# Research progress of signaling pathways of the natural substances intervene dyslipidemia (Review)

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**Abstract.** Dyslipidemia is an umbrella term for a range of lipid metabolic disorders in the body. This condition has been widely reported to greatly increase the risk of cardiovascular diseases, threatening human health. In recent years, advances in molecular biology have deepened understanding of the dyslipidemia-related signaling pathways and specific mechanisms underlying dyslipidemia. Signaling pathways possess the ability to transmit an extracellular signal to the inside of the cell, leading to specific biological effects. Lipid metabolism disorders and lipid levels in the blood are frequently affected by aberrant alterations in the dyslipidemia-related signaling pathways. Therefore, further investigations into these pathways are required for the prevention and treatment of dyslipidemia. The present review summarizes the characteristics of six dyslipidemia-associated signaling pathways: Peroxisome proliferator-activated receptor, adenosine monophosphate-activated protein kinase, farnesoid X receptor, forkhead box O, adipocytokine and cyclic adenosine monophosphate signaling pathways. In particular, specific focus was placed on previous experimental studies and reports on the intervention effects of natural substances (compounds from animals, plants, marine organisms and microorganisms) on dyslipidemia.

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## 1. Introduction

Dyslipidemia is a lipid metabolism disorder in which the levels of total cholesterol (TC), triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C) in the blood are abnormally elevated and/or those of high-density lipoprotein cholesterol (HDL-C) in the blood are abnormally reduced (1). According to the World Health Organization, the total number of deaths associated with cardiovascular diseases worldwide reached 17.9 million in 2019 (2). In particular, dyslipidemia is considered to be a major risk factor of cardiovascular diseases, including atherosclerosis, coronary artery disease and myocardial infarction, all of which pose a serious threat to human health (3). Therefore, development of novel treatment options for dyslipidemia is required.

Following advances in molecular biology, previous studies have demonstrated that multiple signaling pathways, including the peroxisome proliferator-activated receptor (PPAR), adenosine monophosphate-activated protein kinase (AMPK), farnesoid X receptor (FXR), forkhead box O (FOXO), adipocytokine and cyclic adenosine monophosphate (cAMP) signaling pathways, are closely associated with the occurrence and development of dyslipidemia (4-9). Specifically, certain drugs can target specific aspects of lipid metabolism and serve a role in lowering the levels of lipids by activating or inhibiting these signaling pathways (4-9). Therefore, it is key to study the aforementioned signaling pathways for the development of novel treatment options and for the prevention of dyslipidemia. The majority of previous studies on signaling pathways altered by natural substances that have been proposed to treat dyslipidemia are experimental (4-11). However, at present, review

articles on natural substances (components or metabolites of animals, plants, marine organisms and microorganisms as well as endogenous active components of organisms) that can be used to treat dyslipidemia remain lacking. Therefore, the present review summarizes the mechanistic information of these six signaling pathways following treatment with the natural substances that have been reported to effectively control dyslipidemia. In addition, it provides an overview on the available experimental data to provide a basis for the treatment of dyslipidemia.

## 2. PPAR signaling pathway in dyslipidemia

The PPAR signaling pathway is one of the most widely studied dyslipidemia-associated signaling pathways. PPARs are ligand-activated transcription factors that consist of the following three subtypes: PPARα, PPARβ and PPARγ (12). Following endogenous ligand (e.g., lipids such as polyunsaturated fatty acid and arachidonate) binding, PPARs form heterodimers with retinoic X receptors and become activated to transcribe target genes associated with lipid metabolism (Fig. 1; generated using Adobe Illustrator CC version 23.0; Adobe Systems, Inc.) (13).

*PPARα signaling pathway in dyslipidemia*. PPARα can upregulate the expression of cholesterol 7 alpha-hydroxylase (CYP7A1), acyl-CoA oxidase (ACOX), carnitine palmitoyl transferase 1 (CPT1) and adenosine triphosphate (ATP)-binding cassette transporter A1 (ABCA1) (14-16). This in turn increases HDL synthesis, cholesterol conversion and fatty acid oxidation (14-16). CYP7A1 is a rate-limiting enzyme of bile acid synthesis that promotes the transformation of cholesterol to bile acids, thereby reducing TC levels in the blood (17). By contrast, ACOX and CPT1 are rate-limiting enzymes in the fatty acid oxidation pathway that reduces free fatty acid (FFA) and TG levels in the blood (18-20). ABCA1 is a rate-limiting factor in the process of HDL assembly that promotes the production and secretion of HDL to enhance the levels of HDL-C in the blood (21).

To investigate the hypolipidemic mechanisms mediated by Danhe granules (Danhe is a mixture prepared based on a prescription in clinical settings consisting of *Salvia miltiorrhiza* Bunge, *Reynoutria japonica* Houtt, *Crataegus pinnatifida* Bunge, *Citrus x aurantium* L., *Coix lacryma-jobi var. ma-yuen* (Rom.Caill.) Stapf and *Nelumbo nucifera* Gaertn), Chen *et al* (22) administered 3.30 g/kg Danhe to hyperlipidemic hamsters by oral gavage for 8 weeks. The results of this study demonstrated that Danhe administration significantly increased the expression levels of liver PPARα, CYP7A1 and ABCA1, decreased serum TC levels by 32.41% and enhanced serum HDL-C levels by 40.96% in hyperlipidemic hamsters (22). These results suggest that Danhe exerted hypolipidemic effects by activating the PPARα signaling pathway. To evaluate the effects of K-877 (a novel selective PPARα agonist) on lipid metabolism, LDL receptor-knockout mice were fed with a high-fat diet (HFD) supplemented with 0.001% K-877 for 1 week. K-877 administration was found to increase the expression of PPARα, ACOX, CPT1 and ABCA1 in the liver and increased the plasma levels of HDL-C in the plasma whilst decreasing the levels of TG in the plasma. Therefore, K-877 improved lipid metabolism by activating the PPARα signaling pathway (23).

*PPARβ signaling pathway in dyslipidemia*. Following activation, PPARβ upregulates the expression of ABCA1 and CPT1 to increase HDL synthesis and fatty acid oxidation (24,25). To unravel the cholesterol-lowering mechanism of ombuin-3-O-β-d-glucopyranoside (ombuine), HepG2 cells were supplemented with oleic acid. Treatment with 10 $\mu$mol/l ombuine was found to significantly increase the expression of PPARβ and ABCA1 whilst reducing intracellular cholesterol concentrations in HepG2 cells. This suggests that ombuine exerts a cholesterol-lowering role by activating the PPARβ signaling pathway (24). In another previous study, Jiang *et al* previously (26) investigated the effects of Li-Gan-Shi-Liu-Ba-Wei-San (LGSLBWS; a type of Mongolian medicine comprising eight types of Chinese herbal medicine, namely, pomegranate, cinnamon, cardamom, piper longum, safflower, amomum tsao-ko, dried ginger and nutmeg) on lipid metabolism in rats with non-alcoholic fatty liver disease (NAFLD). Following the administration of LGSLBWS (1.5 g/kg/day) for 4 weeks, the expression of PPARβ and the levels of fatty acid oxidation were markedly increased, whilst TG and FFA levels in the serum were decreased. Although CPT1 levels were not detected, the serum FFA and TG levels were decreased, suggesting that LGSLBWS may increase fatty acid oxidation through the PPARβ signaling pathway.

*PPARγ signaling pathway in dyslipidemia*. Following activation, PPARγ upregulates the transcription of liver X receptor α (LXRα) and ABCA1 to increase HDL synthesis (27). Li *et al* (28) applied a rat model of hyperlipidemia to explore the effects of *Agaricus blazei* Murill acidic polysaccharide (WABM-A) on the regulation of blood lipid levels. WABM-A (640 mg/kg/day) treatment for 8 weeks significantly upregulated the liver expression levels of PPARγ, LXRα and ABCA1, reduced the serum levels of TC and increased the serum levels of HDL-C in rats with hyperlipidemia (28). These results suggest that the lipid-lowering mechanisms underlying WABM-A may be associated with activation of the PPARγ signaling pathway.

## 3. AMPK signaling pathway in dyslipidemia

The AMPK signaling pathway is one of the most important homeostatic signaling pathways in the body and has been implicated in various metabolic diseases, including dyslipidemia and diabetes (29). Specifically, AMPK is a serine/threonine protein kinas that is widely expressed in the liver, heart and other metabolic organs, including skeletal muscle, kidney and adipose tissue (30). AMPK is typically activated by two methods. When the AMP/ATP ratio is increased, which indicates that the intracellular energy levels are low, liver kinase B1 translocates from the nucleus into the cytosol to activate AMPK by phosphorylation at Thr172 (31). Alternatively, AMPK can be activated by adiponectin (APN), which binds to its receptor to activate phospholipase C to convert phosphatidylinositol 4,5-bisphosphate ($PIP_2$) into inositol triphosphate ($IP_3$) (32). $IP_3$ then binds with the $IP_3$ receptor on the endoplasmic reticulum membrane to promote $Ca^{2+}$ release (32). $Ca^{2+}$ then activates calmodulin-dependent protein kinase kinase, which in turn activates AMPK also by phosphorylation at the Thr172 residue (33). AMPK regulates

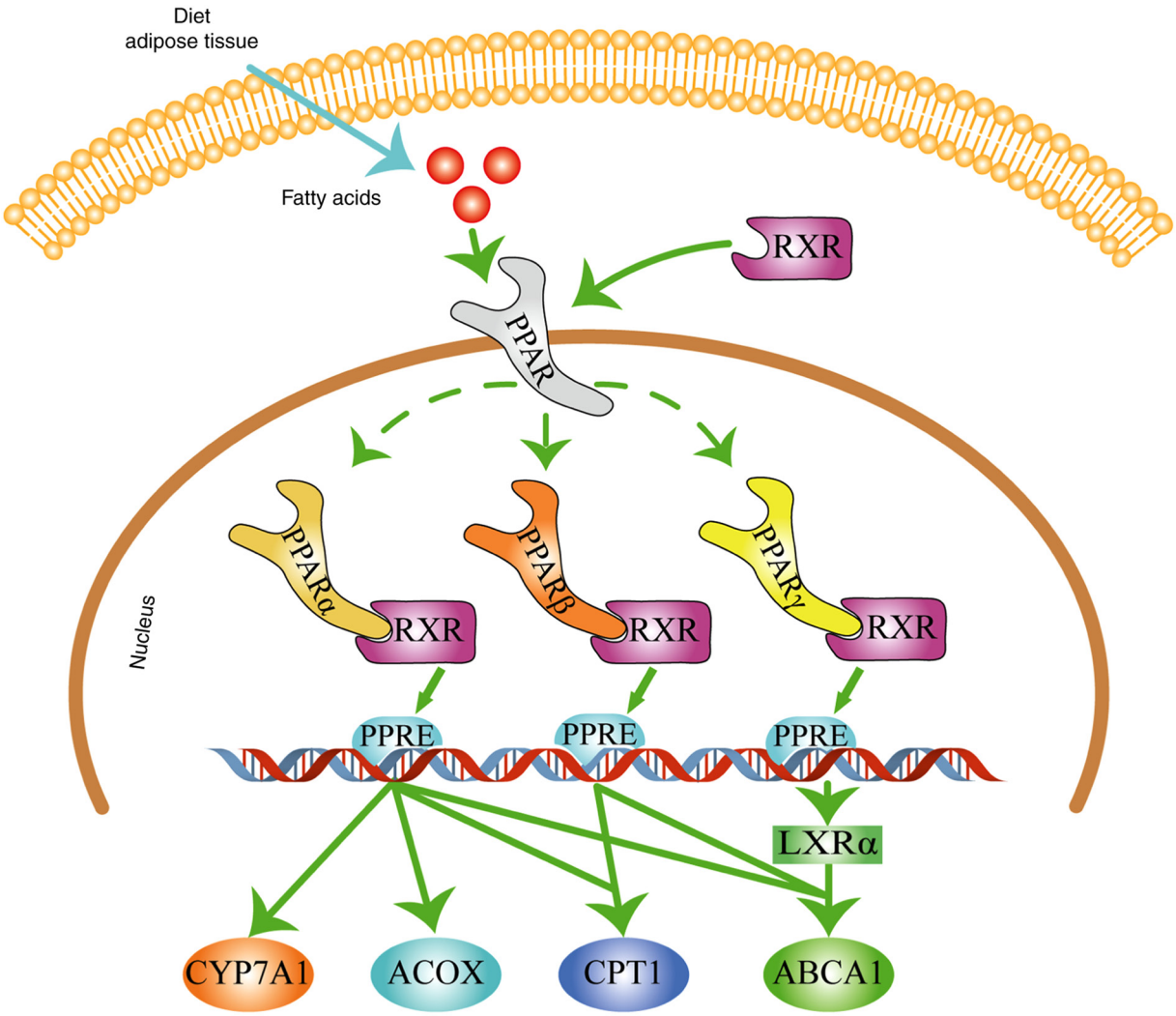


Figure 1. PPAR signaling pathway in dyslipidemia. PPAR regulates lipid metabolism by promoting the expression or activity of CYP7A1, ACOX, CPT1 and ABCA1. The blue arrow represents fatty acids obtained from dietary intake or the breakdown of adipose tissue. The green arrows represent stimulatory modifications. Dashed lines indicate various types of PPAR. The figure was generated using Adobe Illustrator CC version 23.0 (Adobe Systems, Inc.). RXR, retinoid X receptor; PPAR, peroxisome proliferator-activated receptor; LXRα, liver X receptor α; CYP7A1, cholesterol 7 α-hydroxylase; ACOX, acyl-CoA oxidase; CPT1, carnitine palmitoyl transferase 1; ABCA1, ATP-binding cassette transporter A1; PPRE, peroxisome proliferator response element.

lipid metabolism mainly through three mechanistic pathways (Fig. 2; generated using Adobe Illustrator CC version 23.0; Adobe Systems, Inc.). In the first mode of activation, AMPK can downregulate the expression of lipogenic enzymes acetyl CoA carboxylase (ACC) and fatty acid synthase (FAS) by inhibiting the expression of sterol regulatory binding protein-1c (SREBP-1c) (34). Since ACC and FAS are key enzymes in the fatty acid anabolic pathway, lowering their expression levels would reduce fatty acid synthesis (34). In addition, fatty acids are the main component within the molecular structure of TG (20). Therefore, reducing the levels of fatty acids would in turn reduce the levels of TG in the blood (20). In the second mode of mechanism, AMPK serves to inactivate ACC by phosphorylation, reducing the synthesis of the CPT1 inhibitor malonyl-CoA (35). This increases the activity of CPT1, which facilitates fatty acid oxidation to reduce fatty acid and TG content in the blood (36). In the third pathway, AMPK can inactivate 3-hydroxy-3-methylglutaryl CoA reductase (HMGCR) by phosphorylation, which is the rate-limiting enzyme in the cholesterol synthesis pathway (37). Inactivation of HMGCR reduces the production of cholesterol, which in turn leads to lower blood TC levels. Therefore, activation of the AMPK signaling pathway can inhibit fatty acid synthesis, promote fatty acid oxidation and suppress cholesterol synthesis, which finally serves to reduce blood TG and TC levels.

To investigate the effects of the *Herba houttuyniae* aqueous extract (HAE) on hyperlipidemia, Cao *et al* (38) randomly divided male C57BL/6J mice into three groups: Control, model and HAE. The mice in the HAE group were treated with HAE from day 1 to 9. On day 10, all mice except for those in the control group were intraperitoneally injected with 0.5 g/kg poloxamer 407 to induce acute hyperlipidemia, whereas mice in the control group were injected with saline. The results of the study demonstrated that treatment with 200 mg/kg/day HAE significantly decreased the expression levels of SREBP-1c, ACC and FAS in the liver whilst reducing the serum TG content (38). This suggests that HAE exerts protective effects against hyperlipidemia by upregulating the AMPK signaling pathway. In another

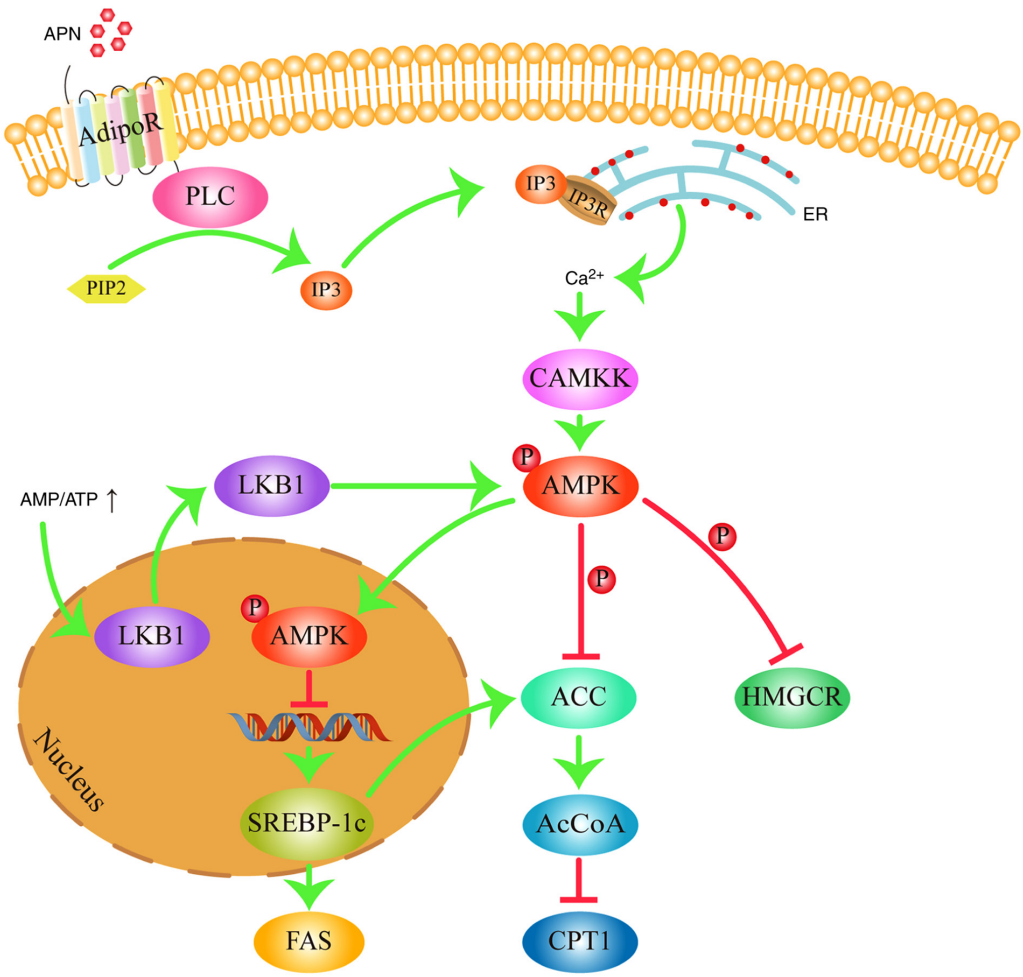


Figure 2. AMPK signaling pathway in dyslipidemia. AMPK regulates lipid metabolism by inhibiting the expression of FAS, decreasing the activity of HMGCR and ACC, and increasing the activity of CPT1. Arrows represent stimulatory modifications. T-shaped arrows represent inhibitory modifications. The picture was generated using Adobe Illustrator CC version 23.0 (Adobe Systems, Inc.). APN, adiponectin; AdipoR, adiponectin receptor; PLC, phospholipase C; $PIP_2$, phosphatidylinositol 4,5-bisphosphate; $IP_3$, inositol triphosphate; $IP_3R$, inositol triphosphate receptor; ER, endoplasmic reticulum; CAMKK, calmodulin-dependent protein kinase kinase; AMP, adenosine monophosphate; ATP, adenosine triphosphate; AMPK, adenosine monophosphate-activated protein kinase; LKB1, liver kinase B1; SREBP-1c, sterol regulatory binding protein-1c; ACC, acetyl-CoA carboxylase; AcCoA, malonyl-CoA; FAS, fatty acid synthase; HMGCR, 3-hydroxy-3-methylglutaryl coA reductase.

study, to explore the pharmacological activity of arctigenin (a phenylpropanoid dibenzyl butyrolactone lignan isolated from *Arctium lappa* Linné using a crystallization method) on lipid metabolism, Song *et al* (39) established a hyperlipidemic rat model by feeding them on an HFD for 8 weeks. Following 4 weeks of arctigenin administration (100 mg/kg/day), the serum levels of TG were significantly reduced compared with those in the model group (39). By contrast, the phosphorylation levels of AMPK and ACC, in addition to the expression of CPT1, were significantly increased compared with those in the model group (39). The results of this study suggest that arctigenin may exert a therapeutic effect on lipid metabolism through activation of the AMPK signaling pathway. In addition, Lee *et al* (40) previously investigated the cholesterolemic effects of unripe *R. coreanus* (5-uRCK) and ellagic acid on a high cholesterol diet-induced hypercholesterolemia rat model. The results demonstrated that 5-uRCK at 150 mg/kg and ellagic acid at 4 mg/kg significantly increased AMPK and HMGCR phosphorylation whilst markedly reducing the serum levels of TC and LDL-C (40). These results suggest that 5-uRCK and ellagic acid can inhibit the activity of HMGCR through activation of the AMPK signaling pathway, which lowered cholesterol levels.

## 4. FXR signaling pathway in dyslipidemia

The FXR signaling pathway is the principal signaling pathway in cholesterol conversion and serves a key role in maintaining lipid homeostasis. It can regulate cholesterol metabolism through two main mechanism (Fig. 3; generated using Adobe Illustrator CC version 23.0; Adobe Systems, Inc.). The first mechanism involves the FXR-small heterodimer partner (SHP) pathway in the liver, which is activated by bile acids (41). FXR activation induces the expression of SHP by binding to the FXR response element (FXRE) within the promoter region of the SHP gene (42). Subsequently, SHP binds to and inactivates liver receptor homolog-1 (LRH-1), which is a transcription factor required for the transcription of the CYP7A1 gene (43). Therefore, LRH-1 inactivation in response to activated FXR results in the inhibition of CYP7A1 transcription (43). CYP7A1 is a

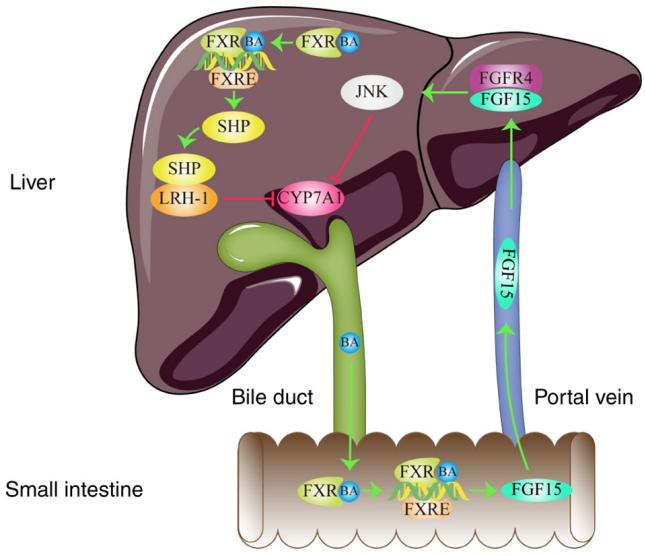


Figure 3. FXR signaling pathway in dyslipidemia. FXR regulates lipid metabolism by inhibiting CYP7A1 expression. Arrows represent stimulatory modifications. T-shaped arrows represent inhibitory modifications. The picture was generated using Adobe Illustrator CC version 23.0 (Adobe Systems, Inc.). BA, bile acids; FXR, farnesoid X receptor; SHP, small heterodimer partner; LRH-1, liver receptor homolog-1; JNK, c-Jun N-terminal kinase; FGFR4, fibroblast growth factor receptor 4; FGF15, fibroblast growth factor 15; CYP7A1, cholesterol 7 alpha-hydroxylase; FXRE, farnesoid X response element.

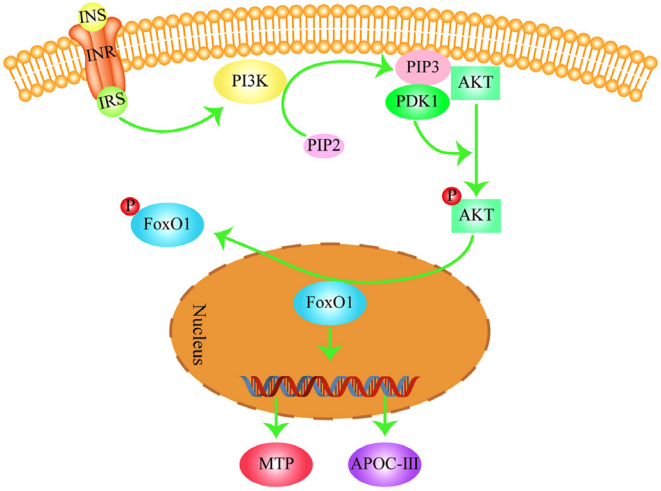


Figure 4. FOXO signaling pathway in dyslipidemia. FOXO1 regulates lipid metabolism by promoting the expression of MTP and APOC-III. Arrows represent stimulatory modifications. The picture was generated using Adobe Illustrator CC version 23.0 (Adobe Systems, Inc.). INS, insulin; INR, insulin receptor; IRS, insulin receptor substrate; $PI_3K$, phosphoinositide 3-kinase; $PIP_3$, phosphatidylinositol 3,4,5-triphosphate; PDK1, phosphoinositide-dependent kinase 1; FOXO1, forkhead box subgroup O1; MTP, microsomal triglyceride transfer protein; APOC-III, apolipoprotein C-III.

rate-limiting enzyme of bile acid synthesis that promotes the transformation of cholesterol into bile acids (17). Reductions in CYP7A1 transcription reduce the conversion of cholesterol and increases the TC content in the blood. The second mechanism is through the FXR/fibroblast growth factor 15 (FGF15) pathway in the small intestine, following activation by bile acids (44). FXR promotes the expression and secretion of FGF15 by combining with the FXRE in the promoter region of the FGF15 gene (45). Subsequently, FGF15 enters the liver through the portal circulation and binds to FGF receptor 4 (FGFR4) on the surface of hepatocytes (45). JNK is then activated following the complex formation between FGF15 and FGFR4 (45). Activated JNK then inhibits the expression of CYP7A1 to increase the TC content in the blood (45). Therefore, activation of the FXR/SHP pathway in the liver and the FXR/FGF15 pathway in the small intestine combine to reduce the expression of CYP7A1, which suppresses the conversion of cholesterol to increase the content of TC in the blood.

To clarify the mechanism underlying the cholesterolemic activity of the bitter gourd fruit (BGF), Matsui *et al* (46) measured the changes in the expression of cholesterol-regulating proteins and serum cholesterol levels in rats fed on a high-cholesterol diet following BGF intake. BGF administration not only increased hepatic LRH-1 and CYP7A1 expression but also significantly decreased hepatic SHP expression, serum TC and LDL-C levels ($P<0.05$). These data suggest that BGF exerted hypocholesterolemic activity by facilitating the conversion of cholesterol to bile acids, which was induced by CYP7A1 upregulation and concomitant downregulation of the FXR signaling pathway in the liver. Huang *et al* (47) also previously established a mouse model with high cholesterol induced by HFD to investigate the underlying cholesterol handling mechanism after theabrownin treatment. The results of this study demonstrated that treatment with 225 mg/kg/day theabrownin for 8 weeks significantly reduced ileal FXR and FGF15 expression whilst increasing the expression levels of hepatic CYP7A1 (47). In addition, theabrownin decreased serum TC levels in mice with high cholesterol (47). These results suggest that the cholesterol-lowering effect of theabrownin depended on the inhibition of the intestinal FXR signaling pathway in the ileum.

## 5. FOXO signaling pathway in dyslipidemia

The FOXO signaling pathway is important in maintaining the balance of blood lipids in the body and regulates the processes of lipoprotein (chylomicron and very low-density lipoprotein) synthesis and hydrolysis (48,49). FOXO1 is a key member of the FOXO family, the activity of which is negatively regulated by insulin (INS) (50). After the INS receptor is activated, it activates the INS receptor substrate (IRS) to activate PI3K, which in turn converts $PIP_2$ into phosphatidylinositol 3,4,5-triphosphate ($PIP_3$) (51). Subsequently, $PIP_3$ binds to phosphoinositide-dependent kinase 1 (PDK1), which contains a PH domain in the cell, to promote the phosphorylation and activation of AKT (52). Activated AKT phosphorylates FOXO1 in the nucleus to induce export into the cytoplasm (53,54). In the nucleus, FOXO1 promotes the expression of its target genes, such as microsomal triglyceride transfer protein (MTP) and apolipoprotein C-III (ApoC-III) (Fig. 4; generated using Adobe Illustrator CC version 23.0; Adobe Systems, Inc.) (53,54). MTP is an essential factor in the assembly and secretion of very low-density lipoprotein (VLDL) by taking part in their rate-limiting steps (55). VLDL is converted to LDL under the influence of lipoprotein lipase

(LPL) (56). MTP can indirectly increase LDL production, contributing to increased blood LDL-C levels. By contrast, ApoC-III is an inhibitor of LPL that reduces the hydrolysis of TG in chylomicrons and VLDL in the blood to increase blood TG levels (48,49). However, following FOXO1 phosphorylation by AKT, it is exported from the nucleus into the cytoplasm, resulting in the reduced expression of MTP and ApoC-III (48,49). This then reduces the content of LDL-C and TG in the blood. Therefore, activation of the FOXO signaling pathway may inhibit VLDL synthesis, decrease TG hydrolysis in the blood chylomicron and VLDL whilst reducing LDL-C and TG content in the blood.

To determine the mechanism underlying the beneficial effects of docosahexaenoic acid (DHA) on lipid homeostasis, 30 weaned crossbred pigs were randomly divided into groups and fed with a standard diet supplemented with either 2% beef tallow, 2% soybean oil or 2% DHA oil for 30 days (54). The results of the study demonstrated that feeding with the 2% DHA-supplemented diets decreased the expression levels of FOXO1, ApoC-III and MTP in the liver, which decreased TG and TC levels in the plasma (54). These findings suggest that the reduced FOXO1 expression may contribute to the beneficial effects of DHA on lipid homeostasis (54). A type 2 diabetes mellitus rat model induced by HFD and streptozotocin was previously used by Xu *et al* (57) to investigate the effects of dioscin (a natural steroidal saponin isolated from the rhizome of *Dioscorea nipponica* Makino, *Dioscorea opposita* Thunb and *Dioscorea zingiberensis* Wright (Dioscoreaceae) by chromatography) on glycolipid metabolism. Administration of 60 mg/kg/day dioscin was found to significantly elevate the expression of PI3K, AKT and FOXO1 phosphorylation, whilst serum TC, TG and LDL-C levels were markedly reduced (57). Although the expression levels of MTP and ApoC-III were not measured, the serum TC, TG and LDL-C levels in this rat model were decreased (57). Therefore, these regulatory effects of dioscin on lipid metabolism may have been due to the regulation of the FOXO signaling pathway. However, the specific mechanism remains to be verified.

## 6. Adipocytokine signaling pathway in dyslipidemia

Adipocytokines, such as APN, leptin (LEP) and resistin. are biologically active polypeptides that are produced and secreted by adipocytes (58). They serve key and complex roles in the maintenance of energy homeostasis, glucose and lipid metabolism (58). In particular, APN and LEP are closely associated with lipid metabolism in the body (59). APN regulates lipid metabolism by activating the AMPK signaling pathway as previously described (32,33). LEP serves a key role in the process of lipid metabolism through a continuous process (Fig. 5; generated using Adobe Illustrator CC version 23.0; Adobe Systems, Inc.). LEP can bind to its receptor (LEPR) to activate Janus kinase 2 (JAK2), which in turn phosphorylates three tyrosine residues on LEPR (Y985, Y1077 and Y1138) (60). Y1138 then recruits and activates the STAT3 by phosphorylation (60). Subsequently, activated STAT3 binds to another STAT3 to form a homodimer and is transported into the nucleus, where they bind to DNA (61). This STAT3 homodimer complex promotes the expression of CPT1 (62), the rate-limiting enzyme in fatty acid oxidation. This promotes fatty acid oxidation into $CO_2$ and $H_2O$, which in turn reduces FFA and TG levels in the blood (19). In addition, this STAT3 homodimer can also inhibit the expression of SREBP-1c and its target gene FAS (63). FAS is a key enzyme in the fatty acid synthesis pathway (34). Reduced FAS expression leads to the reduction of fatty acid synthesis, which decreases TG levels in the blood (34). Therefore, activation of the adipocytokine signaling pathway can promote fatty acid oxidation whilst inhibiting fatty acid synthesis to reduce blood TG levels.

To investigate the effects of Dendrobium mixture (a mixture prepared based on a prescription in clinical settings, comprising dendrobium, astragalus, schisandra, pueraria, salvia, rehmannia and earthworms) on glucose and lipid metabolism in diabetic rats, Lin *et al* (64) established a diabetic rat model induced by high-glucose, HFD and the intraperitoneal injection of streptozotocin. Dendrobium mixture treatment for 15 weeks was demonstrated to significantly increase the protein expression of LEPR, CPT1 and STAT3 phosphorylation in the liver, increased the mRNA expression of LEPR and CPT1 and decreased the plasma TG content (64). These results indicate that the dendrobium mixture may regulate lipid metabolism in diabetic rats by activating the adipokine signaling pathway. In another study, to explore the mechanism underlying the effects of carbenoxolone in the regulation of lipid metabolism, Chen *et al* (65) fed mice on an HFD for 8 weeks and administered carbenoxolone (15 mg/kg) every day by oral gavage for 12 weeks. Treatment with carbenoxolone was observed to increase the activation of JAK2 and STAT3 whilst decreasing the expression of SREBP-1c and FAS, which in turn decreased the concentrations of TG in the serum (65). These results suggest that carbenoxolone may regulate lipid metabolism by improving the activity of the adipocytokine signaling pathway.

## 7. cAMP signaling pathway in dyslipidemia

The cAMP signaling pathway is one of the most extensively studied signaling pathways and regulates lipid metabolism by regulating lipolysis in the adipose tissue (66). cAMP is a second messenger that can transmit vital information inside the cells by activating downstream effector molecules (67). Intracellular cAMP concentrations are modulated by adenylyl cyclases (AC) and phosphodiesterases (PDEs) (68). Growth hormones and other ligands, including adrenaline and glucagon, first interact with G-protein coupled receptors on the cell membrane to activate the G-proteins. This G-protein then binds to guanosine triphosphate (GTP) before binding to AC to activate it, which then catalyzes the biosynthesis of cAMP from ATP (69). PDEs hydrolyzes cAMP into AMP to switch off the signal (70). Under physiological conditions, cAMP synthesis by AC and degradation by PDEs is maintained in a balance. Excessive caloric intake leads to the decreased expression of PDEs, increasing cAMP production in adipose tissues (71). After cAMP binds to the regulatory subunits of protein kinase A (PKA), the catalytic subunits of PKA then dissociate and activate hormone-sensitive lipase (HSL) through phosphorylation at the Ser563, Ser659 and Ser660 residues (Fig. 6; generated using Adobe

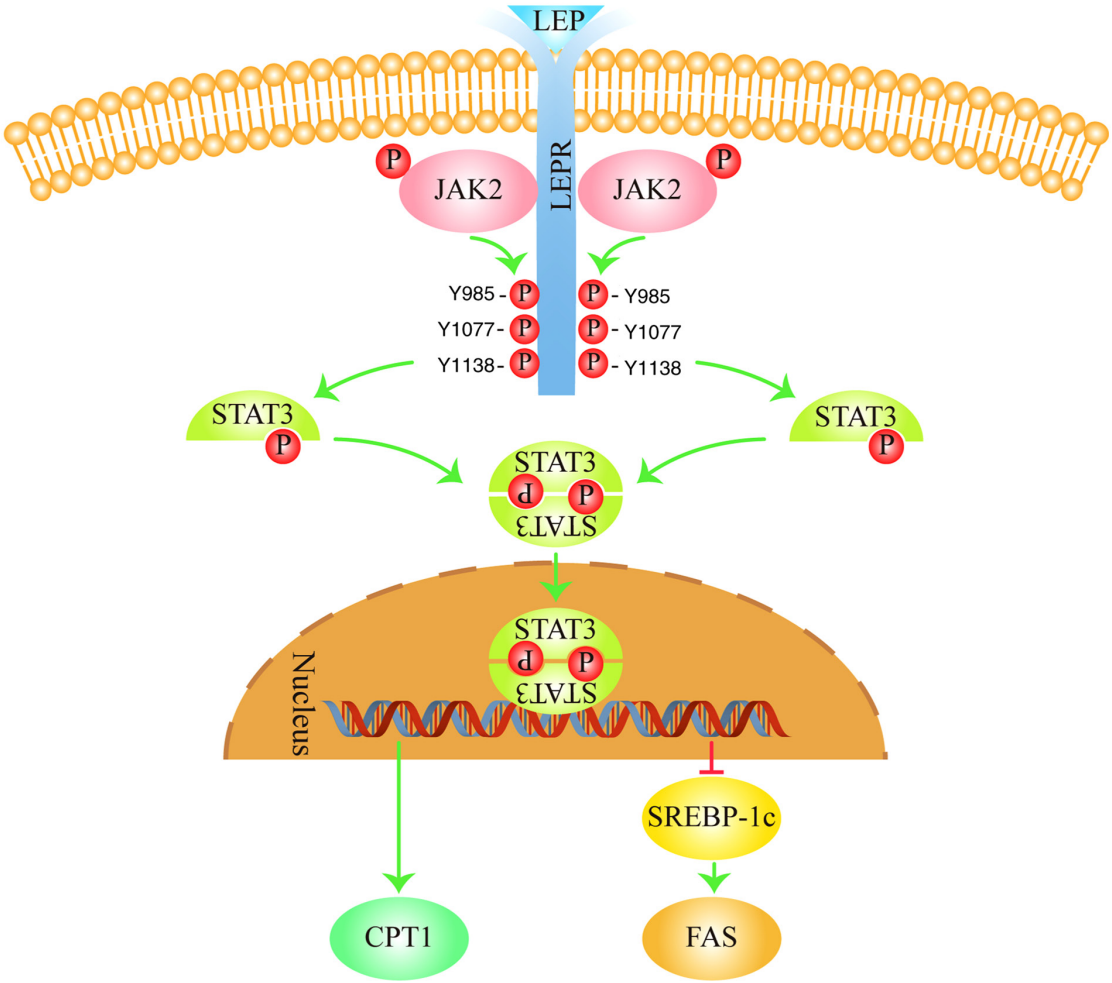


Figure 5. Adipocytokine signaling pathway in dyslipidemia. Adipocytokines regulate lipid metabolism by inhibiting FAS expression and promoting CPT1 expression. Arrows represent stimulatory modifications. T-shaped arrows represent inhibitory modifications. The picture was generated using Adobe Illustrator CC version 23.0 (Adobe Systems, Inc.). LEP, leptin; LEPR, leptin receptor; JAK2, janus kinase 2; CPT1, carnitine palmitoyl transferase 1; FAS, fatty acid synthase; SREBP-1c, sterol regulatory binding protein-1c; Y, tyrosine.

Illustrator CC version 23.0; Adobe Systems, Inc.). HSL is a critical rate-limiting enzyme of adipose degradation and is responsible for the breakdown of TG and cholesteryl esters into glycerin, fatty acid and cholesterol in the adipose tissue, which are then released into the blood (72). Therefore, inhibition of the cAMP signaling pathway can decreases the phosphorylation of HSL to reduce the content of blood TC and TG.

To investigate the effects of ginsenoside Rg5 (the ginsenosides isolated from steamed ginseng by chromatography and crystallization) on the regulation of lipolysis, mice were fed on an HFD for 10 days along with the simultaneous administration of ginsenoside Rg5 (50 mg/kg) by oral gavage every day. Compared with those in the HFD mice, ginsenoside Rg5 treatment markedly increased the expression of PDE3B whilst cAMP accumulation and PKA 62 KDa substrate phosphorylation were reduced in the adipose tissue (73). In line with reduced cAMP accumulation and PKA substrate phosphorylation, oral gavage administration of ginsenoside Rg5 also decreased the phosphorylation of HSL in the adipose tissue, which reduced the levels of FFA, glycerol and TG in the blood (73). These findings suggest that ginsenoside Rg5 can inhibit lipolysis by inhibiting the cAMP signaling pathway (73). In addition, in another study, to investigate the effects of astragaloside IV (a saponin and main active component isolated from the medicinal plant *Astragalus membranaceus* by chromatography) on adipose lipolysis, mice were fed on an HFD for 2 weeks combined with the simultaneous oral gavage administration of astragaloside IV (50 or 100 mg/kg) daily (74). Compared with those in the HFD mice, astragaloside IV treatment significantly increased PDE3B expression and prevented cAMP accumulation (74). Consistent with the reduced cAMP accumulation, oral gavage administration of astragaloside IV also suppressed PKA substrate and HSL phosphorylation. Downstream, the levels of serum FFA and glycerol were also reduced, whilst the content of TC and TG in the serum were not affected (74). This may have been due to the short administration time of 2 weeks (74). These results suggest that astragaloside IV can inhibit lipolysis by downregulating the cAMP signaling pathway (74).

## 8. Conclusions

It should be noted that each of the six signaling pathways aforementioned are not mutually exclusive and can

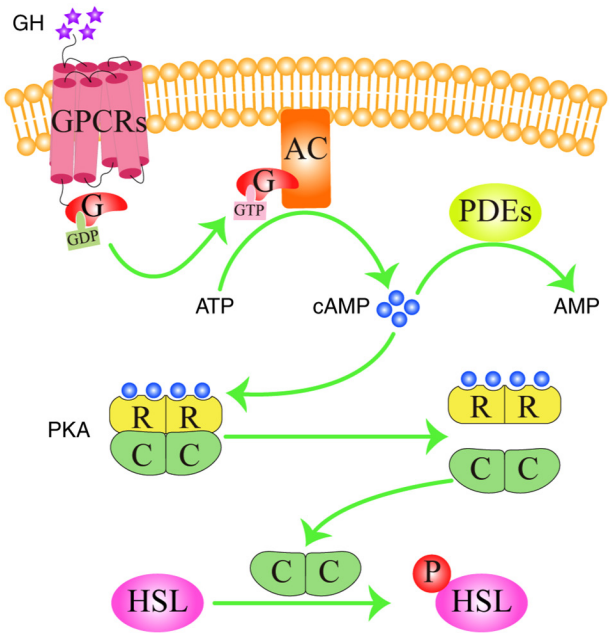


Figure 6. cAMP signaling pathway in dyslipidemia. cAMP binds to the regulatory subunit of PKA, phosphorylates and activates HSL, thereby regulating lipid metabolism. Arrows represent stimulatory modifications. The picture was generated using Adobe Illustrator CC version 23.0 (Adobe Systems, Inc.). GH, growth hormone; GPCRs, G protein-coupled receptors; AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; ATP, adenosine triphosphate; GTP, guanosine triphosphate; GDP, guanosine diphosphate; PDEs, phosphodiesterases; PKA, protein kinase A; HSL, hormone sensitive lipase; P, phosphate group; G, G-protein; R, regulatory subunit; C, catalytic subunit.

coordinate together to maintain lipid homeostasis (75-77). As such, certain drugs can simultaneously activate or inhibit multiple signaling pathways to exert lipid-lowering effects. Gong *et al* (78) previously used a NAFLD mouse model to study the effects of cordycepin on lipid metabolism and the primary molecular mechanisms. Compared with those in the model group, treatment with 50 mg/kg cordycepin markedly increased the protein levels of p-AMPK, CPT-1 and PPARα whilst decreasing the expression of SREBP1-c and ACC in the liver of NAFLD model mice (78). By contrast, cordycepin treatment reduced the levels of TC, TG and LDL-C in the serum of these same NAFLD model mice (78). These results suggest that cordycepin can exert a lipid-lowering role by activating two signaling pathways. Specifically, cordycepin may activate the PPARα signaling pathway to upregulate the expression of PPARα and CPT1 whilst at the same time activating the AMPK signaling pathway to downregulate the expression of SREBP-1c and ACC. Furthermore, Cao *et al* (79) previously investigated the cholesterol-lowering effects and mechanism of coptis alkaloids (50, 100 and 200 mg/kg) on high lipid diet-induced hyperlipidemic rats. Compared with those in the model group, the mRNA expression levels of PPARα and CYP7A1 were increased in a dose-dependent manner, which were accompanied by the decreased levels of FXR mRNA expression, in the livers of coptis alkaloid-treated rats (79). In addition, the levels of serum TC and LDL-C were reduced in a dose-dependent manner following treatment with coptis alkaloids (79). These results suggest that the cholesterol-lowering effects of coptis alkaloid extract may be attributed to the promotion of cholesterol conversion into bile acids, mediated by the increased expression of CYP7A1 (79). This may be associated with the regulation of two signaling pathways, including the positive regulation of the PPARα signaling pathway and the negative modulation of the FXR signaling pathway.

In conclusion, the six dyslipidemia-related signaling pathways, including the PPAR, AMPK, FXR, FOXO, adipocytokine and cAMP signaling pathways, have all been demonstrated to exhibit altered activity in dyslipidemia. The results found by the aforementioned experiments demonstrated that different drugs can mediate effects on dyslipidemia by targeting the six signaling pathways. However, further investigations into alternative dyslipidemia-associated signaling pathways are required. In particular, future studies should focus on the application of multiomics technologies, including transcriptomics, proteomics and metabolomics, to systematically study the dyslipidemia-associated signaling pathways. This may uncover novel signaling pathways to provide novel therapeutic targets for the treatment of dyslipidemia.

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**Availability of data and materials**

Not applicable.

**Authors' contributions**

NC analyzed the literature data and modified the manuscript. XL and WZ wrote the manuscript. QW and YL designed the figures using Adobe Illustrator CC version 23.0 (Adobe Systems, Inc.). FZ and XX revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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