] |
| 12 | Niazirin | Moringa | AMPK | Improving insulin resistance and inflammation | – | C57BL/6J mice | – | 10 and 20 mg/kg BW | [56] |
| 13 | Quercitrin | *Merremia tridentata* | PI3K/Akt | Improving insulin resistance | – | SPF female Sprague Dawley rats | – | 12.5, 25, 50 mg/kg·day | [57] |
| 14 | Naringin | Citrus | FXR/FGF15-CYP7A1, CYP7A1 | Regulating intestinal flora, alleviating atherosclerosis | – | *ApoE*$^{-/-}$ female mice and C57BL/6J mice | – | 100 mg/kg BW | [58] |
| | | | AMPK, HSL, ATGL | Reducing lipid content | 3T3-L1 adipocytes | Obese adult mice | 100 μg/mL for 4 days | 5 g/kg for 60 days | [59] |
| 15 | Hesperidin | | Triphosphate-binding cassette transporter A1 (ABCA1) | Inhibiting cholesterol synthesis | – | *ApoE*$^{-/-}$ female mice and male C57BL/6J mice | – | 100 mg/kg BW | [58] |
| 16 | Astragaloside IV | Astragalus | TNF-α, IL-6, IL-1β | Improving circulating TC, TG, and HDL levels and cardiac lipid accumulation | – | T2DM rats | – | 80 mg/kg·day for 16 weeks | [41,60] |
| | | | AKT | Inhibiting lipolysis | 3T3-L1 cells | Male ICR mice were fed with HFD | 10 μmol/L for 0.5 h | 50, 100 mg/kg for 2 weeks | [61] |

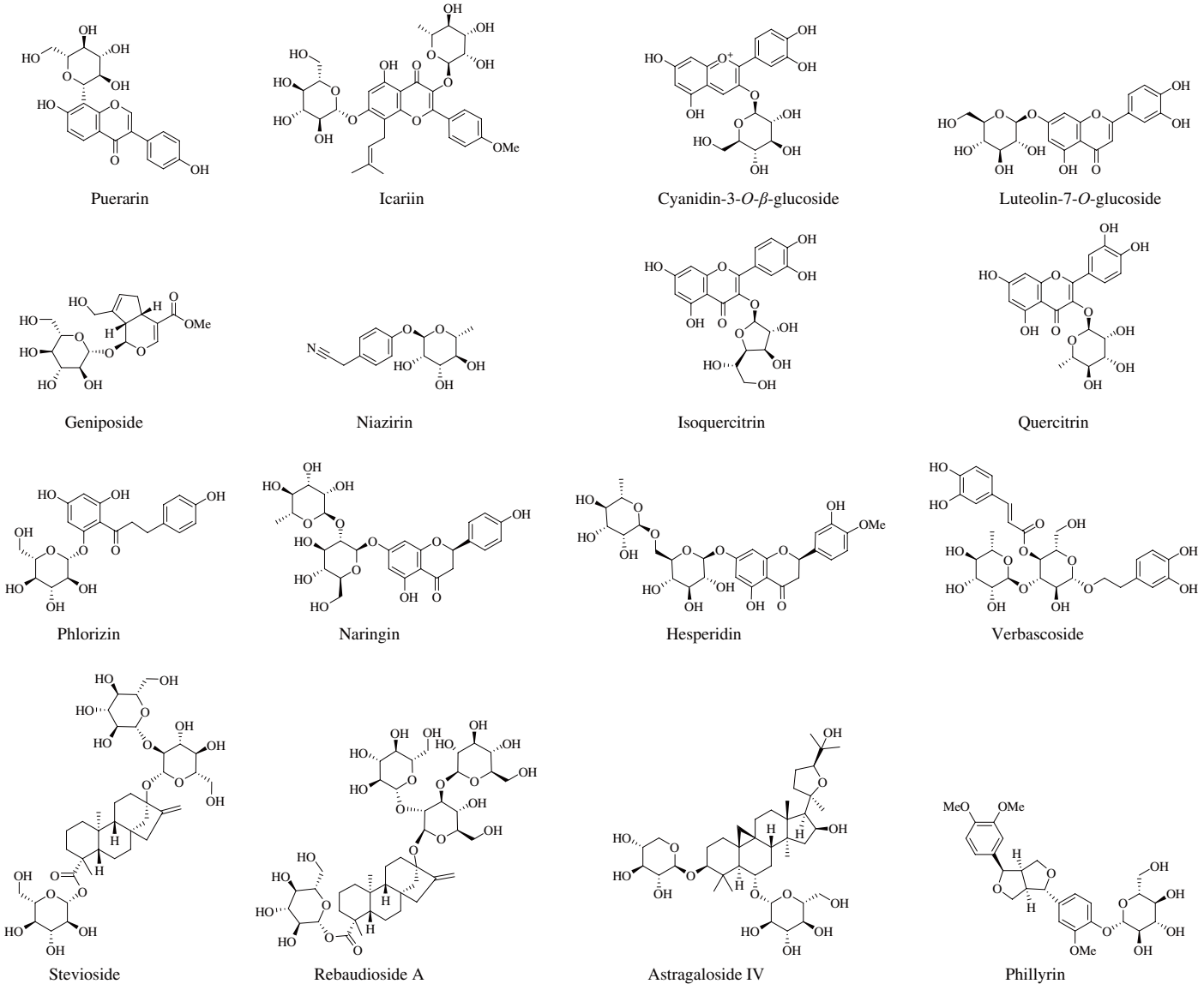


**Fig. 3** Structures of glycosidics with activity in regulating lipid metabolism.

Celastrol, a pentacyclic triterpenoid, is the main active ingredient extracted from *Tripterygium wilfordii*. At present, more and more experiments have proved that celastrol can regulate lipid metabolism disorders. Recent studies have revealed that celastrol inhibits the binding of caveolin-1 (CAV-1) and lectin-like oxidized low-density lipoprotein receptor 1 (LOX-1), thereby reducing lipid accumulation, blocking p-GSK-3β at serine 9, preventing nuclear translocation of *β*-catenin, and ultimately inhibiting tumor growth in clear cell renal cell carcinoma (ccRCC)[63]. In addition, it has been shown that celastrol upregulates adenosine ABCA1 expression by activating liver X receptor α (LXRα) expression, which in turn inhibits lipid accumulation in vascular smooth muscle cells (VSMCs)[64]. Celastrol can regulate lipid metabolism through CAV-1/LOX-1, LXRα/ABCA1-mediated pathways, and is a multi-targeted natural terpenoid that regulates lipid metabolism, which is potentially valuable in the development of lipid-regulating DSs. The mechanism of multi-targeted lipid regulation by celastrol was described in detail by Gu et al.[65].

Lycopene is a tetraterpene that is abundant in red plants such as tomatoes, carrots, and watermelon. One study have demonstrated that lycopene has the ability to inhibit fat accumulation and improve cardiometabolic disorders in obese female rats[66]. Furthermore, research on palmitate-mediated myocardial inflammation in female Wistar rats revealed that lycopene inhibited the NF-κB signaling pathway and regulated lipid metabolism, thereby eliminating myocardial inflammation in rats[67]. Additionally, it was found that the combination of luteolin and lycopene can regulate lipid metabolism by activating the SIRT1/AMPK pathway, thus alleviating NAFLD[67].

Other terpenoids including lactucin, lactucopicrin, rotundic acid, astaxanthin, fucoxanthin, ursolic acid, sclareol, lutein, pedunculoside, calenduloside E (CE), asperosaponin VI (AVI) and bixin. Their structures and therapeutic effects are shown in Table 4 and Fig. 4, respectively.

### *5.3 Polyphenols*

Polyphenols, acids and esters are widely found in fruits and vegetables, originating from the phenylalanine and the manganic acid metabolic pathways, and the activity of polyphenol

**Table 4**
List of bioactive terpenoid compounds and their potential targets and therapeutic effects for regulating lipid metabolism.

| No. | Name | Source | Target | Therapeutic effects | Model | | Dose and duration | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | *In vitro* | *In vivo* | *In vitro* | *In vivo* | |
| 1 | Celastrol | *T. wilfordii* | CAV-1/ LOX-1 | Reducing lipid accumulation | Human ccRCC cell and renal epithelial cells | Male BALB/c nude mice | 0.25, 0.5, 1.0, 1.5, 2.0 μmol/L for 12 h | 0.25, 0.5, 1.0 mg/kg for 4 weeks | [63,65] |
| | | | LXRα/ABCA1 | Regulating lipid accumulation | VSMCs | – | 50, 100, 200, 400, 800 nmol/L for 12, 24, 48 h | – | [64] |
| 2 | Lactucin | Chicory | HADHA, ADAM17, SQSTM1, GBA | Regulating lipid metabolism | HepG2 cells | – | 10 mmol/L | – | [68] |
| | | | JAK2/STAT3 | Anti-adipogenesis | 3T3-L1 cells | Male C57BL/6 mice fed with HFD | 20 μmol/L | 20 mg/kg·day for 7 weeks | [69] |
| 3 | Lactucopicrin | Chicory | HADHA, ADAM17, SQSTM1, GBA | Lowering blood lipids and regulating fatty acid metabolism | HepG2 cells | – | 20 mmol/L | – | [68] |
| 4 | Rotundic acid | *Ilex rotunda* | SREBP-1c/SCD1 | Regulating intestinal bioflora | Rat primary hepatocytes | C57BL/6 male mice fed HFD | 10, 30, 100 mmol/L | 10, 30, 100 mg/kg·day | [70-71] |
| 5 | Astaxanthin | Algae | FGF21/PGC-1α | Alleviating mitochondrial dysfunction | FFA-induced LO2 cells | HFD-fed mice | 90 μmol/L | 60 mg/kg for 10 weeks | [72] |
| 6 | Lycopene | Tomatoes | SIRT1, AMPK | Improving steatosis | – | HFD-induced C57BL/6 J mice | – | 20 mg/kg·day for 8 weeks | [73] |
| | | | – | Regulating lipid accumulation | – | Female Wistar rats | – | 24, 48 mg/kg for 2 weeks | [67] |
| | | | – | Inhibiting fat accumulation | – | Female albino rats fed with Western diet (WD) | – | 24, 48 mg/kg for 2 weeks | [66] |
| 7 | Fucoxanthin | Brown algae | AMPK/Nrf2/TLR4 | Reducing inflammation and oxidative stress, regulating lipid metabolism | FFA-induced normal human Chang liver cells | – | 2 μg/mL for 24 h | – | [74] |
| | | | PI3K/AKT, TLR4/NF-κB | Alleviating atherosclerosis | Mouse arterial endothelial cells | – | 0.25 μmol/L for 48 h | – | [75] |
| 8 | Ursolic acid | *Rosmarinus officinalis* leaves | AMPK | Inhibiting lipid synthesis and promoting lipolysis | FFA-induced HepG2 cells | HFD-induced obese mice | 20 μmol/L for 24 h | 100 mg/kg·day for 15 weeks | [76] |
| 9 | Lutein | Spinach, broccoli | SIRT1 | Reducing insulin resistance and lipid accumulation | – | HFD-fed rats | – | 50 mg/kg for 45 days | [77] |
| 10 | Calenduloside E (CE) | Aralia elata | KLF2 | Reducing inflammation and lipid accumulation | RAW 264.7 macrophages | HFD-induced *ApoE*$^{-/-}$ mice | 1.25 μg/ mL | 11 mg/kg·day for 16 weeks | [78-79] |
| | | | PI3K/AKT/NF-κB | Alleviating hepatic steatosis | The mouse hepatocyte cell line AML-12 (CRL-2254) | *ApoE*$^{-/-}$ mice | 20 μmol/L for 1 h | 5, 10 mg/kg for 4 weeks | [78] |
| 11 | Asperosaponin VI (AVI) | *Dipsacus asper* | AMPK | Reducing inflammation and lipid accumulation | HepG2 cells | C57BL/6J mice | 0, 1, 5, 10, 25, 50 μmol/L | 10 and 20 mg/kg, bid. | [80-81] |
| 12 | Pedunculoside | *I. rotunda* and *I. pubescens* | PPARγ, C/EBPα, SREBP-1 | Alleviating hyperlipidemia | – | HFD-induced rats | – | 5, 15, 30 mg/kg·day for 7 weeks | [82] |
| 13 | Bixin | Annatto | PPARγ | Reducing lipid accumulation | 3T3-L1 cells | C57BL/6 male mice | 10, 25, 50, 75, 100, 150 μmol/L for 48 h | 100 μL/day for 6 weeks | [83] |
| 14 | Sclareol | *Salvia sclarea* | NF-κB/NLRP3 | Alleviating lipogenesis | – | C57BL/6 mice | – | 10 mg/kg for 5 weeks | [84] |

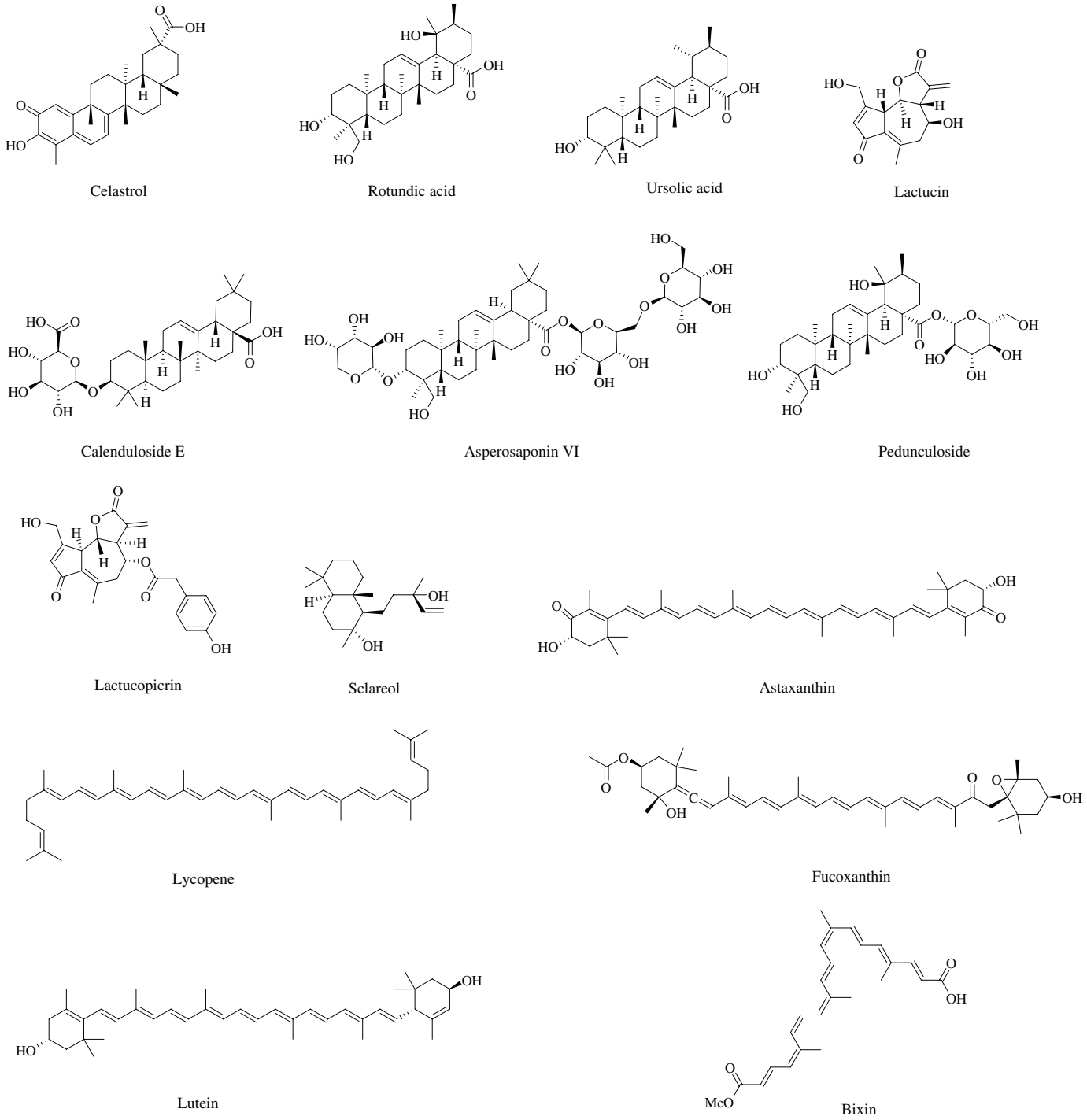


**Fig. 4** Structures of terpenoids with activity in regulating lipid metabolism.

extracts in regulating lipid metabolism has received much attention in recent years[85].

Curcumin is polyphenol active natural product extracted from *C. longa*, a traditional Chinese herb that is also edible. Curcumin has a wide range of pharmacological effects including the treatment of inflammatory diseases, antioxidant and anti-cancer properties. Curcumin also has a lipid-regulating pharmacological effect, the mechanism of action is to reduce plasma cholesterol and triglycerides by increasing lipoprotein lipase activity and altering lipid and cholesterol gene expression. Clinical trials have also shown that curcumin has an ameliorating effect on total cholesterol (TC), triglycerides (TG), LDL-C, and HDL-C levels, and it can be recommended as an adjunctive anti-hyperlipidemic agent[86]. In another study, it was found that curcumin could effectively inhibit FFAs-induced lipid accumulation in cells induced with FFAs after treatment with different concentrations of curcumin[87].

Resveratrol is a polyphenol active compound found in a wide variety of fruits and vegetables such as grapes, mulberries, tomatoes, etc. Resveratrol has demonstrated multifaceted activities across several domains, encompassing antioxidative, anti-aging,

cardioprotective, antihypertensive, antidiabetic, anticancer, anti-inflammatory, and antibacterial realms[88]. It has been shown that in high glucose (HG)-induced HepG2 cells, resveratrol was found to modulate SIRT1-mediated FXR deacetylation, thereby inhibiting the early pathological process of HG-induced hepatic TG accumulation and regulating lipid metabolism disorders[89]. In a study on diabetic nephropathy, resveratrol was found to reduce renal lipid deposition and ultimately ameliorate diabetic kidney damage by modulating the SIRT1 lipid synthesis pathway[28].

Other polyphenols including epigocate-3-gallate (EGCG), phloretin, theasinensin A (TSA), ferulic acid, *p*-coumarie acid, protocatechuic acid, chlorogenic acid, salvianolic acid B, chicoric acid, myricanol, vescalagin, and oryzanol. Their structures and therapeutic effects are shown in Table 5 and Fig. 5, respectively.

### 5.4 Flavonoids

The basic skeleton of flavonoids is in the form C6-C3-C6 units, which are found in large quantities in natural plants, such as fruits, vegetables, grains, barks, roots, stems, flowers, teas, etc. According to the structural differences, flavonoids are generally categorized into flavonols, flavones, isoflavones, anthocyanidins, flavanones, flavanols, and chalcones[112].

Cyanidin is a natural anthocyanidins found in a variety of fruits and vegetables. Cyanidin binds to LXRs, a key transcription factor that regulates cellular lipid metabolism, and induces the transcriptional activation of the LXRs, which in turn reduces intracellular cholesterol and TG concentrations and regulates cellular lipid metabolism[113]. Additionally, another study demonstrated that the inclusion of 1–50 μmol/L cyanidin in adipogenic medium effectively suppressed adipogenesis by down-regulating the expression of key adipogenic marker genes (PPARγ, C/EBPα, adiponectin, and aP2)[114]. Furthermore, experiments involving cell stimulation with 30–100 μmol/L cyanidin revealed that anthocyanidins inhibited the formation of adipocytes through activation of the phospholipase-inositol triphosphate (PLC-$IP_3$) pathway and intracellular $Ca^{2+}$ signaling[114].

Naringenin is found in a variety of fruits and vegetables, and has a variety of pharmacological effects including anti-tumor, anti-

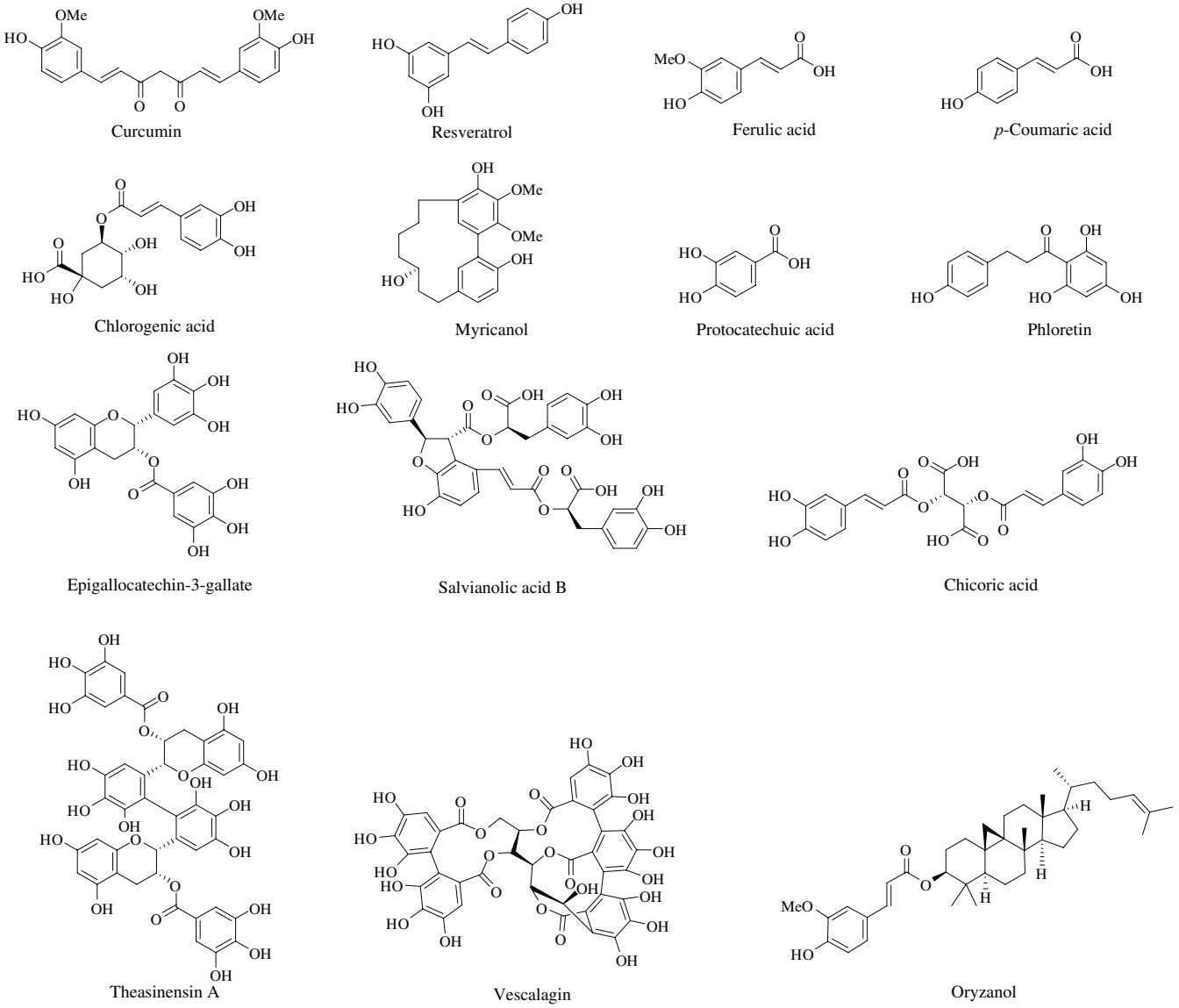


**Fig. 5** Structures of polyphenolics with activity in regulating lipid metabolism.

**Table 5**
List of bioactive polyphenolic compounds and their potential targets and therapeutic effects for regulating lipid metabolism.

| No. | Name | Source | Target/signaling pathway | Therapeutic effects | Model | | Dose and duration | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | *In vitro* | *In vivo* | *In vitro* | *In vivo* | |
| 1 | Curcumin | *C. longa* | TFEB | Regulating autophagy and inhibiting inflammation | ox-LDL-induced human monocytic THP-1 cells | *ApoE*$^{-/-}$ mice | 20 μmol/L for 24 h | 20 mg/kg for 16 weeks | [90-92] |
| | | | AMPK | Inhibiting lipid accumulation | FFAs-Induced HepG2 cells | - | 0, 5, 10, 20, 40 μmol/L for 24 h | – | [87] |
| | | | cAMP/PKA/CREB | Regulating lipolysis and lipogenesis | Colon-26 (C26) murine adenocarcinoma cell line ATCC, 3T3-L1 preadipocytes | C26 tumor-bearing BALB/c mice | 20 μmol/L | 20, 50 mg/kg for 14 days | [27] |
| | | | SREBP-2/HNF1α | Reducing intestinal cholesterol absorption | Caco-2 and HepG2 cells | Male syrian golden hamsters fed with HFD | 1.5, 3, 6, 12, 25, or 50 μmol/L for 24 h | 0.1% (*m*/*m*) curcumin for 12 weeks | [93] |
| 2 | Resveratrol | Grapes, blueberry and peanuts | SIRT1- FXR | Reducing lipid deposition | HepG2 (CL-0103) cells | - | 5, 10, 20 μmol/L for 24 h | – | [89,90,94] |
| | | | JAML/Sirt1 | Inhibiting lipid synthesis | – | Male C57BL/6J mice were fed with HFD | – | 100 mg/kg for 6 weeks | [28] |
| 3 | Epigallocatechin-3-gallate (EGCG) | Green tea | NLRP3 | Reducing inflammation | – | HFD-induced mice | – | 40 μmol/L for 3 h | [94-95] |
| 4 | Phloretin | Apple, pear and cherry | PPARγ, C/EBPα, CD36, FABP4 | Reducing inflammatory stress and hepatic insulin resistance | – | T2DM model induced in male C57BL6/J mice | – | 100 mg/kg·day for 120 days | [51] |
| 5 | Theasinensin A (TSA) | Oolong and black teas | GLP-1R/IRS/PI3K/AKT/GLUT2 | Regulating gut microflora and alleviating diabetes | – | Male C57BL/6J mice fed HFD | – | 20, 50, 100 mg/kg | [96] |
| 6 | Ferulic acid | Foxtail millet | HDAC1, PPAR | Inhibiting free fatty acid uptake | FFA-treated hepatocytes | HFD-induced mice | 60 μg/mL for 24 h | 30 mg/kg·day for 13 weeks | [97] |
| | | | ACSL1 | Ameliorating lipid metabolic disorder | HepG2 cells | Male *db*/*db* diabetic mice | 0.25 mmol/L for 24 h | 25, 50, 100 mg/kg for 6 weeks | [98] |
| 7 | *p*-Coumarie acid | Foxtail millet | HDAC1, PPAR | Inhibiting free fatty acid uptake | FFA-treated hepatocytes | HFD-induced mice | 60 μg/mL for 24 h | 30 mg/kg·day for 13 weeks | [97] |
| 8 | Protocatechuic acid | Vegetables, fruits | SIRT3 | Improving fatty acid metabolism | PA-induced AML-12 cells | HFD-induced rats | 10 μmol/L for 24 h | 20 mg/kg·day for 8 weeks | [99] |
| 9 | Chlorogenic acid | Vegetables, fruits | ALKBH5 Demethylase, | Improving steatosis | Alpha mouse liver 12 cells | Male C57BL/6J mice fed HFD | 12.5, 25, 50, 100 μmol/L for 24 h | 50 mg/kg·day | [100-101] |
| | | | PPARγ | Reducing lipid accumulation | 3T3-L1 cells | – | 0, 20, 40 μmol/L for 24 h | – | [102] |
| 10 | Salvianolic acid B | *Salvia miltiorrhiza* | NLRP3 | Improving NAFLD | – | Male C57BL/6J and *ob*/*ob* mice | – | 10 mg/kg·day for 12 weeks | [41,103] |
| 11 | Vescalagin | *Syzygium samarangense* | – | Reducing triglycerides | – | HFD-induced diabetic Wistar rats | – | 10, 30 mg/kg BW | [104] |
| 12 | Myricanol | Chinese bayberry | AMPK, PPARγ, C/EBPα | Inhibiting lipogenesis and accumulation | 3T3-L1 cells | – | 5 μmol/L | – | [105] |
| 13 | Oryzanol | Rice bran | NF-κB | Inhibiting inflammation and obesity | – | ICR mice | – | 100 mg/kg for 10 weeks | [106-107] |
| 14 | Chicoric acid | Chicoric | NF-κB/NLRP3 | Improving the development of atherosclerotic | TNF-α induced HUVECs | *LDLR*$^{-/-}$ mice were fed HFD for 14 weeks | 0.125, 0.25, 0.5 μmol/L for 12 h | 12.5, 25, 50 mg/kg for 14 weeks | [108] |
| | | | PI3K/Akt/NF-κB | Improving glucolipid metabolic abnormalities | – | Male SPF-grade SD rats were fed with high glucose and fat diet | – | 10 mL/kg·day for 14 days | [109] |
| | | | β3-AR, ERK | Promoting lipid metabolism | 3T3-L1 pre-adipocytes | – | 5, 25, 50, 100, 125 μmol/L for 2 days | – | [110] |
| | | | Nrf2/HO-1, PI3K/AKT, NF-κB | Reducing inflammation and apoptosis | C28/I2 cells | – | 0, 2.5, 5, 10, 20, 40, 80 μmol/L for 24, 48, and 72 h | – | [111] |

inflammatory, antibacterial, and regulation of lipid metabolism. Some experiments have shown that naringenin reduces the serum levels of TC, TG and non-HDL-C, and alleviates HFD induced hepatic steatosis in SD rats, while naringenin can also increase the activity of AMP-activated protein kinase (AMPK) and the expression of the phosphorylation protein of AMPK in adipocytes, regulating the expression of lipid metabolism genes[115]. In C57BL/6J mice fed with a HFD, naringenin also improved their gut barrier function, thereby preventing NAFLD[116].

Other bioactive flavonoids including quercetin, baicalein, apigenin, hesperetin, (−)-epicatechin, kaempferol, nobiletin, silybin, tangeretin, chrysin, and luteolin. Their structures and therapeutic effects are shown in Table 6 and Fig. 6, respectively.

### 5.5 Alkaloids

Alkaloids are alkaline nitrogen-containing organic compounds widely found in plants that exert significant biological activity in regulating lipid metabolism.

Berberine is a class of quaternary amine alkaloids widely found in *Rhizoma coptidis*. It has a variety of pharmacological effects such as anti-inflammatory, antioxidant, anti-tumor and anti-atherosclerosis[138]. It has also been shown that berberine may be an active molecule with great potential to ameliorate the disorders of glucolipid metabolism induced by hepatic injury by modulating the composition and number of intestinal microbiota[138]. Berberine may also reduce cholesterol synthesis in HepG2 cells and alleviate NAFLD by mediating the SIRT1-FoxO1-SREBP2 signaling pathway[139]. In another study, *ApoE*$^{-/-}$ mice were induced to develop atherosclerotic lesions by HFD and streptozocin (STZ), followed by treatment with berberine (200 mg/kg·day for 12 weeks), and it was found that AMPKα, a regulator of lipid consumption, was activated. The subsequent expression of fatty acid synthase (FASN) and SREBP-1, regulators of lipid synthesis, was decreased, suggesting that berberine reduces lipid synthesis and increases lipid depletion[140].

Betaine is an active alkaloid widely found in many plants such as beets and spinach. This active molecule is important for a variety of metabolic disorders, and betaine supplementation has been shown to enhance AMPK and inactivate acetyl coenzyme A carboxylase (ACC) phosphorylation to attenuate hepatic lipogenesis and achieve lipid regulation[141]. In addition, betaine ameliorates hepatic lipid accumulation and achieves lipid regulation by up-regulating LXRα and PPARα expression as well as alleviating endoplasmic reticulum stress[142]. Betaine can regulate lipid metabolism through multiple targets.

Other bioactive alkaloids including nuciferine, piperine, trigonelline, dendrobine, dendrocrepine, isocrepidamine, oxonantenine, *N*-formyllaurotetanine, tetrahydropalmatine, perillartine and hydroxy-*β*-sanshool. Their structures and therapeutic effects are shown in Table 7 and Fig. 7, respectively.

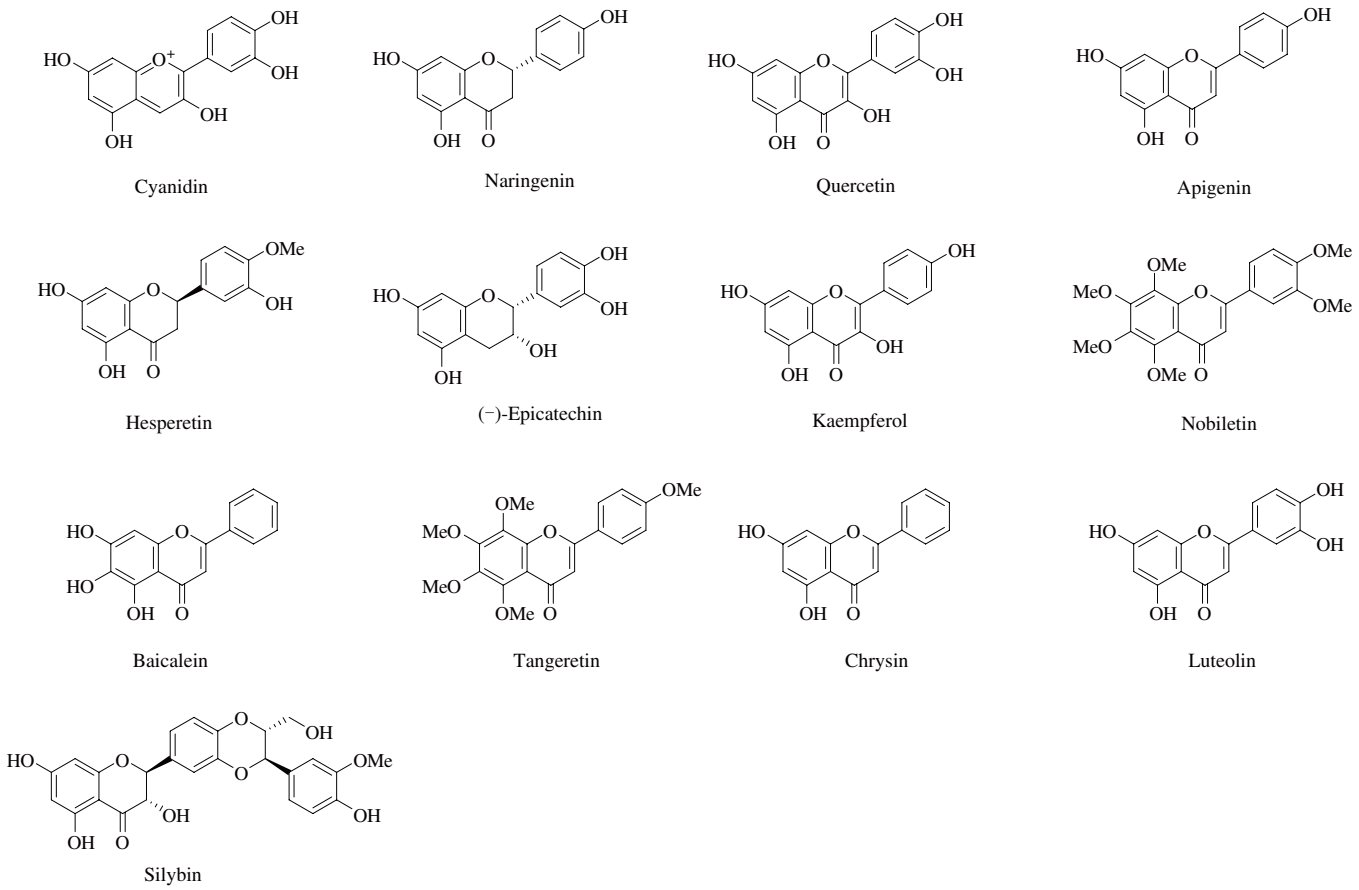


**Fig. 6** Structures of flavonoids with activity in regulating lipid metabolism.

**Table 6**
List of bioactive flavonoid compounds and their potential targets and therapeutic effects for regulating lipid metabolism.

| No. | Name | Source | Target | Therapeutic effects | Model | | Dose and duration | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | *In vitro* | *In vivo* | *In vitro* | *In vivo* | |
| 1 | Cyanidin | Fruits and vegetables | FXR | Lowering of lipid concentration | HepG2 cells | – | 100 μmol/L for 24 h | – | [117] |
| | | | PLC-IP3 | Inhibiting adipogenesis | Mouse 3T3-L1 preadipocytes | – | 50 μmol/L for 4 days | – | [114] |
| 2 | Naringenin | Grapefruit, tomato, grape and citrus fruits | HMGCR | Inhibiting cholesterol synthesis and alleviating atherosclerosis | – | *ApoE*$^{-/-}$ female mice and male C57BL/6 J mice | – | 100 mg/kg BW | [41,58,115] |
| | | | AMPK | Inhibiting lipid accumulation | 3T3-L1 preadipocytes | Male Sprague Dawley rats | 25, 50, 75 μg/mL | 100, 200, 400 mg/kg for 12 weeks | [115] |
| | | | – | Regulating the intestinal barrier function and microbiota | – | Male C57BL/6J mice | – | 0.1% naringenin for 16 weeks | [116] |
| 3 | Quercetin | Buckwheat, fruits and vegetables | NLRP3 | Alleviating atherosclerosis | RAW264.7 (*ox*-LDL-induced) | HFD-induced *ApoE*$^{-/-}$ mice | 50 μmol/L for 24 h | 100 mg/kg BW for 16 weeks | [118-120] |
| | | | AMPK | Reducing lipid accumulation | HepG2 cells | C57BL/6J mice | 10, 30, 60, 100 μmol/L | 20, 80 mg/kg·day for 4 weeks | [121] |
| 4 | Baicalein | *Scutellaria baicalensis* | AMPK | Lowering of lipid concentration | OA-induced HepG2 cells | HFD-induced mice | 5 μmol/L for 24 h | 50 mg/kg·day for 3 months | [41,122] |
| 5 | Apigenin | Fruits and vegetables | Keap1 | Improving insulin resistance and blood lipids | – | High fructose-fed mice | – | 50 mg/kg·day for 4 weeks | [41,118,123-124] |
| | | | – | Relieving the blocked autophagic flux and lipid accumulation | HepG2 cells | – | 10, 20, 40 μmol/L | – | [125] |
| 6 | Hesperetin | Paulownia flowers | HMGCR | Inhibiting cholesterol synthesis and alleviating atherosclerosis | – | *ApoE*$^{-/-}$ female mice, male C57BL/6J mice | – | 100 mg/kg BW | [58,118] |
| | | | AMPK/CREB | Suppressing inflammation | RAW 264.7, AML12 and 293T cell | Male BALB/c mice | 0, 5, 10, 25, 50, 100 μmol/L | 50 mg/kg for 5 days | [126] |
| 7 | (−)-Epicatechin | *Camellia sinensis* | APLNR | Enhancing lipolysis and reducing fat | – | Male rats descended from obese mothers. | – | 1 mg/kg BW for 15 days | [127] |
| 8 | Kaempferol | Tea, strawberries, grapes, cruciferous vegetables | AMPK | Enhancing lipolysis and inhibiting fatty acid synthesis | HepG2 cells | Male Kunming mice | 1 μmol/L for 12 h | 29, 58, 116 mg/kg for 6 weeks | [128] |
| | | | SIRT1/FXR | Alleviating lipid droplet accumulation | – | Alcohol induced mice | – | 50 mg/kg BW for 8 weeks | [129] |
| 9 | Nobiletin | Citrus fruits | AdipoR1 and gp91$^{phox}$ | Relieving liver oxidative stress and lipid accumulation | – | Sprague-Dawley rats | – | 20, 40 mg/kg·day for 4 weeks | [1,130] |
| | | | PPARα, PPARγ, FAS, ACC-1 | Ameliorating hepatic steatosis | – | Male *ApoE*$^{-/-}$ and C57BL/6J mice | – | 50, 100, 200 mg/kg·day for 24 weeks | [131] |
| 10 | Silybin | *S. marianum* | Sirtuin 2 | Reducing inflammation and steatosis | HepG2 cell | Male C57BL/6 mice fed HFD for 12 weeks | 50 μmol/L | 40, 80 mg/kg·day for 4 weeks | [132-133] |
| 11 | Tangeretin | Citrus peel | AMPK/ULK1 | Improvement of steatosis and activating mitochondrial autophagy | Mouse AML-12 normal hepatocyte line | chronic-binge alcohol feeding C57BL/6J mouse | 20 μmol/L for 24 h | 20, 40 mg/kg for 16 days | [134] |
| | | | PPAR-UCP1 | Ameliorating hepatic steatosis | – | Male C57BL/6 mice | – | 100 mg/kg for 12 weeks | [135] |
| 12 | Chrysin | Blue passion flower, propolis | AMPK/PI3K/AKT | Inhibition of gluconeogenesis and fatty acid synthesis | HepG2 Cells | HFD/STZ-induced C57BL/6J mice | 15 μmol/L for 24 h | 15, 30 mg/kg for 5 weeks | [136] |
| 13 | Luteolin | Carrot, pepper, celery | SIRT1, AMPK | Improving steatosis | – | HFD-induced C57BL/6J mice | – | 20 mg/kg·day for 8 weeks | [73] |
| | | | PPARα, CPT1A | Mediating endoplasmic reticulum stress and autophagy | AML12 mouse hepatocytes and primary hepatocytes | – | 7.5, 15 μmol/L for 12 h | - | [137] |

**Table 7**
List of alkaloidal bioactive compounds and their potential targets and therapeutic effects for regulating lipid metabolism.

| No. | Name | Source | Target | Therapeutic effects | Model | | Dose and duration | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | *In vitro* | *In vivo* | *In vitro* | *In vivo* | |
| 1 | Berberine | *C. chinensis* | SIRT1-FoxO1-SREBP2 | Alleviating insulin resistance | HepG2 cells | – | 25 μg/mL for 24 h | – | [90,94,132,139] |
| | | | RhoA/ROCK | Inhibiting intestinal lipid absorption | Primary HDLECs | Male C57BL/6J mice fed HFD | 20, 40 μmol/L for 6 h | 300 mg/kg·day for 4 weeks | [143] |
| | | | PPARγ-FGF21-GLUT2 | Inhibiting liver lipid accumulation | HepG2 cells | C57BL/6J mice | 25 μmol/L for 12 h | 200 mg/kg BW for 6 weeks | [144] |
| | | | AMPKα, KLF16 | Alleviating diabetic atheosclerosis | – | *ApoE*$^{-/-}$ mice | – | 200 mg/kg·day for 12 weeks | [140] |
| 2 | Betaine | Spinach and beet | LXRα/PPARα | Relieving ER stress and preventing lipid accumulation | – | Male Sprague-Dawley rats | – | 62.5, 125, 250 mg/kg | [94,142] |
| 3 | Nuciferine | Leaves of nelumbo nucifera gaertn | LKB1/AMPK | Ameliorating apoptosis and lipid accumulation | Bovine Mammary Epithelial Cells | – | 50, 100, 200 μmol/L for 12 h | – | [94,145] |
| | | | Calmodulin (CaM) | Anti-atherosclerotic effect | Mouse aortic vascular smooth muscle cells | *ApoE*$^{-/-}$ mice | 1, 5, 10 μmol/L for 24 h | 5, 20, 40 mg/kg·day | [146] |
| | | | Vanilloid 1 (TRPV1) | Regulating glucose metabolism | HepG2 cells | – | 0, 2.5, 5, 10, 20, 40, 80,160 μmol/L for 24 h | – | [94,147] |
| 4 | Piperine | Black pepper | C/EBPα | Regulating the lipogenic and lipolytic | – | HFD-induced obese mice | – | 15, 30 mg/kg BW for 12 weeks | [148] |
| | | | AMPK, PI3K-Akt | Improving lipid accumulation and insulin resistance | – | HFD-induced adult Sprague-Dawley male rats | – | 2.7, 13.5, 27 mg/kg for 8 weeks | [149] |
| 5 | Trigonelline | Onion and corn | AMPK-SREBP-1c-SIRT1 | Accelerating lipid oxidation | FFA and BSA induced SMMC-7721 and BEL-7402 cells | Male C57BL/6J mice fed HFD | 50, 75, 100 μmol/L | 40, 80 mg/kg·day for 8 weeks | [94,150] |
| 6 | Dendrobine | | PPARα | Improving steatosis and lipid accumulation | HepG2 cells | Male C57BL/6J mice | 10, 100 nmol/L, 1 μmol/L for 24 h | 5, 10, 15 mg/kg for 17 weeks | [151-152] |
| 7 | Dendrocrepine | *D. moniliforme* | – | Increasing glucose consumption | HepG2 cells | – | 25, 50 μmol/L for 24 h | – | [151,153] |
| 8 | Isocrepidamine | | – | Reducing blood glucose | HepG2 cells | – | 50, 100, 200 μmol/L for 24 h | – | [151,154] |
| 9 | Oxonantenine | *Xylopia aethiopica* | α-Glucosidase | Increasing glucose consumption and decreasing TG production | HepG2 cells | – | 50 μmol/L for 24 h | – | [155] |
| 10 | *N*-formyllaurotetanine | | α-Glucosidase | Increasing glucose consumption and decreasing TG production | HepG2 cells | – | 50 μmol/L for 24 h | – | [155] |
| 11 | Tetrahydropalmatine | *Corydalis yanhusuo* | AMPK-SREBP-1c-SIRT1 | Improving steatosis | SMMC-7721 and BEL-7402 cells | HFD-fed C57BL/6J mice | 50, 75, 100 μmol/L | 40, 80 mg/kg·day for 8 weeks | [150,156] |
| 12 | Perillartine | *Perilla frutescens* | RORγ | Reducing lipid accumulation | 3T3L-1 cells and HepG2 cells | Male C57BL/6 mice | 10 mmol/L for 24 h | 0.08%, 0.16% perillartine | [157] |
| 13 | Hydroxy-*β*-sanshool | *Z. bungeanum* | AMPK/Nrf2 | Improving NAFLD | - | HFD-fed C57BL/6J mice | – | 5, 10, 20 mg/kg for 12 weeks | [158] |

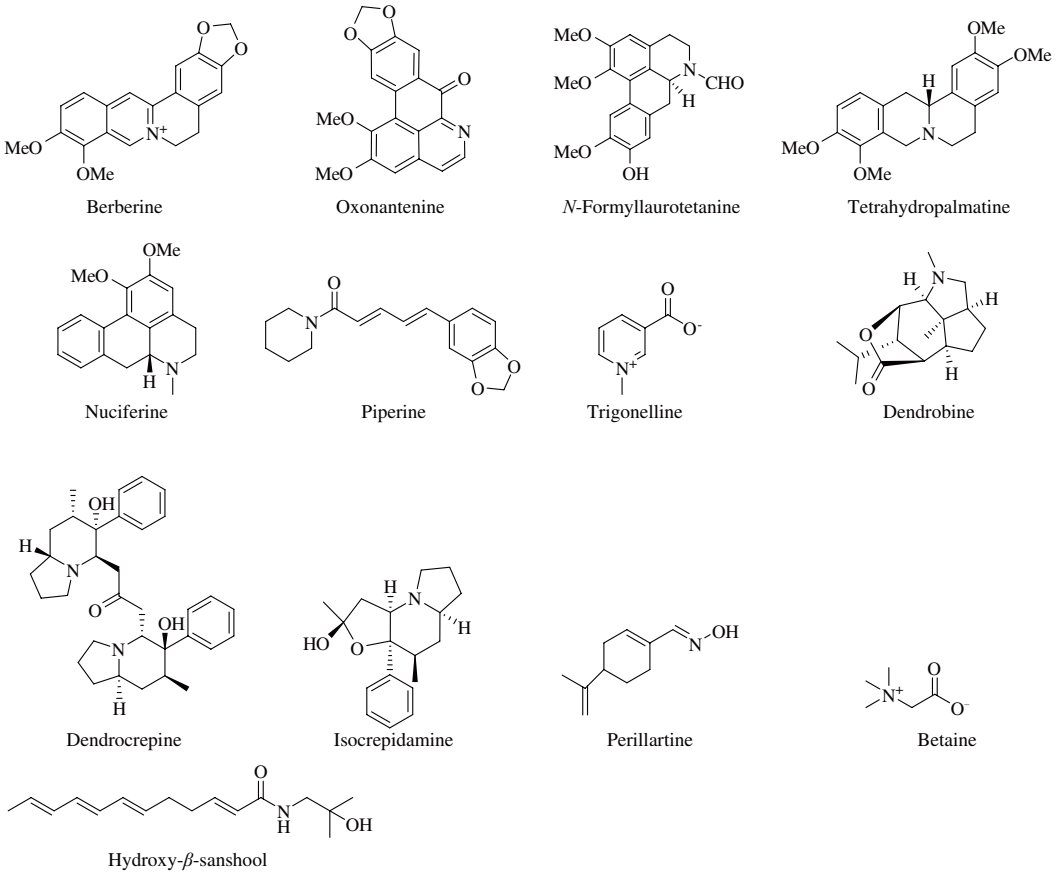


**Fig. 7** Structures of alkaloids with activity in regulating lipid metabolism.

### *5.6 Others*

In addition, there are many other natural products have great potential in regulating lipids. Schizandrin (SCH) A, an important active compound in *Schisandra chinensis*, belongs to lignans. It has been shown that SCH A significantly increased the expression of hepatic *β*-oxidation and fatty acid oxidation-related genes as well as fecal excretion of free fatty acids and triglycerides. Meanwhile, SCH A could significantly decrease the plasma free fatty acid and triglyceride levels of high cholesterol-fed mice, elevated plasma HDL-C levels and regulated lipid metabolism[159]. Cinnamaldehyde (CA) is a natural flavor, and it has been shown that CA and kaempferol can significantly improve dyslipidemia in *db*/*db* mice by activating the AMPK signaling pathway, and that the optimal ratio of CA and KP at a concentration of 39:58 (mg/kg) is the most effective in improving glycemic and lipid parameters[128]. Moreover, schizandrin B has the potential inreducing obesity-induced fat tissue weight gain and increases skeletal muscle mass[160]. AMPK is a ubiquitously expressed serine/threonine protein kinase, which is closely related to the regulation of lipid metabolism, and it has been demonstrated that tanshinone IIA can increase the activity of AMPK and ameliorate the disorders of glucose metabolism[161]. Fucosterol is classified as a steroidal compound that has the ability to impact adipogenesis and facilitate lipid metabolism[162]. The targets, therapeutic effects, and their chemical structures of these compounds are shown in Table 8 and Fig. 8, respectively.

With in-depth studies, the mechanism of action of various active natural products in regulating lipid metabolism has been revealed. Fig. 9 illustrated the signaling pathways of several multi-targeted natural products that regulate lipid metabolism. These natural products can reduce lipid accumulation, cholesterol synthesis and absorption, and improve lipid metabolism disorders by reducing inflammatory responses and atherosclerotic lesions. With the advantages of multi-pathway and multi-target, natural products have a broad development and application prospect as a new way to regulate lipid metabolism disorders.

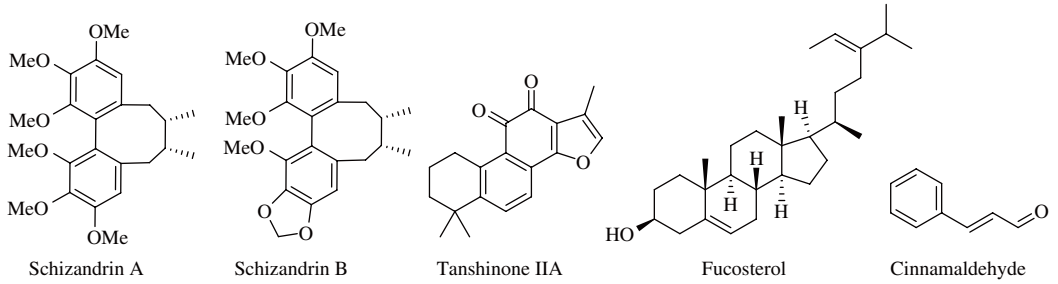


**Fig. 8** Structures of other type natural products with activity in regulating lipid metabolism.

**Table 8**
List of other bioactive compounds and their potential targets and therapeutic effects for regulating lipid metabolism.

| No. | Name | Source | Target | Therapeutic effects | Model | | Dose and duration | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | *In vitro* | *In vivo* | *In vitro* | *In vivo* | |
| 1 | SCH A | *S. chinensis* | – | Regulating triglyceride levels | – | Male C57BL/6J mice | – | SCH A (0.05%, *m/m*) for 15 weeks | [159] |
| 2 | SCH B | *S. chinensis* | Smad/FOXO | Increasing muscle protein synthesis and suppressing muscle protein breakdown | C2C12 myoblast cells | HFD-induecd male C57BL/6 mice | 0, 0.25, 0.5 μmol/L for 24 h | High-fat and 0.25% omiza extract fed for 8 weeks | [41,160] |
| 3 | CA | Cinnamomum trees | AMPK | Enhancing lipolysis and inhibiting fatty acid synthesis | HepG2 cells | *db/db* diabetic mice | 1.5 μmol/L for 12 h | 19.5, 39, 78 mg/kg for 6 weeks | [128] |
| | | | – | Regulating lipid metabolism, autophagy and endoplasmic reticulum stress | – | Wistar rats | – | 40 mg/kg BW for 29 days | [163] |
| 4 | Tanshinone IIA | *S. miltiorrhiza* | AMPK | Reducing insulin resistance | primary mouse hepatocytes | *db/db* mice | 20 μmol/L for 24 h | 100 mg/kg for 2 weeks | [161] |
| 5 | Fucosterol | *Ecklonia kurome* | Keap1-Nrf2-LCN13 | Inhibiting lipogenesis | HepG2 cells | – | 30 and 60 μmol/L | – | [162] |

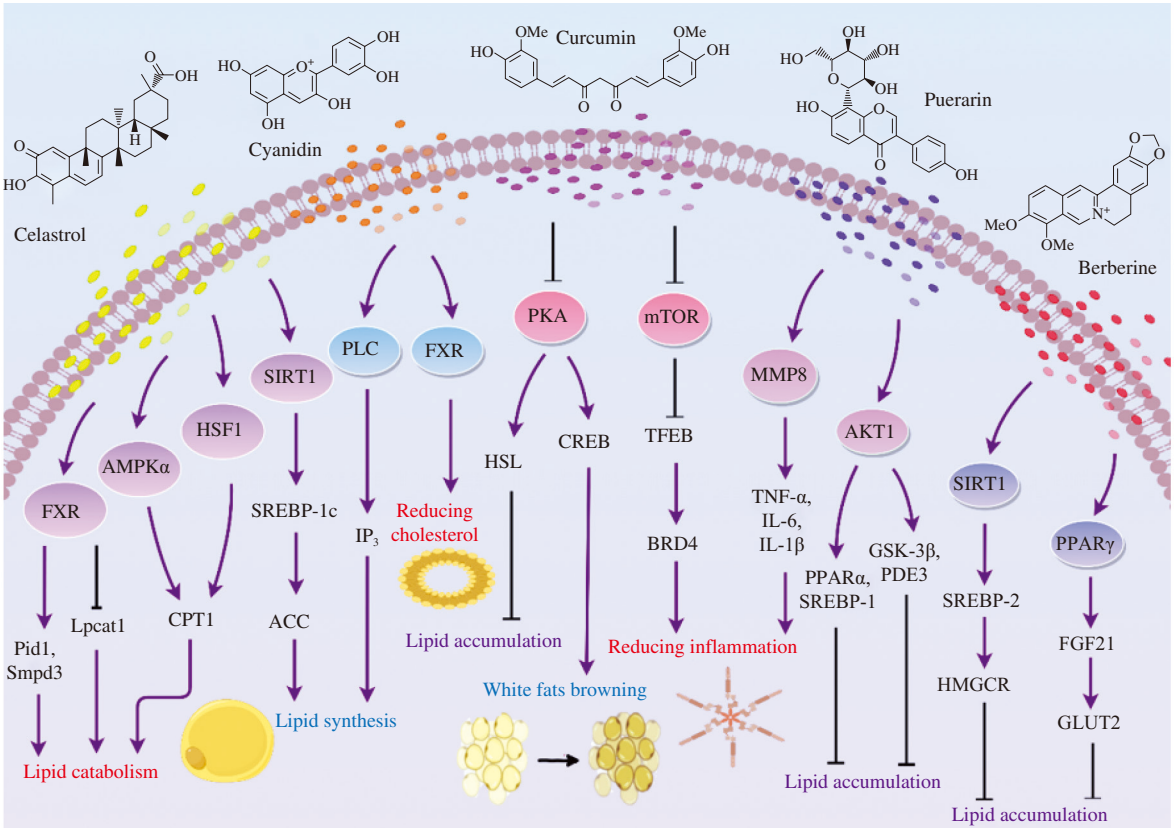


**Fig. 9** Signaling pathways of representative natural products regulating lipid metabolism. Materials provided by figdraw (www.figdraw.com).

## 6. Summary and discussion

In recent years, there are increasing number of functional foods developed from medicinal and edible plants for regulating lipid metabolism. Their presence in our daily life as dietary or functional foods and their development as a natural DSs may be of great significance for human health. Highland barley has attracted a lot of attention as a natural product for the development of dietary supplements, which can regulate the expression of genes related to lipid metabolism and play a role in lowering lipids[164]. Discovering new leads from medicinal and edible plants has the advantages of being green and healthy, rich in structural types, and multi-targeted. There is a great deal of interest in finding clues to curing diseases from these plants, where numerous active ingredients exist that can exert anti-AD, and have potential therapeutic effects on NAFLD and steatohepatitis (NASH), as well as some antitumor activity. Although these medicinal and edible plants play an important role in promoting human health and preventing disease, when processed into edible products, some food processing techniques may improve the properties of absorption by the human body, but at the same time add additives that may affect the metabolic health of the human body. Therefore, the choice of processing technology that preserves the active ingredients is critical for human health, and new technologies such as ultra-fine grinding and non-thermal processing technologies that have emerged are important for promoting the market for medicinal and edible plants[5].

These medicinal and edible plants regulate lipid metabolism through a variety of pathways, commonly regulating the AMPK pathway to inhibit lipogenesis and reducing lipid deposition by regulating the SIRT1 lipid synthesis pathway. Additionally, a limited number of studies have indicated that the active compounds present in these plants are capable of regulating microRNA (miR)-320-3p or MMP8. In recent years, there have also been some discoveries of new targets. Wang et al.[165] found that inhibition of the expression of long noncoding RNA (IncRNA) *Snhg9* could regulate lipid metabolism in the mouse intestine. Another study identified a hormone choline, cholesin, which inhibits cholesterol synthesis in the intestine[166]. Recent studies have found that natural product regulation of miRNAs and IncRNAs may offer a promising option for disease treatment. For example, the natural product 6-Shogaol ameliorates intestinal epithelial barrier dysfunction *via* miR-216a-5p/TLR4/NF-κB axis[167], and the natural product secoisolariciresinol diglucoside regulating oxidative stress, inflammation and apoptosis *via* miR-101a/MKP-1-mediated p38 and ERK pathway[168]. lncRNAs have important roles in disease and health, and natural flavonoids may regulate acute and chronic inflammation, adipogenesis, and lipid metabolism through this target, thereby affecting the physiological and pathological processes of cardiovascular disease[169]. The discovery of these novel targets has enriched our understanding of the regulatory mechanisms of lipid metabolism and provided new directions and targets for the treatment of related diseases.

Natural products are an important source for the development of new DSs, which are highly effective and multi-targeted, however, there are many challenges in developing them. Many natural active products are multi-targeted and their mechanism of action is complicated, and more novel and precise ways of target identification need to be explored. Nowadays, some efficient analytical techniques such as the use of UPLC-Q-TOF/MS and network pharmacology to predict the active ingredients and their targets in traditional Chinese medicine have emerged, which provide new ideas for the study of the mechanism of active ingredients in medicinal plants[170]. New methods and strategies for accurate identification and discovery of bioactive compounds in medicinal and edible plants based on Nuclear magnetic resonance (NMR) and mass spectrometry (MS) are widely discussed[171]. Artificial intelligence (AI) also plays an important role in the confirmation of natural product targets, and a novel Siamese spectral-based graph convolutional network (SSGCN) model has been proposed to infer the protein targets of compounds from gene transcriptional profiles, and the application of AI techniques to launch research can effectively improve the accuracy of target prediction[172].

Natural products have superiority than synthetic products in some ways however, because of their toxicity and biocompatibility issues, most of the research on natural products stays in the preclinical stage, and solving the toxicity and solubility issues of natural products is a tricky problem. In addition, most natural products do not have specific targeting characteristics, resulting in a variety of side effects and even off-target effects in the body after drug administration. Exploring an effective delivery method or dosage form is an inevitable issue in applying natural product targeting to the clinical stage. In the past, most of the natural products are in the form of oral or topical application, which can reduce the occurrence of side effects, but the oral drug bioavailability is low and cannot play a therapeutic role. In recent years, some studies have pointed to the application of nanotechnology in the study of natural drug preparations, nanotechnology plays an important role in the targeting of drugs, natural products controlled release and delivery, and can improve the bioavailability, drug dissolution and so on[173]. Nanotechnology is important for the study of natural products in future research.

## 7. Conclusion

The study of lipid metabolism has become a topic of wide interest because of the close relationship between lipid metabolism disorders and the occurrence and development of CVD, cancer, AD, etc., and therapeutic modalities to regulate lipid metabolism can provide new directions for the treatment of these diseases. However, most of the existing lipid regulators have poor compliance and specificity, and the search for new therapeutic leads becomes very necessary. Currently, medicinal and edible plants show great potential in modulating lipid metabolism, and some traditional Chinese medicines (e.g., *C. chinensis*, *T. wilfordii*, *G. jasminoides*, *C. communis*, etc.) and some fruits and vegetables (e.g., apple, watermelon, citrus, tomato, spinach, etc.) have been shown to have properties that regulate lipid metabolism.

By summarizing 75 natural active compounds in medicinal and edible plants, it was determined that their mechanisms of regulating lipid metabolism primarily involve the inhibition of lipid accumulation, amelioration of ER stress, improvement of the lipotoxic environment, alleviation of inflammation, and amelioration of mitochondrial dysfunction. It was also found that through these regulatory mechanisms, they can potentially play a therapeutic role in diseases related to lipid metabolism disorders. However, comprehensive studies and in-depth clinical trials are necessary to determine their modulatory effects on lipids, and we still face a significant challenge. DSs as nutritional aids, play a pivotal role in disease prevention and symptomatic improvement and offer a promising approach to intervening in various health conditions. New therapeutic strategies in the treatment of lipid metabolism disorders using medicinal and edible plants may unlock the full therapeutic potential of natural lipid metabolism modulators in the clinic.

## Declaration of interest statement

Zhang Yu is an editorial board member for *Food Science and Human Wellness* and was not involved in the editorial review or the decision to publish this article. All authors declared they have no conflict.

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