

Review Article

Traditional Chinese medicine for lipid metabolism disorders

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Abstract: Dyslipidemia significantly contributes to the development of cardiovascular disease (CVD), which is the most common cause of morbidity and mortality in China. Statins are the first-line therapy for reducing LDL-C serum levels. However, they have adverse effects, which restrict their clinical application. Traditional Chinese medicine (TCM) preparations have been increasingly described for their beneficial effects in hyperlipidemic patients. Existing data show that the lipid-regulating effects of TCM may be related to: (1) inhibiting intestinal absorption of lipids; (2) reducing endogenous cholesterol synthesis; (3) regulating cholesterol transport; (4) promoting the excretion of cholesterol in the liver; (5) regulating transcription factors related to lipid metabolism. This study provides an overview of recent studies and elaborates the underlying mechanisms of lipid-regulation by TCM.

Keywords: Dyslipidemia, traditional Chinese medicine, underlying mechanisms

Introduction

Risk factors for cardiovascular disease (CVD) currently show an increasing trend in China, leading to a sustained increase in associated mortality. At present, there are estimated 290 million cardiovascular patients in China. According to a survey in 2012, CVD prevalence rates among men and women ≥ 18 years with total cholesterol (TC) ≥ 6.22 mmol/L, respectively, were 3.4% and 3.2%. With triglyceride (triglyceride, TG) levels ≥ 2.26 mmol/L, morbidity rates are 13.8% and 8.6%, respectively [1]. Dyslipidemia significantly contributes to the occurrence and development of atherosclerosis (AS) and CVD, which are the most common causes of morbidity and mortality worldwide. Therefore, effective control of blood lipids can reduce the risk of cardiovascular events [2, 3]. Previous data from cohort studies showed that a serum cholesterol concentration decrease of 0.6 mmol/L (about 10%) is associated with a decrease in incidence of ischemic heart disease of 54% at the age 40 years, 39% at 50, 27% at 60, 20% at 70, and 19% at 80 [4]. A meta-analysis combining non-overlapping data of 312,321 participants indicated that naturally random allocation to long-term exposure to lower low-density lipoprotein cholesterol (LDL-C) is linked to a 54.5% (95% confidence interval

[CI]: 48.8% to 59.5%) reduction in the risk of CHD for each mmol/L (38.7 mg/dl) reduction of LDL-C [5]. In China, the treatment rate of statins in hospitalized patients is 88.9%, with 38.5% individuals not reaching the target LDL-C treatment. Statins are the first-line therapy for reducing LDL-C serum levels, and act by inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. However, statins have adverse effects, including muscle myopathy and hepatic function derangements [6]. Some patients are even at an unacceptable risk for failing to tolerate high-dose statin therapy. Statin resistance and intolerance attract increasing attention from scientists and the public, but there are no other effective methods. Traditional Chinese medicines (TCMs) have been widely used in China since ancient times to treat several diseases. Recently, such medicines have been increasingly described for their benefits in hyperlipidemic patients [7]. In this study, we focused on the underlying mechanisms of the lipid-regulation effects of TCMs.

Inhibition of cholesterol absorption in the intestine

Cholesterol is an essential constituent of the cell membrane that can be acquired by *de novo* synthesis from acetyl-CoA, or obtained from the

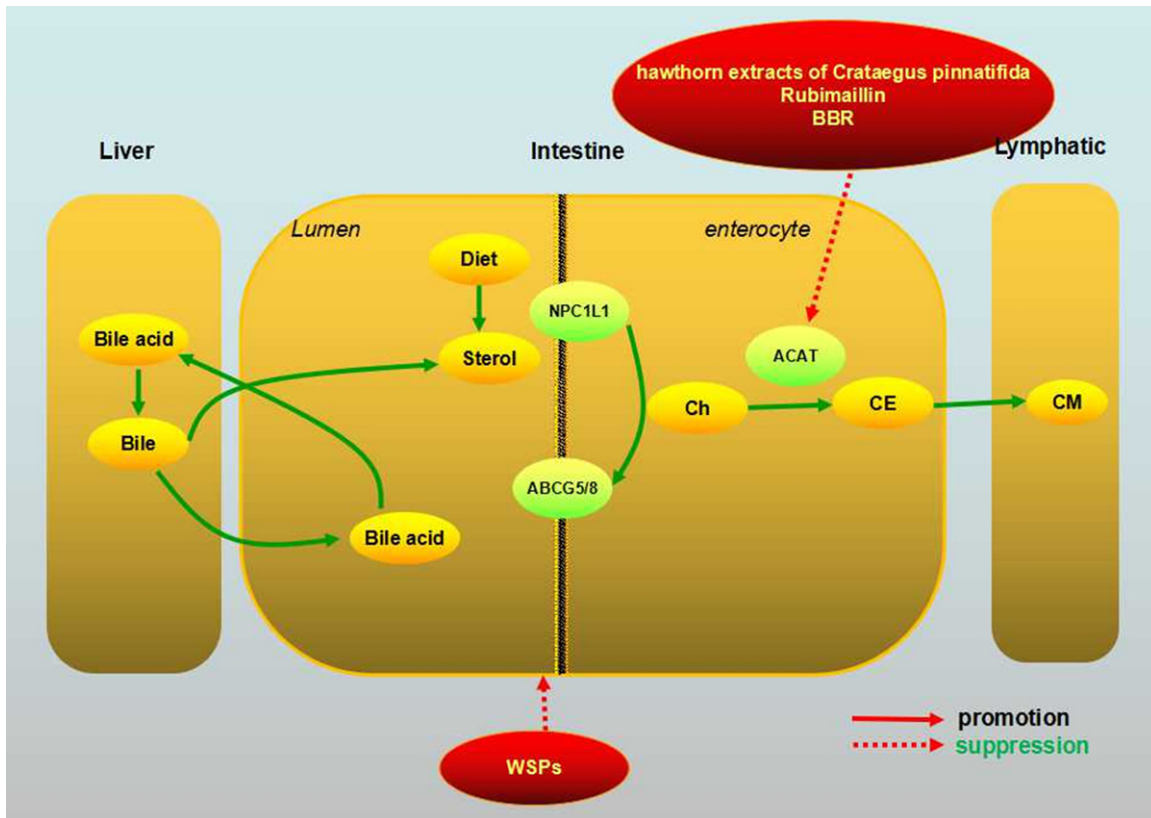


Figure 1. Intestinal cholesterol mainly derives from the diet and bile. Cholesterol enters the enterocytes through the Niemann-Pick C1-like 1 protein (NPC1L1). After entering the intestinal cells, this lipid is esterified by acyl-coenzyme A cholesterol acyltransferase (ACAT); the esterification product must be hydrolyzed by cholesterol ester hydrolase. ATP-binding cassette G5/G8 (ABCG5/8) promotes the efflux of cholesterol from the enterocytes into intestinal lumen for excretion. The combined regulatory effects of NPC1L1 and ABCG5/8 may play a critical role in modulating cholesterol amounts that reach the lymph. Once cholesterol is in the enterocyte, multiple processes occur to produce chylomicrons (CMs). Water-soluble polysaccharides (WSPs) from Cassia seeds have the ability to bind bile acids and reduce the amounts of cholesterol available for absorption. Hawthorn extracts of *Crataegus pinnatifida*, rubimallin, and berberine (BBR) could reduce intestinal cholesterol absorption via inhibition of intestinal ACAT activity.

diet. The intestinal absorption of cholesterol is mainly from the diet and bile, which is synthesized by the liver and excreted into the intestine through bile acids. LDL-C levels in circulation and cholesterol absorption are positively correlated [8]. It is well known that cholesterol absorption is affected by many processes. Since the sterol-solubilizing capacity of bile acid micelles is limited, plant sterols competitively inhibit the combination with cholesterol incorporation into dietary mixed micelles [9]. Cholesterol is transported to the brush border membrane of enterocytes in micelles, and can be bound by sterol-sensing domains of the protein Niemann-Pick C1 Like 1 (NPC1L1). After entering the intestinal cells, this lipid is esterified by acyl-coenzyme A cholesterol acyltransferase (ACAT); the esterification product must

be hydrolyzed by cholesterol ester hydrolase, to enable absorption. After cholesterol passes through the enterocyte membrane, it heads to the endoplasmic reticulum for esterification by ACAT2. Unesterified cholesterol is excreted from intestinal cells back into the intestinal lumen by ATP binding cassette transporter G5/G8 (ABCG5/8) (Figure 1). ABCG5/8 expression in enterocytes facilitates the efflux of cholesterol into the extracellular space; as a result, less cholesterol is absorbed and enters the circulation [10].

Recent findings also suggest that TCMs might have the potential to lower cholesterol absorption. Water-soluble polysaccharides (WSPs) from cassia seeds bind to bile acids and reduce the amounts of cholesterol available for absorp-

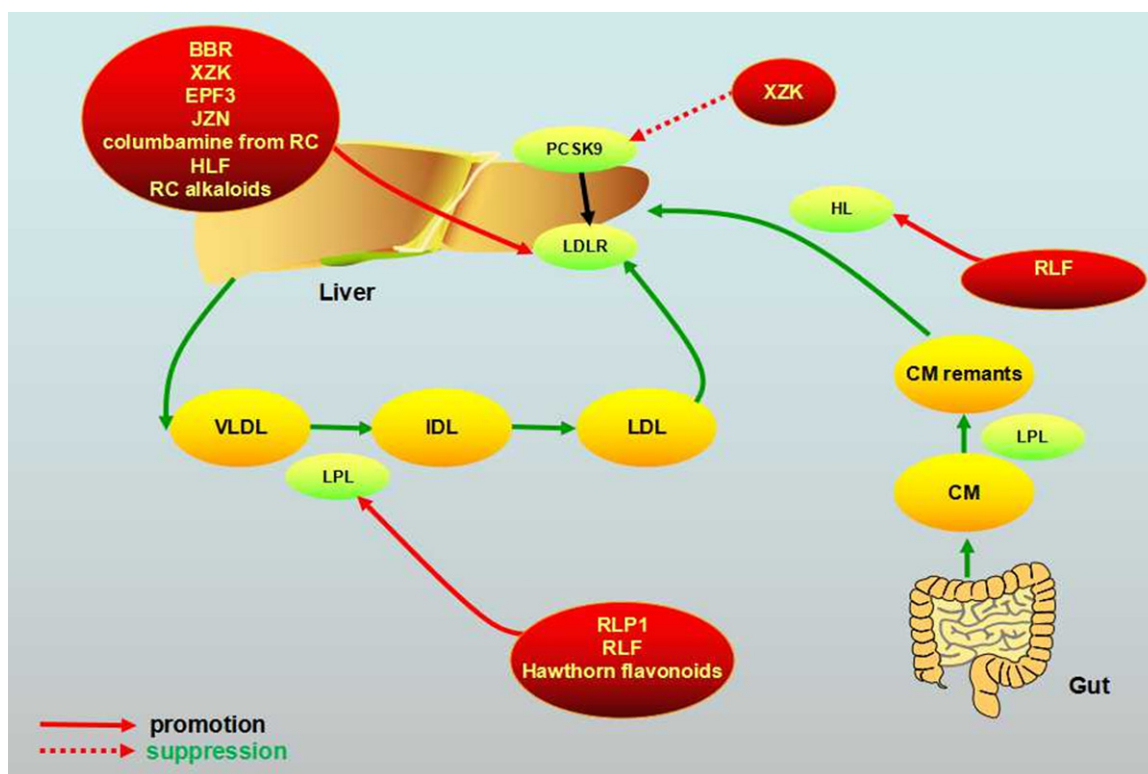


Figure 2. Cholesterol transport starts in the liver, which generates triglyceride-rich very low-density lipoprotein (VLDL) for release into circulation. VLDL is hydrolyzed and forms intermediate (IDL) and low (LDL) density lipoproteins. LDL transport cholesterol to peripheral tissues through LDL receptor (LDLR). A major function of hepatic lipase (HL) may be clearance of phospholipids from hydrolysis of CMs by lipoprotein lipase (LPL); the chylomicrons shrink as well as surface components. Proprotein convertase subtilisin kexin 9 (PCSK9) is a key regulator of LDLR function. Circulating PCSK9 is a ligand for LDLR, leading to reduced LDLR expression on the cell membrane. RLP1, a crude polysaccharide extracted from *RosaeLaevigataeFructus* (RLF) and hawthorn flavonoids might be related to LPL upregulation. RLF could improve lipid profile by enhancing HL activity. The lipid-lowering activities of BBR, XZK (Xuezhi Kang), EPF3 (ethanolic extract of *Eclipta* and fractions), JZN (Jiang-Zhi-Ning), columbamine from RC (*RhizomaCoptidis*), RC alkaloids, and HLF (hawthorn leave flavonoids) are associated with LDLR up-regulation.

tion [11]. Berberine (BBR) is the principal bioactive compound of *Coptischinensis* and many other medicinal plants. Wang Y et al found that treatment with BBR in rats on atherogenic diet lowers blood TC and non-HDL cholesterol levels partly through inhibition of intestinal absorption [12].

Ezetimibe inhibits cholesterol uptake from the small intestine through its binding of the NPC1L1 transporter [13]. When added to statin therapy, ezetimibe reduces plasma LDL levels to 70% [14]. Temel RE et al [15, 16] found that diosgenin, found in food supplements and herbal medicines, promotes fecal cholesterol excretion, despite unaltered expression levels of ABCG5/8 and NPC1L1. So far, there are no studies assessing the effects of TCMs on NPC1L1.

ACAT catalyzes the esterification of cholesterol intracellularly, consequently accelerating the intestinal absorption. Inhibition of ACAT expression may alter the overall serum cholesterol levels. Although multiple ACAT1 and ACAT2 inhibitors have been described, they have not been clinically investigated for their efficacy, side effects and other restrictions as lipid-lowering drugs. ACAT2-selective inhibitors may be more potent therapeutics for AS and hypercholesterolemia [17]. However, some researches have evaluated TCMs in this aspect. Lin Y [18] et al investigated the effect of hawthorn extracts of *Crataeguspinnatifida* on cholesterol metabolism in hamsters and human CaCo-2 cells. They found that the hawthorn extract lowers plasma non-HDL-C by 8% without changing HDL-C. Oleanolic acid (OA) and ursolic acid (UA) are the bioactive compounds responsible for the ben-

eficial effects of hawthorn, and reduce intestinal cholesterol absorption via inhibition of intestinal ACAT2 activity. Rubimaillin, which was isolated from an ethanolic extract of *Rubiocordifolia* roots, inhibits lipid droplet accumulation by blocking ACAT activity in mouse peritoneal macrophages. The latter study further indicated selectivity towards the ACAT2 isozyme [19]. BBR reduces gene and protein expression levels of ACAT2 in the small intestine and CaCo-2 cells [12].

Inhibition of endogenous cholesterol synthesis

A third of the body's cholesterol comes from food supply, and the rest from endogenous synthesis. 3-Hydroxy-3-methylglutaryl-CoA reductase (HMGCR) is a restricted enzyme in cholesterol synthesis, and regulated by the cell levels of dissociated cholesterol. Statins reduce intracellular cholesterol synthesis mainly by competitive inhibition of HMGCR. Xuezhikang (XZK), a partially purified red yeast rice (RYR) fermented by *Monascuspurpureus* under controlled pharmaceutical manufacturing conditions, contains monacolin K, which is identical to lovastatin. In a study, 116 adults were randomized to either placebo or XZK (1200 or 2400 mg) daily, and treated for 12 weeks [20]. They showed that daily XZK 1200 mg and 2400 mg for 4 to 12 weeks significantly reduce both non-HDL-C (by 24%) and LDL-C (by 27%) compared with placebo; in addition, XZK was safe and well-tolerated in the latter study. In a randomized, double-blind, placebo-controlled trial, a parallel-group study was carried out with 4,870 patients with documented previous myocardial infarction (MI) for an average of 4 years [21]. Treatment with XZK also showed absolute decrease of 4.7% in major coronary events compared with placebo. Patients treated with XZK (600 mg, bid, p.o.) also experienced 1/3 reduction in cardiovascular events, total mortality, and the need for coronary revascularization compared with the placebo group. These findings demonstrated that long-term therapy with XZK improves lipoprotein regulation, and is safe and well-tolerated [21].

Jiang-Zhi-Ning (JZN), which contains four Chinese herbs (FleeceflowerRoot, FructusCraetegi, FoliumNelumbinis and Semen Cassiae), has been used in clinic for many years. The extract and effective fraction of JZN significantly decrease plasma TC, TG, and LDL-C levels compared with the hyperlipidemia model group,

while increasing HDL-C in rats. Effective fraction and active constituents of JZN inhibit the expression of HMGCR mRNA [22-24].

PolygoniMultiflori Radix (PMR, Heshouwu in Chinese) and PolygoniMultiflori Radix Preparata (PMRP, Zhiheshouwu in Chinese), originating from the root of *Polygonummultiflorum* Thunb, have been used for the prevention and treatment of hyperlipidemia in oriental countries for centuries. PRM and PRMP demonstrate good TC-lowering effects both in non-alcoholic fatty liver model rats and steatosis hepatic L02 cells [25-27]. The water extract of raw PMR shows much remarkable TG-regulation effects than PMRP [25, 26]. PMR presents significant alterations in TC, in association with the down-regulation effects on HMGCR [25].

Regulation of cholesterol transport

Forward cholesterol transport

The forward cholesterol transport starts from the liver, which generates triglyceride-rich very low-density lipoproteins (VLDL) for releasing into circulation. VLDL are progressively hydrolyzed, and form intermediate-density lipoproteins (IDL) and low-density lipoproteins (LDL). LDLs, as major cholesterol carriers, transport cholesterol to peripheral tissues for use through LDL-receptor (LDLR) (Figure 2) [28].

Regulation of heparinized plasma lipase activity: Heparinized plasma lipase contains lipoprotein lipase (LPL) and hepatic lipase (HL), and plays a key role in the overall lipidtransport and metabolism. The main biological function of LPL is to catalyze the hydrolysis of TGs in chylomicrons (CMs) and VLDL at the luminal surface of capillaries, generating progressively smaller VLDL and subsequently IDL [29-31]. Some IDLs are taken up by the liver, and some catabolized by LPL and HL to produce LDL particles. A major function of HL may be clearance of phospholipids from the hydrolysis of CMs by LPL; the CMs shrink and surface components are partly transferred to HDL particles [32].

Purified from crude polysaccharides extracted from *RosaeLaevigataeFructus*, a polysaccharide, RLP1, significantly decreases the levels of TC, TG, and LDL-C, while decreased serum levels of HDL-C could not be elevated in HLP rats for 4 weeks. This result might be related to LPL upregulation [33]. Qi Wang et al [34] also found

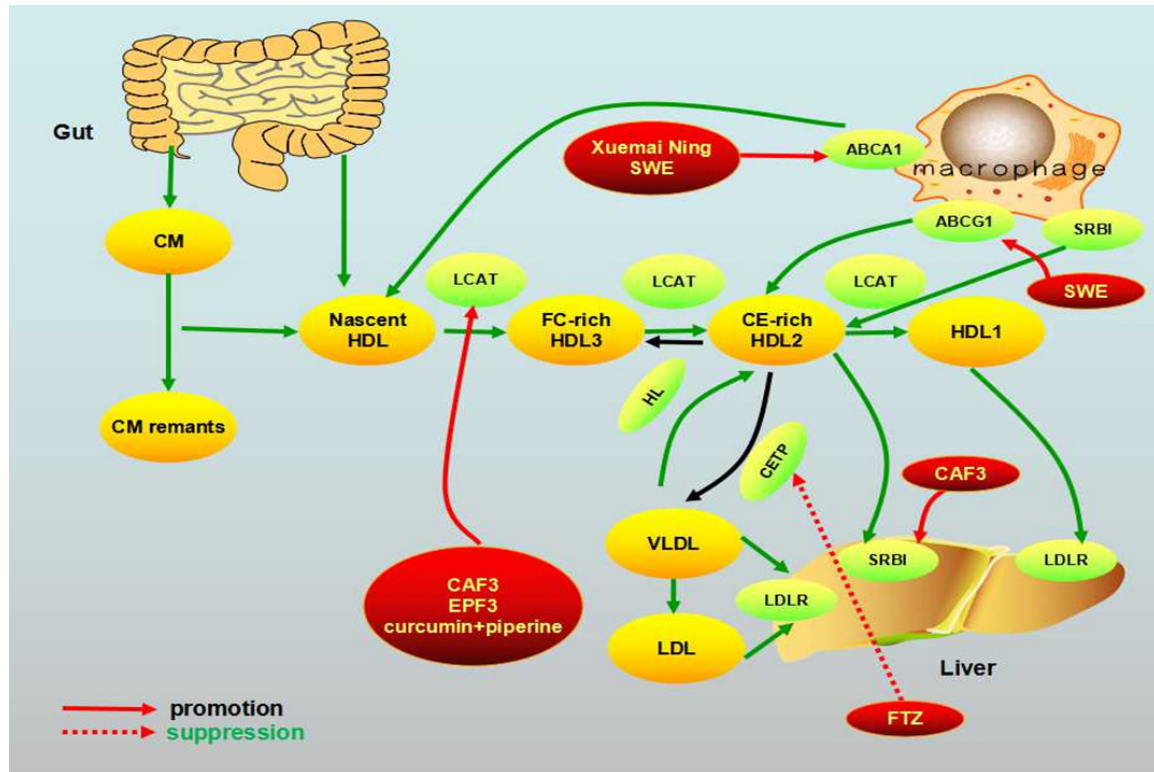


Figure 3. To remove the excess accumulated cholesterol from peripheral tissues, cholesterol is transported through lymphatic vessels and veins, back to the liver for excretion directly into bile or conversion to bile acids, a process called reverse cholesterol transport (RCT). Nascent HDL, HDL3, and HDL2 can accept cholesterol from RCT. Efflux to nascent and mature HDL occurs via the transporters ABCA1 and ABCG1. HDL cholesterol is returned to the liver via the hepatic receptor SR-BI by the cholesterol ester transfer protein (CETP). HDL2 or HDL1 deliver cholesterol to the liver directly via LDLR. EPF3, CAF3 (a fraction of the ethanolic extract of *Centallaasiatica*), and curcumin plus piperine enhance LACT expression. XuemaiNing and SWE (sage weed extract) boost cholesterol efflux of lipid-laden macrophages via ABCA1 upregulation. SWE also has an effect on ABCG1. The hypolipidemic effect of CAF3 might be associated with increased expression of SRBI. FTZ might regulate the expression of CETP.

that RLF (total flavonoids), another extract from *RosaeLaevigataeFructus*, could improve lipid profile by enhancing LPL and HL activities in the rat liver.

noids may reduce lipid accumulation in the adipose tissue by up-regulating LPL *in vivo* [38].

LDLR and PCSK9: Packaging of cholesterol esters (CEs) in lipoproteins solves the problem of transporting cholesterol into the cell membrane; however, CEs are too hydrophobic to pass through membranes. LDLRs, which are cell surface transmembrane proteins, bind LDL and translocate them into the cell by receptor-mediated endocytosis. This is the main route for plasma cholesterol clearance in the body. Then, CEs are degraded in lysosomes. The hydrolyzed cholesterol is used by cells for plasma membrane, bile acid, and steroid hormone synthesis, or stored in the form of cytoplasmic cholesterol ester droplets. Therefore, when LDL receptor function is inappropriately diminished, cholesterol builds up in plasma [39]. BBR is too poorly absorbed and rapidly metabolized for its

pharmacological effects to be explored *in vivo*. Zhou Y et al [40] indicated that both BBR and its metabolites exhibit lipid-lowering effects by up-regulating LDLR expression, and BBR and its four metabolites (jatrorrhizine, columbamine, berberrubine and demethyleneberberine) might be the *in vivo* active forms of BBR produced after oral administration.

It was hypothesized that RhizomaCoptidis (RC) alkaloids exert hypolipidemic effects primarily by targeting the gastrointestinal tract and liver. Thus, He K et al evaluated the anti-hyperlipidemic mechanisms of RC alkaloids (at a daily dose of 140 mg/kg for 35 days) in high-fat and high-cholesterol induced hyperlipidemic B6 mice. The results indicated that RC alkaloids reduce serum TC, TG, and LDL-C in B6 mice. The observed anti-hyperlipidemic effects of RC alkaloids can also be attributed to their function as activators of LDLR and inhibitors of HMGCR [41]. Columbamine from RhizomaCoptidis is one of the RC alkaloids. Wang Y et al found similar results for columbamine from RC in hamsters and HepG2 cells [42].

In mice fed 20 mg/kg HLF (Hawthorn leave flavonoids), TC levels decrease by 18.6% and VLDL-C+LDL-C levels decrease by 23.1%, while HDL-C and TG levels remain similar compared to control values. LDLR mRNA and protein amounts increase by 84.2% ($P<0.05$) and 98.8% ($P<0.05$) in the 20 mg/kg group [43]. HLF not only reduces lipid accumulation in the adipose tissue by up-regulating LPL expression *in vivo* [38], but also regulates lipids in mice by inducing LDLR mRNA and protein synthesis.

Proprotein convertase subtilisin kexin 9 (PCSK9) is a key regulator of LDLR function. Circulating PCSK9 is a ligand for LDLR, targets and degrades LDLR in the lysosomes, leading to reduced LDLR levels on the cell membrane, decreased LDL internalization and increased plasma levels of LDL-C [44]. Statin administration results in significant LDL-C reduction due to LDLR upregulation; this effect may be diminished by the concomitant increase of PCSK9 [45]. Therefore, patients with dyslipidemia may benefit more from PCSK9 inhibitors. Fully human mAbs (evolocumab and alirocumab), currently the most advanced PCSK9 inhibitors, consistently decrease LDL-C levels by ~60%, either in addition to statins or as a monotherapy. Further clinical trials regarding the safety,

tolerability, and efficacy of PCSK9 inhibitors are underway [46]. The combination of daily ezetimibe and XZK does not increase PCSK9 levels compared with monotherapy, and PCSK9 levels are significantly lower than combination therapy with ezetimibe plus pitavastatin in rats; these findings indicated that combination of ezetimibe plus XZK may be clinically better than ezetimibe plus pitavastatin [47].

Reverse cholesterol transport (RCT)

To remove the excess accumulated cholesterol from peripheral tissues, cholesterol is transported through lymphatic vessels and veins, back to the liver for excretion directly into bile or conversion to bile acids, a process called reverse cholesterol transport (RCT) (**Figure 3**). The RCT pathway mainly involves three steps.

First step: efflux of cellular cholesterol: Cholesterol is effluxed from macrophages in free form by the concerted action of several parallel pathways, involving primary active ATP-binding cassette transporters and HDL scavenger receptor class B type I (SR-BI). RCT is initiated from arterial macrophages by the interaction of lipid-poor Apo lipoprotein (Apo) A-I with cellular ATP-binding cassette transporter A1 (ABCA1), a transfer-mediated transfer of phospholipids to generate nascent HDL. SR-BI mediates bidirectional lipid transport in macrophages, depending on cholesterol content in lipid-laden macrophages [48].

Second step: cholesterol esterification: Lecithin cholesterol acyltransferase (LCAT) esterifies the unesterified nascent HDL cholesterol. CEs are then packaged into the hydrophobic core of the discoidal particle, converting it to spherical HDL3, which can continue to accept unesterified cholesterol and phospholipids from SR-BI. Through continued action of LCAT, the core expands and the particle size increases, forming HDL2. In addition, ATP-binding cassette subfamily G member 1 (ABCG1), found on macrophages, contributes to HDL2 formation [49].

Third step: cholesterol removal: HDL2 is partly transferred by cholesterol ester transfer protein (CETP) to LDL and VLDL, subsequently binds LDLR, and is absorbed in the liver. Alternatively, HDL2 can directly transfer CE to the liver via SR-BIs.

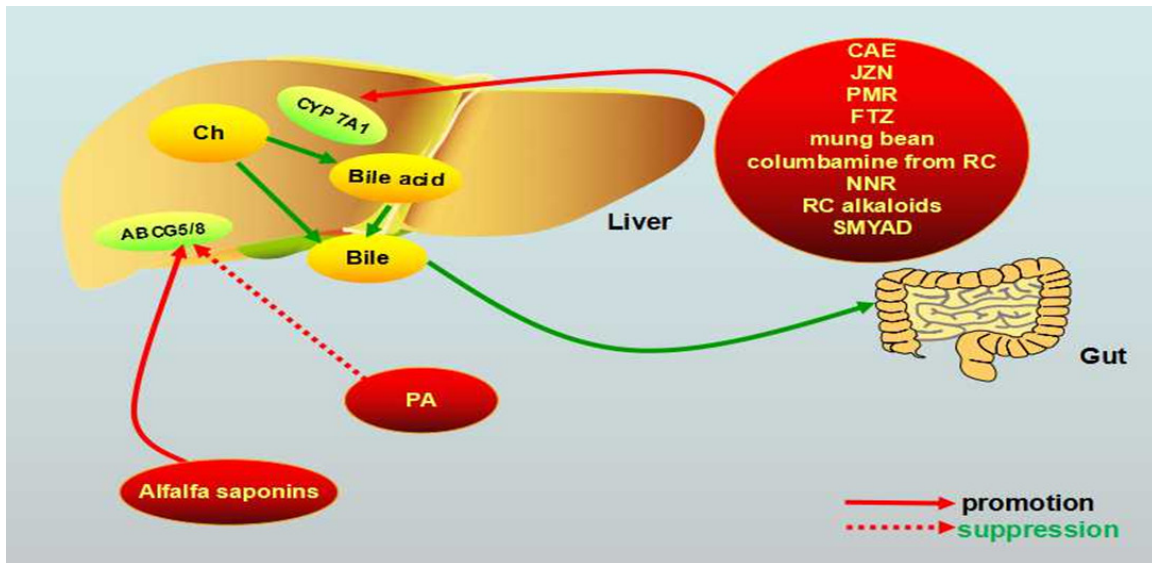


Figure 4. Cholesterol transported into the liver and endogenously synthesized is lost from the body via biliary secretion after conversion to bile acids. Cholesterol 7- α hydroxylase (CYP7A1) is the first and rate-limiting enzyme in the neutral pathway of bile acid synthesis. The major pathway for cholesterol elimination is via secretion into bile, which is mediated by ABCG5 and ABCG8 (as a heterodimer at the apical membrane of hepatocytes). CAF3 (the ethanolic extract of *Centella asiatica*), JZN (Jiang-Zhi-Ning), FTZ (Fufang Zhen Zhu Tiao Zhi), PMR (Polygoni Multiflori Radix), mung bean, columbamine from RC (Rhizoma Coptidis), NNR (Notoginseng Radix Et Rhizome), RC alkaloids, SMYAD (Si-miao-yong-an decoction) upregulate CYP7A1 at the gene and/or protein levels. Alfalfa saponins, extracted from *Medicago sativa* (alfalfa), upregulate ABCG5/8 at the mRNA level. Meanwhile, PA (extracted from the unsaponifiable oil of long pepper) regulates blood lipid by simultaneously decreasing the expression levels of the hepatic proteins ABCG5, ABCG8 and LXR.

Eclipta prostrata (Linn.) exhibits hypolipidemic effects, with EPF3 (ethanolic extract of *Eclipta* and fractions) as the most active fraction. Compared with the normal chow diet (NCD) group, administration of EPF3 significantly lowers the body weight gain and regulates lipid levels in a hamster model of high-fat diet (HFD)-induced hyperlipidemia (HLP). The lipid-lowering activity of EPF3 was shown to be associated with reduced mRNA expression of HMGCR and increased LDLR, LCAT, and SR-BI levels in the liver. LCAT and SR-BI upregulation in hamsters receiving EPF3 suggests that EPF3 effects in promoting lipid elimination are partly due to RCT [49].

In a male Sprague-Dawley rat model of HLP, administration of curcumin (a hydrophobic polyphenol derived from rhizomes of the herb *Curcuma longa*) plus piperine (PA, the pungency of spices from *Piper nigrum* and *Piper longum*) results in significantly decreased serum TC, TG and LDL-C levels compared with the HLP and HLP plus curcumin groups. In that study, only curcumin plus PA also markedly increased HDL-C and ApoA1 levels, as well as LACT mRNA

expression, indicating that curcumin plus PA enhances cholesterol efflux to HDL particles by inducing ApoA1 and LCAT activities, which result in significantly increased HDL-C [50].

A fraction (CAF3) of the ethanolic extract of *Centella asiatica* (perennial herbaceous creeper of the Apiaceae family) decreases cholesterol levels by 79% and TC by 95% in intraperitoneal injection of Triton WR-1339 induced-acute hyperlipidemia mouse model. Further study in an HLP hamster model found that the hypolipidemic effect of CAF3 might be associated with RCT upregulation via increased LACT and SR-BI expression [51].

Xuema Ning, a traditional Chinese medicine preparation, is composed of Radix Astragali (20 g), Gynostemma pentaphyllum (20 g), hawthorn (25 g), Poria (15 g), salvia (15 g), Rhizoma ligustici wallichii (10 g), Alisma (10 g), orange peel (10 g), Bamboo shavings (10 g), pseudoginseng (3 g), and Salvia miltiorrhiza (15 g). This preparation regulates lipid metabolism of hyperlipidemia and AS model in rabbits. In addition, it effectively promotes the removal of

lipids in foam cell and enhances ABCA1 expression, at the gene and protein levels [52].

Park SH et al [53] found that sage weed (*Salvia plebeia*) extract (SWE) ≥ 10 $\mu\text{g/ml}$ boosts cholesterol efflux of lipid-laden macrophages by upregulating ABCA1 and ABCG1 in murine macrophages.

CETP transfers CE from HDL to VLDL and LDL, leading to increased HDL-C levels and reduced LDL-C levels, which may cause a reduction of cardiovascular risk. The first trials with CETP inhibitors (torcetrapib) failed due to multiple off-target adverse effects. However, newer CETP inhibitors (anacetrapib and TA-8995) with more promising effects on lipids are presently being tested with the hope that they may reduce cardiovascular risk [54]. TMCs have not been extensively investigated in this area.

Promotion of cholesterol excretion in the liver

Cholesterol transported into the liver and endogenously synthesized is lost from the body via biliary secretion after conversion to bile acids. Cholesterol 7- α hydroxylase (CYP7A1) is the first and rate-limiting enzyme in the neutral pathway of bile acid synthesis, which is the main route of cholesterol removal from the body. CYP7A1 catalyzes about 2/5th of synthesized cholesterol converted into bile acids in the liver, and enhancing its activity may accelerate cholesterol dependent synthesis of bile acids [55]. The major pathway for cholesterol elimination is secretion into bile, and is mediated by ABCG5 and ABCG8 (as a heterodimer at the apical membrane of hepatocytes) (**Figure 4**).

Coptis alkaloids extract (CAE, ethanolic extract of *RhizomaCoptidis*), JZN, columbamine from RC, RC alkaloids and PMR regulate lipids associated with increased cholesterol conversion into bile acids by up-regulating CYP7A1 at the mRNA level [23, 24, 26, 41, 42, 56].

FufangZhenzhuTiaoZhi (FTZ) extract, from eight Chinese herbs, is associated with HMGCR downregulation and increased gene expression and activity of CYP7A1 in the liver of HLP rats. Meanwhile, FTZ extract could increase total bile acid levels and decrease cholesterol levels in hyperlipidemic rats [57].

Whole mung bean (*Vignaradiatae*L.) powder (1% or 2%) supplemented to control diet (0.1%

cholesterol diet) increases HMGR mRNA levels, with no effect on protein expression. In addition, mung bean increases CYP7A1 protein and gene expression levels compared with the control group in hamsters. The hypocholesterolemic activity of mung bean is mainly due to enhanced bile acid excretion and CYP7A1 up-regulation [58].

Raw and processed Notoginseng Radix Et Rhizome (NRR) are widely used in the treatment of metabolic syndromes and related diseases, including nonalcoholic fatty liver disease (NAFLD). Raw NRR and NRR heated with sand (NRR-B) show remarkable lipid-lowering effects in steatotic L02 cells, and could significantly reduce HMG-CoAR levels while increasing CYP7 α amounts [59].

Si-miao-yong-an decoction (SMYAD), a traditional Chinese medicine formula, significantly reduces plasma TC and LDL-C levels, and increases LDL-C levels in hyperlipidemia rats. SMYAD shows remarkable effects in promoting cholesterol excretion from the liver by accelerating cholesterol transport into bile acids and their glycine and taurine conjugates, suggesting that promotion of bile acid biosynthesis is mainly through the classic neutral pathway (activation of CYP7A1) [60].

ABCG5/8 expression increases cholesterol flux from hepatocytes to bile, thus directly enhancing the lithogenicity of bile while indirectly reducing plasma LDL-C and risk of MI [61]. Alfalfa saponins, extracted from *Medicago sativa* (alfalfa), lower cholesterol levels in the liver of HLP rats. The main mechanism might be associated with ABCG5/8 mRNA expression in rats [62]. Administration of PA extracted from the unsaponifiable oil of long pepper (*Piper longum*L.) results in significantly declined TC and TG amounts, and increased HDL/LDL ratio compared with the control group in C57BL/6 mice fed a lithogenic diet for 10 weeks. Indeed, paradoxically, in that study, PA prevented cholesterol gallstone formation by simultaneously decreasing the expression levels of the hepatic proteins ABCG5, ABCG8 and LXR [63].

Related nuclear transcription factors

Nuclear hormone receptors comprise a superfamily of ligand-activated transcription factors that coordinate genetic networks regulating lipid metabolism. These transcription factors

do not only regulate gene expression but also serve as intracellular receptors by binding lipid molecules. The challenges facing TCM discovery efforts for this class of targets are highlighted below.

Several receptors, including peroxisome proliferator-activated receptors (PPARs), liver X receptors (LXRs), and Sterol regulatory element-binding proteins (SREBPs), appear to function by directly sampling fatty acids and cholesterol derivatives via their respective receptor ligand binding domains [64]. SREBPs are major transcription factors that regulate genes involved in fatty acid, TG and cholesterol metabolism in the liver; they include SREBP-1a, SREBP-1c, and SREBP-2. SREBP-1c that control genes involved in fatty acid biosynthesis, while SREBP-2 activates cholesterol metabolism genes [65]. PPARs are linked to metabolic pathways that control fatty acid oxidation, adipocyte differentiation, and insulin sensitivity. PPARs include the alpha (α), beta (β) and gamma (γ) subtypes [66]. PPAR γ is predominantly expressed in the adipose tissue and macrophages, affects genes involved in lipid synthesis and storage, and glucose homeostasis [67]. PPAR α stimulates lipid consumption by upregulating fatty acid oxidation genes, which results in ameliorated hyperlipidemia [68].

Kangen-karyu, a crude drug developed from a traditional Chinese prescription consisting of six herbs (*Paeoniae Radix*, *CnidiiRhizoma*, *Floscarthami*, *CyperiRhizoma*, *Aucklandiae Radix*, and *SalviaeMiltiorrhizae Radix*), significantly inhibits adipocyte differentiation and lipid accumulation in 3T3-L1 adipocytes. Kangen-karyu downregulates PPAR- γ at the gene and protein levels. It also reduces hyperlipidemia in *db/db* type 2 diabetic mice by reducing SREBP-1 mRNA in the liver [69]. Plasma levels of TC, TG and LDL-C are decreased by shanzha (*Crataeguspinnatifida*) treatment, while HDL-C is elevated compared with the vehicle-treatment control group in HLP hamsters. These effects of shanzha could be reversed by combined treatment with PPAR antagonist (MK886), which abolishes the inhibition of fat droplet accumulation by shanzha in 3T3-L1 adipocytes [70]. FTZ might regulate SREBP1-c mRNA, CETP, and LXR expression levels [71].

Conclusion

In summary, the clinical use of statins has certain limitations. Meanwhile, TCMs can regulate all steps of lipid metabolism. TCMs of multi-target features combined with available modern interventions can further reduce cardiovascular complications by lipid-lowering mechanisms. In this study, how Chinese herbal medicines affect lipid metabolism was briefly described. The interaction between statins and TCM to inhibit hyperlipidemia attracts increasing attention, but such therapy has not been assessed in high-quality controlled clinical trials. Taking advantage of TCM effects on drug-metabolizing enzymes and enhancing statin bioavailability may be another breakthrough for integrated medicine. We have demonstrated that Jiangzhi Decoction (JZD) (*RhizomaEt Radix PolygoniCuspidati*, *RhizomaAlismatis*, *RhizomaAtractylodis*, *Radix Et RhizomaGlycyrrhizae*, *Cortex MagnoliaeOfficinalis*, and *Spica prunellae*) and its separated prescriptions have inhibitory effects on CYP3A4, in a concentration dependent manner. CYP3A4 inhibition by JZD and constituent herbs was positively correlated with prevention of Atorvastatin (AVT) from first-pass metabolism [72]. Clinical studies have confirmed that administration of JZD with AVT might have synergistic lipid-lowering effects, with JZD well-tolerated [73].

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Disclosure of conflict of interest

None.

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