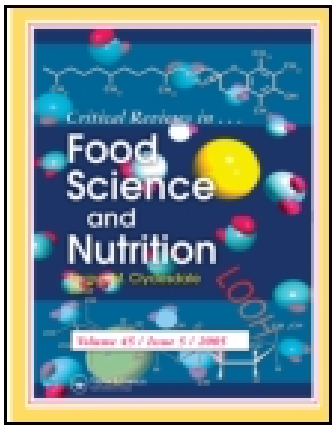

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Nutraceuticals and Functional Foods in the Management of Hyperlipidemia

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Nutraceuticals and Functional Foods in the Management of Hyperlipidemia

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Hyperlipidemia is one of the major risk factor for the development of cardiovascular disease. Hypolipidemic nutraceuticals and functional foods help improve serum lipid profiles as reducing total cholesterol, triglyceride, and low-density lipoprotein cholesterol, while elevating high-density lipoprotein cholesterol. The effectiveness of omega-3 polyunsaturated fatty acid, phytosterols, dietary fiber, and tea catechin in management of hyperlipidemia has been clearly demonstrated in epidemiological and interventional trials. Studies on mechanism reveal that they act as inhibitor or activator of critical enzyme, agonist or inhibitor of transcription factor, competitor of transporter, and sequestrant of bile acid to modulate lipid homeostasis. Hypolipidemic effects are also claimed in dietary proteins, many polyphenols, other phytochemicals, raw extract, or even whole food. This review attempts to give an overview of lipid homeostasis and summarize recent findings of hypolipidemic nutraceuticals and functional foods according to their active ingredients, focusing on the efficacy and underlying mechanisms.

Keywords Hypolipidemic, cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, nutraceuticals

INTRODUCTION

Cardiovascular diseases (CVD) remain the leading cause of morbidity and mortality worldwide. Hyperlipidemia, resulting from the abnormalities of lipid homeostasis, is a common risk factor for the development of CVD (Jain et al., 2007). Reducing serum lipids can reduce the probability of CVD as well as other related metabolic syndromes, such as obesity and diabetes. Healthy diet and exercise are well recognized to have beneficial effects on improving the serum lipid profiles: reducing total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C, the bad cholesterol), while elevating high-density lipoprotein cholesterol (HDL-C, the good cholesterol) (Kelly, 2010). A healthy diet may include reducing intake of saturated and *trans* fatty acids and dietary cholesterol, increasing intake of hypolipidemic nutraceuticals and functional foods. During the past few decades, numerous hypolipidemic nutraceuticals and functional foods have been discovered from epidemiological and interventional studies (Chen et al., 2008). Meta-analyses of human clinical trials provide evidence of their efficacy, while responsive mechanisms and targeted molecular processes are explored in animal models and/or cell lines. This paper attempts to give an overview of lipid homeostasis and review recent findings of hypolipidemic nutraceuticals and functional foods according to their active ingredients, such as protein, lipid, carbohydrate, and polyphenols.

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LIPID HOMEOSTASIS: A CONCERTO PERFORMED BY VARIOUS PATHWAYS

Cholesterol Homeostasis

Cholesterol is important constituent of membrane lipid and also precursor of steroid hormones, vitamin D and bile acids. But high level of cholesterol, especially LDL-C is dangerous for human health and the risk of CVD decreases by 2% with a 1% decrease in serum cholesterol (Maxfield and Tabas, 2005; Steinberg, 2006).

Human body obtains cholesterol from *de novo* synthesis mainly in the liver (700–900 mg/d) and absorption from diet

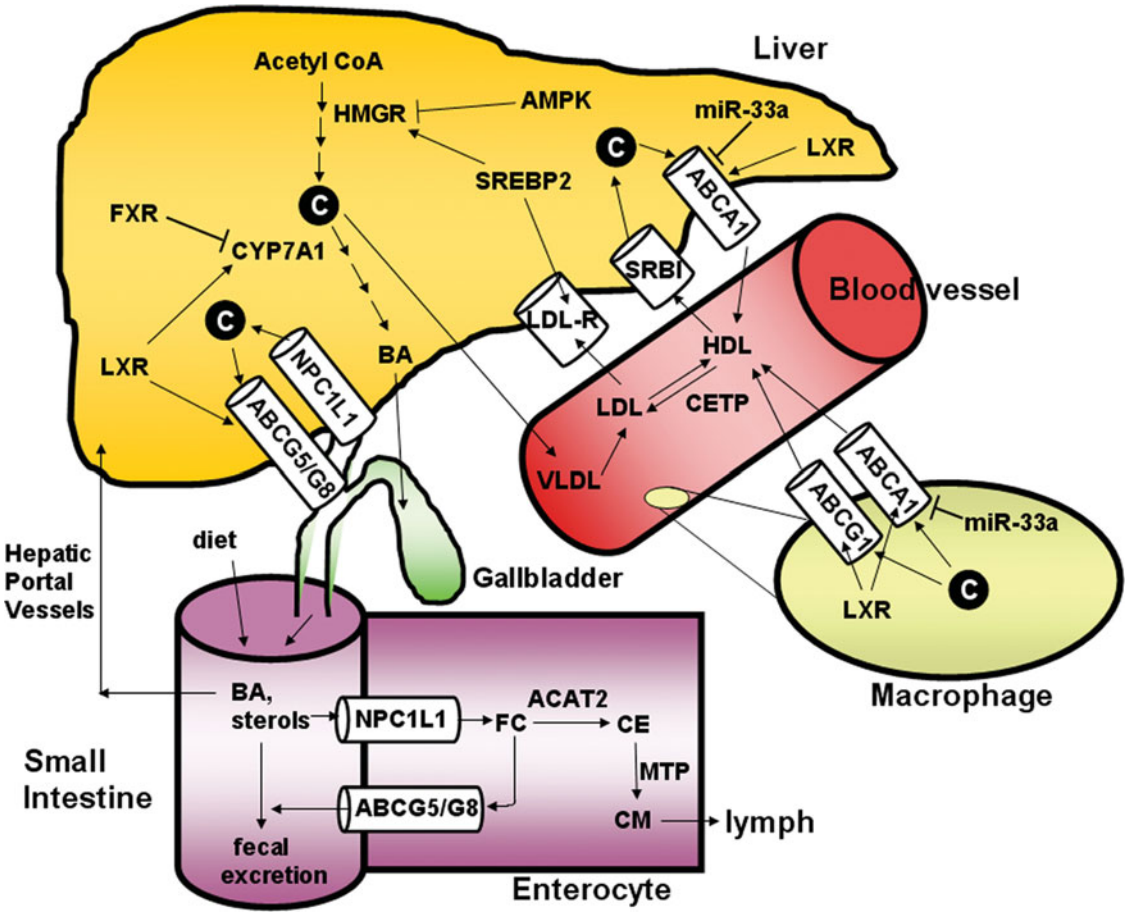

Figure 1 Overview of cholesterol homeostasis and regulation in the liver, small intestine, macrophage, and plasma. Modified from figures in (Chen et al., 2008). ABCA1, ABCG1, and ABCG5/G8: ATP-binding cassette transporters; ACAT2: acyl CoA:cholesterol acyltransferase 2; AMPK: AMP-activated protein kinase; BA: bile acid; C: cholesterol; CETP: cholesteryl ester transport protein; CE: cholesteryl ester; CM: chylomicrons; CYP7A1: cholesterol 7α-hydroxylase; FC: free cholesterol; FXR: farnesoid X receptor; HDL: high-density lipoprotein; HMGR: 3-hydroxy-3-methylglutaryl-CoA reductase; LDL: low-density lipoprotein; LDL-R: low-density lipoprotein receptor; LXR: liver X receptor; miR-33a: microRNA-33a; MTP: microsomal triglyceride transfer protein; NPC1L1: Niemann-Pick C1-Like 1; SREBP2: sterol regulatory element binding protein-2; SRB1: scavenger receptor B class 1; VLDL: very low density lipoprotein. (Color figure available online).

(300–500 mg/d). Cholesterol circulates as a component of lipoproteins, such as chylomicron, VLDL (very low-density lipoprotein), LDL (low-density lipoprotein), and HDL (high-density lipoprotein). And it is eliminated from body via fecal excretion (~600 mg/d), conversion to bile acid (~400 mg/d), and through loss of dead skin cells (~100 mg/d). Cholesterol homeostasis in the body is regulated mainly by intestinal absorption, endogenous synthesis, and hepatic conversion and excretion (Fig. 1).

Cholesterol Absorption

Cholesterol absorption is controlled by at least two types of transporters, Niemann-Pick C1-Like 1 (NPC1L1) as influx transporter and ATP-Binding Cassette (ABC) proteins as efflux transporters. In both enterocyte and hepatocyte, sterol influx via NPC1L1 is balanced by efflux via ABCG5/G8 (Fig. 1).

Intestinal cholesterol comes from both biliary and dietary sterols, and is solubilized by bile acid and phospholipids to form micelles. NPC1L1 enriched in the apical membrane of small intestine absorptive enterocytes transports cholesterol from intestinal lumen into enterocytes. NPC1L1 is also highly expressed in the canalicular membrane of hepatocytes, where it reabsorbed free cholesterol back into hepatocyte from bile canaliculus probably to limit excessive biliary cholesterol loss. NPC1L1 is the molecular target of ezetimibe, a potent cholesterol absorption inhibitor that reduce plasma cholesterol in humans (Jia et al., 2011).

Several ABC proteins are involved in lipid homeostasis as cholesterol transporters (Matsuo, 2010). ABCG1 and ABCA1, expressed in peripheral cells, including macrophages, remove excess cholesterol from peripheral tissues to the liver. ABCA1, through transporting of cholesterol and phospholipid to apolipoprotein acceptors in the bloodstream, is crucial for the formation of HDL particles (Attie, 2007). ABCG5 and ABCG8, highly expressed in intestine and liver, excrete absorbed sterols to intestinal lumen and exclude sterol from liver to the bile duct. ABCG1 and ABCG4, expressed in the brain, play important

roles in lipid metabolism in central nervous system. As sterol transporters, ABC proteins can be targets of functional foods to cue and prevent hyperlipidemia.

After entering enterocytes, cholesterol is first esterified to cholesteryl ester (CE) by intestinal acyl-CoA:cholesterol acyltransferase 2 (ACAT2). Then CE is packed with microsomal triacylglycerols by microsomal triacylglycerol transport protein (MTP) into chylomicrons (CM), which is transferred into blood through the lymphatic system.

Cholesterol Biosynthesis

De novo synthesized cholesterol accounts for more than 70% cholesterol in humans. Therefore, control on the cholesterol biosynthesis is an effective strategy to control level of cholesterol. Cholesterol synthesis starts with acetyl CoA, which is sequentially converted to mevalonate, activated isoprenes, squalene, and finally to cholesterol. In this multienzyme pathway to synthesize cholesterol, 3-Hydroxy-3-methylglutaryl (HMG-CoA) reductase (HMGR) mediates the rate-limiting step and is the inhibition target of statin class of drugs. These drugs are effective to reduce plasma cholesterol but associated with unfavorable side effects. Squalene synthase is another important enzyme in cholesterol biosynthesis, and can be target of hypolipidemic nutraceuticals and functional food (Charlton-Menys and Durrington, 2008).

When the hepatic cellular cholesterol level is low, expression of HMGR is upregulated by transcription factor SREBP-2 (sterol regulatory element binding protein 2) (Brown and Goldstein, 2009). When the cellular active cholesterol level is high, HMGR diminishes rapidly through proteolytic degradation (Steck and Lange, 2010).

Hepatic Conversion and Excretion

Excessive cholesterol from peripheral tissues is collected into plasma, and the removal of LDL-C from plasma is mainly mediated by LDL receptors (LDL-R) in the liver (Fig. 1). When the hepatocyte cellular cholesterol level is low, LDL-R expression is activated by SREBP-2. Upregulation of LDL-R helps to uptake more plasma LDL-C and lower plasma LDL-C. On the other hand, LDL-R gene expression is downregulated by high level of hepatic cellular cholesterol (Brown and Goldstein, 2009).

Excessive liver cholesterol is eliminated via two pathways. It can be excreted directly as biliary sterols and eliminated through feces. It can also be converted to bile acids and excreted as fecal bile acids. Bile acids facilitate absorption of cholesterol, dietary lipid, and fat-soluble vitamins in intestinal lumen. Through the enterohepatic circulation of bile acids, most conjugated bile acids are reabsorbed by hepatic portal vessels, while unconjugated ones are excreted in the feces (about 200–600 mg/d in human). If the bile acid reabsorption is inhibited, for example, by dietary fiber or cholesterol-lowering drug (i.e., cholestyramine and colestipol), compensatory bile acids will be synthesized from cholesterol, which leads to the decrease of hepatic cholesterol. Lower level of hepatic cholesterol upregulates expression of LDL-R, resulting in an increased influx of plasma cholesterol to the liver.

Cholesterol 7α-hydroxylase (CYP7A1) is a critical regulatory point that initiates the classical bile acid biosynthetic pathway from cholesterol in the liver. CYP27A1 (sterol 27-hydroxylase) and CYP7B1 (oxysterol 7a-hydroxylase) control the alternative synthesis pathways in the liver and macrophages. In the liver, bile acids activate FXR (farnesoid X receptor), a nuclear receptor, which subsequently inhibits several nuclear receptors and results in inhibiting transcription of CYP7A1 (Chiang, 2009). Therefore lower level of bile acid in hepatocyte liberates the feed back inhibition on CYP7A1 and increases the removal of hepatic cholesterol, as well as plasma cholesterol. Other than the negative regulation through FXR, CYP7A1 transcription is stimulated via activation of oxysterol receptor, LXRα (liver X receptor α) in rat and hamster (Gupta et al., 2002).

Balance Between HDL and LDL Particles

It is well known that LDL-C is positively associated while HDL-C is inversely related with the risk of CVD. HDL and LDL contain different apolipoprotein. Apolipoprotein A1 (apoA1) is the major protein component of HDL. As antiatherogenic particles, HDLs transport cholesterol from extrahepatic tissues to liver for further processing and elimination. Apolipoprotein B (apoB) synthesized primarily by enterocyte and hepatocyte is the core protein of LDL and VLDL particles. Control on the concentration of apoA1 and apoB can be the mechanism to regulate HDL/LDL ratio in plasma (Parish et al., 2009).

In human plasma, cholesteryl ester transport protein (CETP) transfers one CE from HDL to LDL with an exchange of one triacylglycerol (Fig. 1). Inhibition of CETP activity in plasma theoretically can increase the HDL/LDL ratio and favor plasma cholesterol homeostasis (Shah, 2007). Therefore, CETP inhibition is a promising approach to control hyperlipidemia and reduce cardiovascular disease risk (Mitka, 2011).

Triglyceride and Fatty Acids Homeostasis

Elevated plasma TG is a risk factor for CVD, though it is not as robust as LDL-C. Excessive accumulation of TG results in obesity, which is the major risk factor of metabolic syndrome. Severe hypertriglyceridemia is also a risk factor for pancreatitis (Yuan et al., 2007) and excessive TGs accumulated in the liver will give rise to fatty liver disease (nonalcoholic steatohepatitis) (Ferre and Foufelle, 2010).

Plasma TGs and fatty acids come from three sources. Exogenous ones come from dietary fat and are carried in CM. Endogenous ones come from liver *de novo* lipogenesis and are carried in VLDL particles. Additional endogenous ones come

from lipolysis in adipocyte and are maintained as nonesterified fatty acid (Yuan et al., 2007). Hypertriglyceridemia results from increased intake of dietary fat and excess caloric intake, upregulated lipogenesis, and decreased peripheral catabolism, which mainly includes lipoprotein hydrolysis by lipase and fatty acid oxidation (Ong et al., 2011).

Absorption

TG is absorbed from micelles formed in intestinal lumen as fatty acids and monoglycerides after hydrolysis by lipase. Pancreatic lipase is the key enzyme to hydrolyzed dietary TG in small intestine. CD36 (fatty acid translocase) and intestinal alkaline phosphatase work coordinately to transport fatty acid into enterocytes (Lynes and Widmaier, 2011). In the enterocyte, TG is resynthesized and combined with apoB48 to form chylomicron with the help of MTP.

Lipogenesis

The biosynthesis of long-chain fatty acids occurs in two distinct steps. Acetyl-CoA carboxylase (ACC), a biotin-containing multienzyme system, catalyzes the conversion of acetyl-CoA to malonyl-CoA, while fatty acid synthetase (FAS) catalyzes the conversion of acetyl-CoA and malony-CoA to palmitate (Wakil et al., 1983; Kim, 1997). Suppression on ACC and FAS expression contributes to lower hepatic TG.

De novo lipogenesis in the liver is an insulin- and glucose-dependent process, which is positively controlled by transcription factors, SREBP-1c (sterol regulatory element binding protein 1c), and ChREBP (carbohydrate response element binding protein). SREBP-1c is activated by insulin as well as endoplasmic reticulum (ER) stress, while ChREBP is activated by glucose (Ferre and Foufelle, 2010). Lipogenesis is down-regulated by AMP-activated protein kinase (AMPK).

Fatty Acid Oxidation

Fatty acids are removed from the liver either by secretion in VLDL-triacylglycerol or by oxidation. Through oxidation fatty acids convert into acyl-CoA and generate energy. Fatty acid β-oxidation occurs in mitochondria and peroxisomes. Mitochondria catalyze β-oxidation of most short-, medium-, and long-chain fatty acids to generate ATP. Peroxisomes are involved in β-oxidation of long-chain and very-long-chain fatty acyl-coenzyme for detoxification. Long-chain and very-long-chain fatty acids are also metabolized by the microsomal ω-oxidation system (Reddy and Hashimoto, 2001). ACO (acytl-CoA oxidase) in peroxisomes and ACD (Acyl-CoA dehydrogenase) in mitochondria are the key enzymes for fatty acid oxidation. The genes encoding oxidation enzymes are transcriptionally upregulated by peroxisome proliferator–activated receptor α (PPARα).

Regulation of Lipid Homeostasis

AMP-Activated Protein Kinase

AMPK is a critical player in energy homeostasis at both cellular and whole body levels. Generally, AMPK is activated under conditions of low energy charge (increased AMP/ATP ratio) to inhibit anabolism that consumes ATP, such as fatty acid synthesis, cholesterol synthesis, and gluconeogenesis, while promote catabolism that generates ATP, such as fatty acid oxidation and glycolysis (Steinberg and Kemp, 2009). Now it is clear that AMPK is a highly integrated signaling junction for many biochemical pathways and is recognized as a target for the treatment of obesity and metabolic syndrome.

AMPK regulates lipid metabolism at multiple points (Steinberg and Kemp, 2009) (Fig. 1 and 2). It inactivates HMGR and ACC through phosphorylation and therefore suppresses malony-CoA content, resulting in reduced fatty acid synthesis and increased mitochondrial β-oxidation respectively. AMPK reduces fatty acid synthesis by inhibiting SREBP-1c, which controls the entire lipogenesis pathway or by inhibiting FAS activity directly. Activated AMPK also phosphorylates ChREBP and inhibits its entry into nucleus, thus suppressing the ChREBP induced lipogenic gene expression. AMPK inhibits the expression and activity of GPAT (glycerol-3-phophate acyl-transferase), which is the rate-limiting enzyme catalyzing the first committed step in phospholipid and TG synthesis. AMPK also inhibits hormone-sensitive lipase activation through phosphorylation. HSL is responsible for the hydrolysis of fatty acids from TG. AMPK induces the translocation of CD36 to the plasma membrane to facilitate the uptake of fatty acids.

SREBPs

Sterol regulatory element-binding proteins (SREBPs) are key transcription regulators of genes involved in lipid synthesis and uptake (Brown and Goldstein, 1997; Brown and Goldstein, 1999). They are synthesized as precursor membrane proteins in ER. Their activation is unique since it is regulated by the sequential proteolysis by site 1 proteases (S1P) and site 2 protease (S2P), which is later proved to be a conserved mechanism in regulating transmembrane signaling throughout different kingdoms (Chen and Zhang, 2010).

SREBP family consists of three isoforms: SREBP-1a, SREBP-1c, and SREBP-2. SREBP-2 is responsible for the upregulation of cholesterol and fatty acid biosynthesis and LDL receptor synthesis and is regulated by cellular sterol balance (Brown and Goldstein, 2009). In sterol depleted cells, SCAP (SREBP cleavage-activating protein) binds and escorts SREBP to COPII (coat protein II) vesicles, which transport SREBP from ER to Golgi apparatus. In the Golgi, two sequential proteolytic events by S1P and S2P release the active transcriptional region of bHLH (basic helix-loop-helix) to nuclear. In cells with high level of sterol, Insig (insulin-induced gene) traps and retains the SREBP-SCAP complex at ER, thus inhibiting the

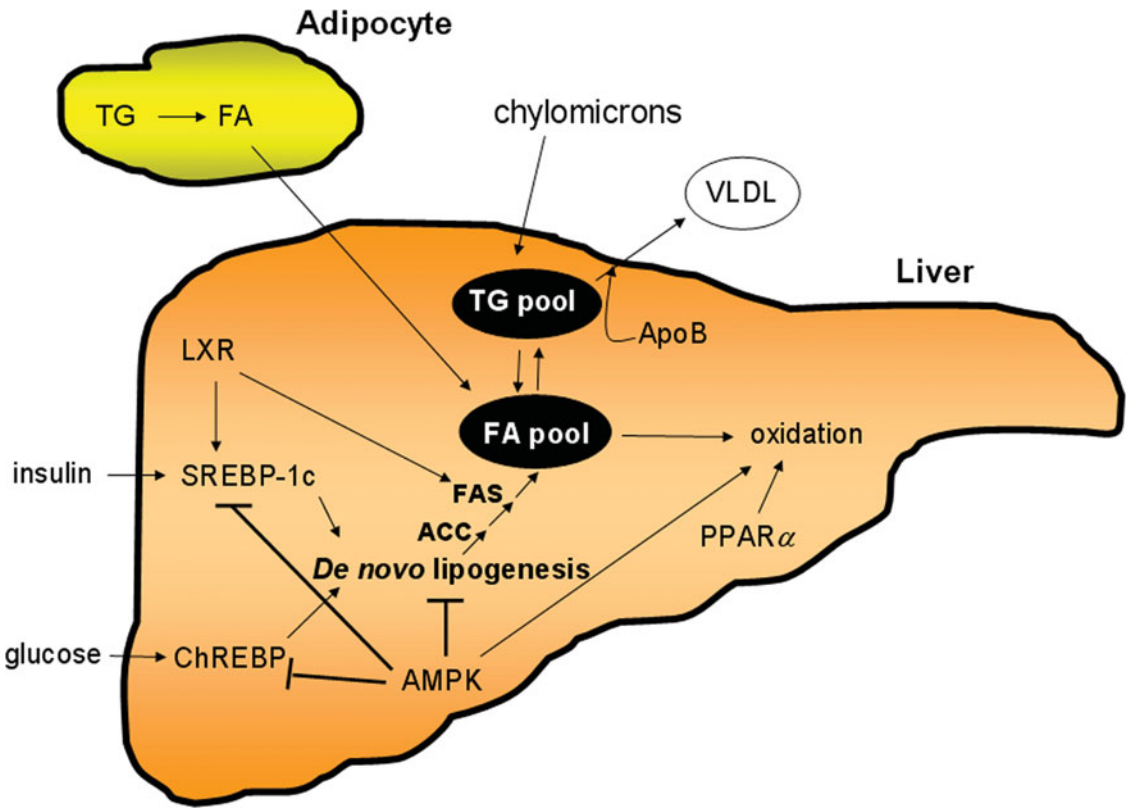

Figure 2 Overview of fatty acid and triglyceride metabolism and regulation in the liver. Modified from figures in (Browning and Horton, 2004; Hodson and Frayn, 2011). ACC: acetyl-CoA carboxylase; AMPK: AMP-activated protein kinase; ApoB: apolipoprotein B; ChREBP: carbohydrate response element binding protein; FA: fatty acid; FAS: fatty acid synthetase; LXR: liver X receptor; PPARα: peroxisome proliferator–activated receptor α; SREBP-1c: sterol regulatory element binding protein-1c; TG: triglyceride; VLDL: very low density lipoprotein. (Color figure available online).

SREBP proteolytic activation in Golgi (Brown and Goldstein, 2009).

SREBP-1c regulates transcription of genes involved in fatty acid and TG synthesis, such as ACC, FAS, and SCD (stearoyl-CoA desaturase). Under overnutrition, SREBP-1c is activated to enhance lipogenesis, while it is downregulated under fasting and starvation. It is now known that the protective effects of polyunsaturated fatty acids (PUFAs) against CVD are mediated partially through their inhibition on SREBP-1c (Yahagi et al., 1999; Yoshikawa et al., 2002).

SREBP-1a, an alternative splicing isoform of SREBP-1c, is highly expressed in growing cells and is suggested to regulate cell cycle through supplying membrane lipids (Shimano, 2009). It activates biosynthesis of fatty acids, TGs, phospholipids and cholesterols.

microRNAs

miRNAs, as non-coding RNAs of 21–24 nucleotide long, are important regulators of mRNA stability and translation through partially complementary binding to target region (Bartel, 2009). miRNAs inhibit translation of target transcripts and/or lead to their degradation (Bommer and MacDougald, 2011).

Recent studies from five independent groups have shown that miR-33a (microRNA-33a), embedded within intron of SREBP-2 gene, collaborates with SREBP host genes to control cholesterol homeostasis (Gerin et al., 2010; Horie et al., 2010; Marquart et al., 2010; Najafi-Shoushtari et al., 2010; Rayner et al., 2010). miR-33a targets in mRNA of ABCA1 (cholesterol efflux transporter) for posttranscriptional repression, thereby attenuates cholesterol efflux to apoA1 for HDL synthesis (Fig. 1). Other likely targets of miR-33 includes ABCG1 (another cholesterol efflux transporter), NPC1 (Niemann-Pick C1), enzymes involved in β-oxidation of fatty acids, and proteins involved in the import of fatty acids into mitochondria (i.e., CPT1A and carnitine octanoyl-CoA transferase; CROT) (Gerin et al., 2010).

Understanding the posttranscriptional regulation of lipid homeostasis may provide novel targets for future therapeutic and dietary intervention of hyperlipidemia.

Nuclear Receptors

Nuclear receptors are a group of ligand-activated transcription factors that regulate cell growth, development, and metabolism (Schulman, 2010). Among 48 members in human genome, several nuclear receptors sample the levels of fatty acids and cholesterol derivatives via the receptor ligand binding domain and use this signal to control synthesis, transport, and breakdown of the cognate ligands. Examples include

peroxisome proliferator activated receptors (PPARs), the LXRs, FXR, and retinoidrelated orphan receptors (RORs) etc. (Forman et al., 1997; Repa and Mangelsdorf, 1999; Chawla et al., 2001; Edwards et al., 2002).

PPARs

PPARs have three distinct members: PPARα, PPARγ, and PPARβ/δ (also referred as PPARδ). All of them bind to DNA as heterodimers with retinoid X receptors (RXR, another nuclear receptor) when activated.

PPARα is highly expressed in liver, kidney, and muscle. It directly upregulates transcriptions of genes involved in fatty acids β-oxidation, uptake, cholesterol catabolism and ketogenesis (Bensinger and Tontonoz, 2008). Thus, activation of PPARα promotes the utilization of fat as an energy source.

PPARγ is enriched in adipose tissue and its activation promotes lipid storage (Beaven and Tontonoz, 2006). As the master transcriptional regulator of adipogenesis, activation of PPARγ in adipose has been proposed to increase the number of adipocytes and promote the relocalization and storage of fat in adipose, protecting peripheral tissues from lipotoxicity (Medina-Gomez et al., 2007). PPARγ activation redirects effluxed cholesterol from liver toward adipose tissue uptake via SR-BI (scavenger receptor type-BI) (Toh et al., 2011).

PPARδ appears to be ubiquitously expressed. Its activation elevates HDL level through increasing the expression of ABCA1 (Oliver et al., 2001), reduces cholesterol absorption through decreasing the intestinal expression of NPC1L1 (van der Veen et al., 2005), and increases fecal neutral sterol secretion via increasing transintestinal cholesterol efflux (Vrins et al., 2009). PPARδ activation increases β-oxidation of fatty acids (Wang et al., 2004b). PPARδ inhibits SREBP-1 activation and suppresses hepatic lipogenesis in obese diabetic mice (Qin et al., 2008).

LXR

LXRs are comprised of LXRα and LXRβ. LXRα is highly expressed in the liver, kidney, and intestine while LXRβ is more ubiquitously expressed. Both LXRs bind to DNA and regulate transcription as heterodimers with RXRs.

In macrophage, several proteins involved in reverse cholesterol transport were identified as direct LXRs target genes, including ABCA1, ABCG1, ABCG4 and apoE (Kennedy et al., 2001; Laffitte et al., 2001; Wagner et al., 2003). In the liver, activation of LXRs enhances the elimination of hepatic cholesterol through CYP7A1, ABCG5, and ABCG8, and also decreases cholesterol uptake by up-regulating Idol (inducible Degrader of LDL receptor) (Peet et al., 1998; Repa et al., 2002; Zelcer et al., 2009). Activation of LXR also upregulates fatty acid synthesis through increasing expression of SREBP-1c, FAS and SCD-1 (stearoyl CoA desaturase 1) (Repa et al., 2000; Wang et al., 2004a). Though the LXRs activation leads to reduced hepatic cholesterol, the complexity of LXRs activation results in the elevations in plasma cholesterol and TG in LXR agonist treated animals (Groot et al., 2005), which illustrates the challenges in targeting nuclear receptors when treating dyslipidemia.

HYPOLIPIDEMIC NUTRACEUTICALS AND FUNCTIONAL FOODS

Proteins

Soy Proteins

Consumption of soy proteins or peptides successfully improved dyslipidemia in animal and human, though the extent was varied among different trials (reviewed in (Sirtori et al., 2009)). Taku et al. (2007) found that soy protein significantly improved lipid profiles whether contained enriched or depleted isoflavones. The 7S and 11S globulins are major storage proteins of soybean, and hypolipidemic effects of 7S globulins (beta-conglycinin) were confirmed in animal and human trials (Kohno et al., 2006; Ferreira et al., 2011). In cholesterol-fed rats, alpha subunits of 7S reduced plasma TC and TG dramatically through up-regulation of liver P-VLDL receptors activity (Castiglioni et al., 2004). Hydrolysates of 7S globulin inhibited FAS activity and lipid accumulation of human adipocytes *in vitro*, while alpha and alpha' subunits were suggested as sources of the active peptides (de Mejia et al., 2010). Consonni et al. (2010) expressed and purified a truncated form of the 7S globulin alpha′ subunit in yeast, and found it could elevate LDL uptake and degradation in HepG2 cells. Recently, in a screening of soy protein-derived hypotriglyceridemic di-peptides in HepG2 cells and obese rats, 3 di-peptides, Lys-Ala, Val-Lys, and Ser-Tyr, were reported to reduce TG synthesis, while Ser-Tyr additionally reduced apoB secretion in HepG2 cells (Inoue et al., 2011).

Other Legume Proteins

The consumption of other legumes, such as lupin, pea, chickpea, bean, lentil, and butter bean, also showed favorable effects in preventing dyslipidemia, though most data came from animal models and few in clinical trials (reviewed in (Sirtori et al., 2009)). The legume proteins are suggested as part of the active ingredients. For example, purified pea protein lowered hepatic TC in rats through stimulating bile acid excretion (Spielmann et al., 2008). Pea protein isolated from Pisum sativum markedly lowered plasma TC and TG in rats by upregulating LDL-R expression and downregulating fatty acid synthesis genes (Rigamonti et al., 2010). In a human trial, lupin protein compared to casein slightly lowered concentration of LDL-C in hypercholesterolemic subjects, without altering HDL-C (Weisse et al., 2010).

Buckwheat Protein

Based on epidemiological studies and intervention trials, buckwheat intake was associated with reduction of plasma TC

and LDL-C, and was suggested as a preventative factor of hyperlipidemia, hypertension, and hyperglycemia (Cao et al., 2007). Other than rich rutin and little quercitrin in buckwheat herb and seeds (Fabjan et al., 2003), buckwheat protein was suggested as the active ingredient responsible for hypocholesterolemic activity in animal models through enhancing fecal excretion of neutral sterols and bile acids (Tomotake et al., 2000; Tomotake et al., 2007). In Caco-2 cells, insoluble fraction of buckwheat protein showed cholesterol-binding properties that reduced micelle cholesterol solubility and uptake (Metzger et al., 2007). Ma and Xiong (2009) demonstrated by *in vitro* experiments that digestion-resistant peptides of buckwheat protein were largely responsible for bile acid binding and elimination.

Marine Proteins

Marine proteins attracted a lot of attention and hypolipidemic effect was investigated in water-insoluble fish protein from Alaska pollock (Kato et al., 2009, 2011), tuna protein and scallop ovary protein (Narayan et al., 2009). Animal studies in rats and pigs with fish proteins vs. casein have suggested their hypocholesterolemic effects, which were primarily mediated by increasing fecal excretion of bile acid and cholesterol (Shukla et al., 2006; Hosomi et al., 2009; Kato et al., 2009; Narayan et al., 2009; Spielmann et al., 2009; Hosomi et al., 2011), or coupled with decreased reabsorption of bile acids from the ileum through a decrease in IBAT (ileal bile acid transporter) (Kato et al., 2011). The increased fecal cholesterol and bile acid excretion may due to the digestion products of fish protein which reduced micellar solubility of cholesterol and increased bile acid binding capacity (Hosomi et al., 2011). The protein fractions of freshwater clam (*Corbicula fluminea*) extract and freshwater clam hydrolysate were recently shown to reduce serum and hepatic cholesterol through enhancing excretion of neutral sterols and bile acids (Chijimatsu et al., 2011; Tsai et al., 2011).

Lipids

omega-3 Polyunsaturated Fatty Acid (ω-3 PUFA)

Dietary ω-3 PUFAs usually mentioned are DHA (docosahexaenoic acid, 22:6 ω-3), EPA (eicosapentaenoic acid, 20:5 ω-3), and ALA (α linolenic acid, 18:3 ω-3). Many epidemiological and interventional studies have demonstrated the beneficial effects of ω-3 PUFAs against CVD, including hypotriglyceridemic, antithrombotic, anti-inflammatory, antiarrhythmic, and antiangiogenic effects (Smith et al., 2007; Petrovic et al., 2008; Micallef and Garg, 2009). Several mechanisms are suggested for its hypotriglyceridemic effects. Gani and Sylte (2008) found that ω-3 PUFAs upregulated gene expression involved in fatty acid oxidation through activating PPARα and PPARγ. Jump et al. (2005) showed that ω-3 PUFAs inhibited hepatic fatty acid synthesis through suppressing SREBP-1c transcription, and enhancing SREBP-1c protein degradation and mRNA decay. Howell et al. (2009) found that ω-3 PUFAs suppressed insulin-induced SREBP-1c transcription via reducing trans-activating capacity of LXRα. In addition to modulating hepatic gene expression, fish oil rich in ω-3 PUFA was found to increase fatty acid β-oxidation, ω-oxidation, and malic enzyme activities in the small intestine of mice (Mori et al., 2007).

As essential fatty acids, ω-3 PUFAs must be obtained from diet. DHA and EPA are rich in deep ocean fish and fish oils, which originally came from algae. ALA is found in plant seeds, such as flax, rape, walnuts, perilla, and chia, as well as in chloroplasts of deep green vegetables. Once consumed, ALA is converted to EPA, DPA (docosapentaenoic) and DHA. Another PUFA, ω-6 PUFA (i.e., LA, linoleic acid, 18:2 ω-6), which is found in nuts and vegetable oils, shares the same converting pathway as ω-3 PUFA *in vivo*, so that they compete for the same enzymes. A lower ratio of ω-6/ω-3 PUFA is suggested to be more desirable in reducing risks of many chronic diseases (Simopoulos, 2008; Wang et al., 2009b; Wan et al., 2010), however the effects of individual fatty acids need to be addressed in the future.

Phytosterols (Plant Sterols and Stanols)

Phytosterols (including plant sterols and stanols) are the analogous compounds of cholesterols in animals. They are structurally and functionally similar with cholesterols. Among more than 250 different phytosterols, the most common ones are β-sitosterol, campesterol, stigmasterol, and their saturated stanols.

The hypocholesterolemic effects of phytosterols were first discovered in the early 1950s. So far, a lot of clinical trials and meta-analysis have demonstrated that consumption of 1.5–2.0 g/d of phytosterols is effective in lowering plasma LDL cholesterol by 10–15%, with little effects on HDL cholesterol and TGs (Hansel et al., 2007; Micallef and Garg, 2009; Marangoni and Poli, 2010).

The intestinal absorption of phytosterols are poor compared with cholesterols (<5% vs. 20–60%). Phytosterols inhibit cholesterol absorption from intestinal tract through competing with cholesterol for incorporation into the mixed micelles (Miettinen and Gylling, 1999). Other mechanisms are suggested to be involved. Phytosterols use the same infflux transporter NPC1L1 as cholesterol, but they are less efficiently esterified by ACAT2 in enterocytes (Temel et al., 2003) so that they are more likely to be effluxed by ABCG5/G8 transporters (Calpe-Berdiel et al., 2009). Phytosterols may also decrease cholesterol synthesis through inhibition on HMGR, or activation of the LXR target pathways (Calpe-Berdiel et al., 2009).

Phytosterols are mainly found in vegetable oils, rice bran oil, nuts and seeds, cereals, vegetables, and fruits (Marangoni and Poli, 2010). Recent advancements in food technologies have made it possible to combine nutraceutical phytosterols with a variety of food, such as margarines, yogurts, milk, juices, salad dressing, and cereal bars. While the associated reduction of plasma carotenoid with consumption of phytosterols can be

balanced by consumption of carotenoid-rich vegetables and fruits (Marangoni and Poli, 2010).

In the past few years, the hypolipidemic efficacy and mechanisms of many dietary lipids or lipid related products were extensively investigated in animal models. And some of the examples are summarized in Table 1.

Carbohydrate-Dietary Fibers

Dietary fibers are a large group of bioactive carbohydrate polymers. Current definitions of dietary fiber include naturally occurring edible carbohydrate polymers, along with extracted or synthetic carbohydrate polymers. Dietary fibers are resistant to hydrolyzation by the endogenous enzymes in the small intestine of humans and have physiological effects of health benefit as demonstrated by scientific evidence (Phillips and Cui, 2011).

Dietary fiber can be classified as soluble/insoluble, viscous/nonviscous, and well fermentable/partially fermentable ones according to their chemical properties and physiological benefits (Li and Uppal, 2010). As a large fraction of dietary fiber, nonstarch polysaccharides are principally found in plant cell wall and consisting of a large number of monosaccharide residues joined by glycosidic linkage. This group includes cellulose and hemicelluloses from vegetables, fruits, nuts, legumes, cereals grains, and bran. It also includes pectins (from citrus fruits and apples), beta-glucans (from cereal grains particularly oats and barley, yeast, bacteria, algae and mushroom), gums (i.e., gum arabic and tragacanth from plant exudates, agar, carrageenans, and alginates from seaweed, as well as guar gum and locust beans gum) and mucilages (i.e., psyllium). Resistant starch is another fraction of dietary fiber and is contained in partly milled cereals, seeds, legumes, bananas, and potatoes. They are mostly insoluble and partially fermented in the colon. Resistant oligosaccharides (i.e., fructooligosaccharide) are comprised of 3 to 10 monosaccharide molecules and are typically fermentable and have prebiotic effects. Whether or not to include resistant oligosaccharides in dietary fiber is up to the decision of different national authorities. Nowadays, there are several synthetic dietary fibers, such as polydextrose, methylcellulose, carboxymethylcellulose, and hydroxypropylmethyl cellulose. Lignin, intimately associated with hemicellulose in plant cell wall, is not a polysaccharide but a polymer of phenylpropane units. However, it is usually included as dietary fiber and found in foods with woody components, such as the outer layers of cereal grains (Li and Uppal, 2010).

Dietary fiber has long been accepted as an essential constituent of a healthy diet. Consumption of different types of dietary fiber has been shown by human trials and meta-analysis to reduce risk of CVD, diabetes, obesity, and other metabolic syndrome. The beneficial physiological properties of dietary fiber include improved laxation, fermentability by colon microbiota, attenuation of blood TC, LDL-C, glucose, and insulin, as well as protection against cancers according to specific type of dietary fiber (Chawla and Patil, 2010; Raninen et al., 2011).

Epidemiological studies and controlled intervention studies have shown that several types of soluble dietary fibers (i.e., beta-glucan, psyllium, pectin, and guar gum) effectively lower serum LDL-C without significantly affecting HDL-C or TG (Theuwissen and Mensink, 2008; Anderson et al., 2009; Wei et al., 2009). Controlled clinical trials were summarized to show that intakes of guar gum of 9–30 g/d reduced LDL-C for 10.6%; consumption of pectin of 12–24 g/d resulted in 13% reduction in LDL-C; intake of barley beta-glucan of 5 g/d lowered LDL-C of 11.1%; intake of hydroxypropyl methylcellulose of 5 g/d indicated 8.5% reduction in LDL-C; while consumption of 6 g/d of oat beta-glucan or psyllium decreased LDL-C by around 5% (Anderson et al., 2009).

Three major mechanisms have been proposed to explain the hypocholesterolemic effects of dietary fibers. Firstly, dietary fibers hinder bile salt re-absorption from small intestine which results in excess fecal bile salt excretion. The reduced reabsorption of bile salts via enterohepatic circulation promotes hepatic conversion of cholesterol into bile acids and reduces hepatic cholesterol, which up-regulates LDL-R to accept more cholesterol from plasma thus lowering plasma LDL-C (Gunness and Gidley, 2010). Secondly, viscous dietary fibers delay gastric emptying and slow down intestinal digestion and absorption, which may decrease the postprandial release of glucose into circulation, thereby reducing insulin concentration. Reduced insulin attenuates hepatic synthesis of fatty acid and cholesterol (Theuwissen and Mensink, 2008). Finally, colonic fermentation of dietary fiber with production of short-chain fatty acids, such as acetate, propionate, and butyrate, may contribute to hypocholesterolemia through inhibition of hepatic cholesterol synthesis (Alvaro et al., 2008). But evidence for this mechanism is inconclusive in human.

Wolever et al. (2010) investigated the effect of beta-glucans molecular weight (related to viscosity) on serum LDL-C in human intervention trial. It was shown that oat beta-glucans of high molecular weight (2,210,000 g/mol) or medium molecular weight (530,000 g/mol) lowered LDL-C similarly by approximate 5%, but efficacy was reduced by 50% when molecular weight was reduced to 210,000 g/mol. Another recent research using DNA microarray analysis revealed that administration of short-chain fructooligosaccharide changed the expression of nuclear receptors PPARα and FXR target genes in the rat liver (Fukasawa et al., 2010), from which new mechanism was hypothesized but need further confirmation.

Dietary Polyphenols

Phytochemicals are bioactive non-nutrient plant compounds that have been associated with reduced risk of major chronic diseases (Liu, 2004). Among several thousand individual identified so far, phytochemicals can be classified as phenolics, carotenoids, alkaloids, nitrogen-containing compounds, and organosulfur compounds (Liu, 2004) and the most extensively investigated phytochemicals in management of hyperlipidemia

Table 1 Examples of dietary lipid in the management of hyperlipidemia in animal models

Lipid source	Active ingredients	Effect in animal model	Investigated mechanisms	Reference
Algal lipid	Algal lipid (38.56% DHA)	Decreased plasma TC and non-HDL-C in hamsters	Downregulated intestinal NPC1L1, hepatic HMGR and LDL-R.	(Chen et al., 2011)
Fish oil	ω-3 PUFA	Lowered plasma and liver TG in mice, the hypotriglyceridemic effect was not affected by PPARs antagonists.	Fish oil inhibited SREBP-1c and fatty acid synthesis via PPARs independent mechanism.	(Wakutsu et al., 2010)
Ethanol extract of masou salmon	ω-3 PUFA	In high-fat diet induced obese mice, reduced plasma, and liver TC.	Decreased HMGR mRNA expression.	(Oh et al., 2009)
Krill oil	Phospholipid, ω-3 fatty acid, astaxanthin	In mice, krill oil reduced liver weight, hepatic TG and TC, serum TC, and blood glucose.	Reduced hepatic gene expression of FAS, ACC, SCD-1, SREBP-2, SREBP-1c, PPAR-α, HMGR, LDLR. Increased serum adiponectin.	(Tandy et al., 2009)
Adlay seed oil	Unsaturated fatty acid	Adlay seed oil reduced abdominal fat tissue and LDL-C, and increase total antioxidant capacity in hyperlipidemic rats.		(Yu et al., 2011)
Tea (seed) oil and three vegetable oils	Greatest oleic acid and least phytosterol in tea oil	In hypercholesterolemic hamsters, tea oil reduced TC, non-HDL-C, and TG as well as grape, canola, and corn oil, while had no or little effect on HDL-C.	Up-regulate SREBP-2 and LDL-R. Tea oil-fed hamsters excreted less neutral but greater acidic sterols.	(Guan et al., 2011)
Seed oil mixture of flax/sesame and flax/peanut	Oleic acid, linoleic acid, and linolenic acid	In rats, seed mixture ameliorated lipid parameters, such as TG and LDC-C, and improved the efficiency of antioxidant defense system.		(Makni et al., 2010)
Bamboo shoot oil	LA (28.14%) and ALA (17.57%), phytosterols (28.74%).	In rats, decreased serum TC, TG, LDL-C, hepatic lipase, liver lipids, and relative liver weight. Increased fecal cholesterol and plasma phytosterols.	The mechanisms were speculated to be the inhibition of cholesterol absorption and increase of cholesterol excretion.	(Lu et al., 2010)
Flaxseed oil	Rich in Oleic acid (20.7%), LA (14.8%) and ALA (53.1%)	Compared with coconut oil and butter, flaxseed oil reduced serum lipid, liver size, and hepatic TC and TG, attenuated nonalcoholic fatty acid liver and increased fecal TG and TC in hyperlipidemic hamster.	Increased LDL-R and CYP7A1 expression. Reduced liver damage index: glutamic oxaloacetic transaminase and glutamic pyruvic transamiase, and higher glutathione and lower malondialdehyde in liver.	(Tzang et al., 2009; Yang et al., 2009)
Phospholipid-rich dairy milk extract	Phospholipids (47.9%)	In high-fat fed mice, decreased liver weight, liver TG and TC, serum TG, TC, and phospholipid.	Decreased mRNAs of enzymes involved in fatty acid synthesis, such as ACC, ELOVLF, FAS, and SCD-1, as well as CYP7A1.	(Wat et al., 2009)
Microalgae ethyl ester of DHA	DHA, EPA	In rats fed a high-fructose diet, compared to corn oil, DHA and EPA reduced TG and TC.		(Ryan et al., 2009)

are phenolics (polyphenols). Polyphenols are the most abundant antioxidants in diets and important constituents of fruits, vegetables, cereals, and beverages, such as tea, coffee, and wine. Several thousand polyphenols have been identified in plants so far. Some groups among them, such as phenolic acids, flavonoids, stilbenes and lignans, draw a lot of attention for their beneficial effects against degenerative disease, such as cancer and CVD (Manach et al., 2004). Flavonoids share a common structure consisting of two aromatic rings (A and B) linked together by three carbon atoms that form an oxygenated heterocycle (ring C). Differences in ring C divide flavonoids into six subclasses: flavonols (i.e., quercetin and kaempferol), flavones (i.e., luteolin and apigenin), flavanols (i.e., catechins and proanthocyanidins), flavanones, anthocyanidins, and isoflavonoids (phytoestrogens) (Liu, 2004; Manach et al., 2004).

It is well known that polyphenols have potent antioxidant activity which may prevent free radical damage to macromolecules. But the extent and precise role played by polyphenols in human health is yet to be elucidated.

Polyphenols in Tea

Tea is a popular beverage brewed from the leaves of *Camellia sinensis*. It can be classified according to the level of polyphenols oxidation, i.e., green tea (nonoxidized), oolong tea (partially oxidized), and black tea (oxidized). In green tea, the most abundant flavonoids are tea catechins, which consist mainly of epigallocatechin-3-gallate (EGCG) (account for 50–80% tea catechins), epicatechin-3-gallate (ECG), epigallocatechin (EGC), epicatechin (EC), and catechin. In black tea, about half of the tea catechins are converted to theaflavins and thearubigins (Crespy and Williamson, 2004).

Epidemiological, clinical, and experimental data have demonstrated the positive relationship between green tea consumption and cardiovascular health (Velayutham et al., 2008). In a meta-analysis of five studies on green tea, a significant association was indicated between highest green tea consumption and reduced risk of coronary artery disease, and an increase in green tea consumption of 1 cup/d was associated with a 10% decrease in the risk of coronary artery disease (Wang et al., 2011). But meta-analysis of 13 studies on black tea did not support a protective role against coronary artery disease (Wang et al., 2011). A recent meta-analysis of 14 randomized controlled trials showed that consumption of green tea beverages or extracts significantly lowered serum TC by 7.2 mg/dL and lowered LDL-C by 2.19 mg/dL, while no significant effect on HDL-C was observed (Zheng et al., 2011).

As major polyphenolic compounds, tea catechins, especially EGCG, may exert cardioprotective effects through multiple mechanisms, such as antioxidative, anti-hypertensive, anti-inflammatory, antiproliferative, antithrombogenic, and hypolipidemic effects (Velayutham et al., 2008). For the hypolipidemic effects, several mechanisms are proposed based on animal and cellular experiments. First, tea polyphenols hindered emulsification, hydrolysis, and micellar solubilization of lipids thus interfering intestinal lipid absorption (Shishikura et al., 2006). Tea catechins inhibited the activity of pancreatic lipase dose-dependently, therefore suppressing intestinal TG absorption (Ikeda et al., 2005; Wang et al., 2006). Ikeda et al. (2010) showed that black-tea polyphenols rich in theaflvins and tea catechins decreased *in vitro* micellar solubility of cholesterol dose-dependently and inhibited intestinal absorption of cholesterol in rats. Second, tea catechins inhibit biosynthesis of cholesterol and fatty acid (Lu and Hwang, 2008). Tea catechins inhibited rat squalene epoxidase, a likely rate limiting enzyme of cholesterol biosynthesis (Abe et al., 2000). EGCG is a FAS inhibitor *in vitro* (Puig et al., 2008) and potently inhibits the *in vitro* activity of HMGR (*Ki* in the nanomolar range), by competitively binding to the cofactor site of the reductase (Cuccioloni et al., 2011). Pu-erh tea extract rich in EGCG and ECG attenuated lipogenesis in HepG2 cells through activating AMPK through the LKB1 pathway and thus inhibiting expression of FAS and ACC (Way et al., 2009). Green and black tea extracts inhibited HMGR and activated AMPK to decrease cholesterol synthesis in rat hepatoma cells (Singh et al., 2009). Third, tea catechin enhanced clearance of plasma LDL-C by elevating hepatic LDL-R expression and activity in rats (Bursill and Roach, 2007; Lee et al., 2008b). Fourth, EGCG was shown in differentiated 3T3-L1 adipocytes to decrease intracellular lipid accumulation probably through activating hormone sensitive lipase to catalyze the hydrolysis of stored TG (Lee et al., 2009). Lastly, tea catechins enhance elimination of cholesterol through bile acid excretion. In HepG2 cells, EGCG, ECG, EGC, and EC upregulated the CYP7A1 mRNA (Lee et al., 2008a). Tea catechins may hinder intestinal bile acid reabsorption through inhibition of ileal apical sodium-dependent bile acid transporter (ASBT), the transporter responsible for reabsorption of bile acids. In experiments with human embryonic kidney HEK-293 cells stably transfected with ASBT-V5 fusion protein and intestinal Caco-2 monolayers, EGCG inhibited ASBT activity significantly (Annaba et al., 2010). But further *in vivo* experiments are needed to verify these mechanisms.

Polyphenols in Wine and Olive Oil

Mediterranean diets, known for being associated with cardiovascular protection, are characterized by high consumption of vegetables and fruits rich in antioxidant phenolics, as well as olive oil and red wine (Massaro et al., 2010).

Epidemiological observations have showed that moderate wine drinkers have lower cardiovascular morbidity and mortality rates than heavy drinkers or teetotalers (Di Castelnuovo et al., 2002). Other than the contribution from alcohol, most of the beneficial effects of red wine against CVD were attributed to resveratrol (3,4′,5-trihydroxy-trans-stilbene) and other wine polyphenols, such as proanthocyandins, quercetin, catechins, and tannins, which are derived from grapes. In spite of not fully understood, the basic mechanisms involved protection from oxidative stress, facilitating nitric oxide production, and

modulating the expression of adhesion molecules (Kroon et al., 2010; Gresele et al., 2011).

The hypolipidemic activity of grape polyphenols was shown in some animal models to lower LDL-C and increase HDL-C (Auger et al., 2002; Zern et al., 2003; Frederiksen et al., 2007). But the human studies are limited and inconclusive. In a study of pre- and postmenopausal women, lyophilized grape powder lowered plasma TG, LDL-C, and apolipoproteins B and E significantly (Zern et al., 2005). Furthermore, cholesterol ester transfer protein (CETP) activity was decreased too. In a study of hemodialysis patients and healthy subjects, concentrated red grape juice caused a significant decrease in LDL-C and apolipoprotein B-100, while increasing concentrations of HDL-C and apolipoprotein A-I in both subjects (Lasuncion et al., 2006). Recently, the hypocholesterolemic activity of grape seed proanthocyanidin was showed in hamsters, and it was concluded to be most likely medicated by enhancement of bile acid excretion and up-regulation of CYP7A1 (Jiao et al., 2010). Berrougui et al. (2009) showed by *in vitro* experiments that resveratrol enhanced apoA-1-mediated cholesterol efflux by upregulating ABCA-1 receptors, and reduced cholesterol influx or uptake in J774 macrophages.

The health-promoting properties of olive oil have traditionally been attributed to oleic acid (omega-9 mono-unsaturated fatty acid, 18:1 n-9). However, current knowledge indicates that polyphenols such as hydroxytyrosol play important roles in fortifying health (Granados-Principal et al., 2010). As a phenolic acid, hydroxytyrosol decreased TC and TG, while increased HDL-C in hyperlipidemic rabbits and rats (Gonzalez-Santiago et al., 2006; Fki et al., 2007; Jemai et al., 2008, 2009), which may contribute to the cardioprotection effects of olive oil. But clinical trials of purified polyphenols are scant and the responsive mechanisms are still not distinct.

Isoflavonoids (phytoestrogens)

Soybean isoflavones (genistein, daidzein, glycitein, and their glycosides) are the mostly consumed phytoestrogens in humans. Their beneficial effects have been shown in meta-analysis of human trials, such as significantly decreasing blood pressure, being associated with reduced risk of breast cancer, and increasing bone mineral density in menopausal women (Taku et al., 2010a, 2010b; Dong and Qin, 2011). But their hypolipidemic effects are inconsistent in human studies. When provided concurrently with soy protein, soy isoflavones exert synergistic or additive cholesterol-lowering effects (Zhuo et al., 2004; Zhan and Ho, 2005). In a meta-analysis of 11 randomized controlled trials, soy isoflavones significantly reduced serum TC and LDL-C but did not change HDL-C and TG, while reductions in LDL-C were larger in hypercholesterolemic than in normocholesterolemic subjects (Taku et al., 2007). But in a later meta-analysis, about 70 mg extracted soy isoflavones/day did not significantly improve TC and LDL-C levels in normocholesterolemic menopausal women (Taku et al., 2008). And in a recent study, a soy-derived isoflavone-enriched diet did not suggest a hypocholesterolemic effect in hypercholesterolemia children (Zung et al., 2010). Further research is needed to explore their hypolipidemic effects.

Puerarin is an isoflavone derived from Kudzu roots. Its antioxidant and hypocholesterolemic effects were shown in HepG2 cells and rodents, and may be achieved by multiple mechanisms including increasing LDL uptake, reducing cholesterol biosynthesis, and possibly enhancing cholesterol degradation (Guan et al., 2006; Chung et al., 2008). But more clinical studies are needed to clarify its hypolipidemic effect in human.

During the past few years, extensive investigations of dietary polyphenols (i.e., from fruits, nuts, seeds, leaves, and flowers) on their hypolipidemic effects and responsible mechanisms have been carried out in animal models (i.e., rat, mouse, and hamster) and cell lines (i.e., HepG2, Caco2, adipocyte, and preadipocyte 3T3-L1). Examples are summarized in Table 2. However, clinical trials of dietary polyphenols in the management of hyperlipidemia are scarce and further researches are needed to explore their bioavailability and toxicity in human.

Other Phytochemicals

Policosanols

Policosanol is a mixture of very long chain aliphatic alcohols derived from the wax constituent of sugarcane, grains, rice bran, beeswax, and peanut (Cherif et al., 2010). Its hypolipidemic effect was suggested to act via enhancing the activity of AMPK through phosphorylation and inhibiting HMGR activity in animal model and cell lines (Oliaro-Bosso et al., 2009; Banerjee et al., 2011). But the efficacy is not consistent in human and some animal trials (Dulin et al., 2006; Greyling et al., 2006; Kassis et al., 2007; Francini-Pesenti et al., 2008) thus raising questions regarding its true efficacy (Marinangeli et al., 2010).

Organosulfur Compounds

Garlic is widely shown in animal trials to be hypolipidemic, and the organosulfur compounds in garlic, for example, allicin, were proposed to inhibit HMGR activity and/or CETP activity to improve lipid parameters (Liu and Yeh, 2002; Kwon et al., 2003). However, the impact of garlic on human lipid parameters is controversial (Khoo and Aziz, 2009; Reinhart et al., 2009). Recently, hypocholesterolemic effect of other organosulfur compounds, glucosinolates and isothiocyanates from broccoli sprouts, was shown in hamsters (Rodriguez-Cantu et al., 2011).

Monacolin K

Chinese red yeast rice, a natural food obtained after fermenting rice with *Monascus purpureus*, is consistently proved to be effective to lower cholesterol in both animal models and human trials (Li et al., 1998; Liu et al., 2006; Bogsrud et al., 2010; Kalaivani et al., 2010). Monacolin K and its related substances are the major active compounds in red yeast rice and they

Table 2 Examples of food-related polyphenols in the management of hyperlipidemia

	Source	Active ingredients	Efficacy in animal model and/or clinical studies	Investigated mechanisms	Efficacy in cell model and/or in vitro activity	Reference
Apple	Polyphenol from unripe apple	Procyanidins	In rats, decreased liver and serum TC, while increased serum HDL-C.	Increase hepatic CYP7A1 activity and fecal acidic and neutral steroids.		(Osada et al., 2006)
	Apple polyphenol extract	Oligomeric procyanidins	Simultaneous ingestion of apple polyphenol and TG significantly inhibited increase of plasma TG in mice and human.	Inhibited TG absorption by inhibiting pancreatic lipase activity.	Inhibition on pancreatic lipase increased according to degree of polymerization of procyanidins.	(Sugiyama et al., 2007)
	Polyphenols from apple pomace	Catechin, chlorogenic acid, phloridzin, proanthocyanidin B2, EC, quercein, rutin, etc.	In hamsters, increased HDL-C and decreased non-HDL-C, reduced plasma TG at high dosage.	Suppressed plasma CETP activity.	In vitro assays confirmed that apple polyphenols inhibited CETP activity dose-dependently.	(Lam et al., 2008)
Citrus	*Citrus* Juice	Naringin, neoeriocitrin, and neohesperidin	In rats, reduced serum TC, TG, LDL-C, and increase HDL-C.	Increased radical scavenging activity and fecal neutral sterols and bile acid.		(Miceli et al., 2007)
	Citrus depressa Hayata peel extract	Nobiletin; tangeretin	In obese mice, decreased body weight gain, white adipose tissue weight, plasma TG, and leptin. Reduce sizes of the adipocytes.	Decrease adipose tissue mRNA of lipogenesis-related genes: ap2, SCD1, ACC1, fatty acid transport protein, and DGAT1.		(Lee et al., 2011)
Other fruits	Tart cherry	Peonidin 3-glucoside, Isorhamnetin rutinoside, Kaempferol, Quercetin, cyanidine-3-rutinoside, Cyanidin 3-glucosylrutinoside	In insulin resistance and hyperlipidemia rats, whole tart cherry reduced blood glucose, hyperlipidemia, hyperinsulinemia, and hepatic TG and TC.	Enhanced hepatic PPARα and ACO mRNA and activity. Increased plasma antioxidant capacity.		(Seymour et al., 2008)
	Marula juice	Hydrolyzable tannins, catechins, hydroxycinnamic acid derivatives	In healthy humans, reduced serum TC, TG, LDL-C, and oxidative stress, increased serum HDL-C			(Borochov-Neori et al., 2008)
	Mulberry (*Morus alba* L.) extracts	Protein (19.3%), carbohydrate (54.4%), polyphenol (10.3%): cyanidine-3-glucoside, cyanidine-3-rutinoside, etc.	In hamsters fed high fat/cholesterol diets, reduced plasma and hepatic TC and TG.		In HepG2 cells, upregulated LDL-R mRNA and uptake ability of LDL; decreased HMGR, FAS, and GPAT expressions.	(Liu et al., 2009)
	Young persimmon	Tannin, dietary fiber	In mice, lowered hepatic lipids and serum TC. Enhanced fecal bile acid.	Up-regulated SREBP-2, CYP7A1, and LDL-R gene expression.	Young persimmon and its tannin extract absorbed cholic acid.	(Matsumoto et al., 2010)
Nut	Polyphenol-rich extract from walnut	Pedunculagin (5.8%), ellagic acid(5.2%) tellimagrandin I (2.8%), tellimagrandin II	In high fat diet fed mice, reduced liver weight and hepatic and serum TG.	Enhanced hepatic β-oxidation of fatty acid, increased mRNA of hepatic PPARα and ACO1.	Enhanced mRNA expression of PPARα, ACO1, and CPT1A in HepG2 cells.	(Shimoda et al., 2009)
Seed	Coffee bean extract	10.0% caffeine and 27.0% chlorogenic acid	Decreased body weight gain, white adipose tissue weight, serum, and liver TG in rats.	Decreased fatty acid synthetic enzymes activity and increased fatty acid oxidation enzymes in the liver.		(Tanaka et al., 2009)

(Continued on next page)

Table 3 Examples of food-related polyphenols in the management of hyperlipidemia *(Continued)*

	Source	Active ingredients	Efficacy in animal model and/or clinical studies	Investigated mechanisms	Efficacy in cell model and/or in vitro activity	Reference.
	Cocoa powder	Catechins and procyanidins such as: (-)-epicatechin, procyanidin B2, (+)-catechin, procyanidin C1, and cinnamtannin A2			In HepG2/Caco2 cells, increased ApoA1 and slightly decreased ApoB protein and mRNA. Increased SREBPs expression and LDL-R activity in HepG2 cells.	(Yasuda et al., 2011)
	Tartary buckwheat bran extract	Rutin and quercetin	In hyperlipidemic rats, reduced TG and TC in serum and liver, raised serum GSH-Px activity, lower serum malondialdehyde.			(Wang et al., 2009a)
Leaf	Ethanol extract from *Perilla Frutescens* leaves	Flavonoids: apigenin and luteolin	In hyperlipidemia rats/mice, decreased serum TC, TG, LDL-C, adipose tissue lipid accumulation; increased serum HDL-C. Inhibited lipid oxidation / liver steatosis.	Increase ApoA/ApoB, antioxidant enzyme (SOD, GSH-Px) activity. Down-regulated ACC, GPDH, PPARγ expression in adipose tissue.		(Feng et al., 2011)/(Kim and Kim, 2009)
	Nelumbo nucifera leaf water extract	phenolic acids (13.5%), flavonoids (58.3%), polysaccharides (15.2%). gallic acid, rutin, protocatechuic acid, catechin, gallocatechin gallate, caffeic acid, epicatechin, quercetin	In high fat diet fed mice, reduced body weight, body lipid accumulation, serum free fatty acid, TG and TC, and liver TG and TC.	Reduced activity of FAS, glutamic oxaloacetic transaminase and glutamic pyruvic transaminase. Suppressed protein expression of FAS, ACC and HMGR. Increased phosphorylation of hepatic AMPK.		(Wu et al., 2010)
	water extract of *Nelumbo nucifera* leaf	Gallic acid, protocatechuic acid, catechin, EGC, EGCG, caffeic acid, EC, rutin, and quercetin	In rabbits fed with high cholesterol diet, reduced TG and LDL-C, and reduced atherosclerosis.			(Lee et al., 2010)
	Hibiscus sabdariffa polyphenols	Protocatechuic acid (24.24%), catechin (2.67%), gallocatechins (2.44%), caffeic acid (19.85%), and gallocatechin gallates (27.98%)	In hamsters, decreased serum TG, TC and LDL-C, increased HDL-C. Decreased liver TC and TG.		Reduced TG, TC in HepG2 cells via activation of AMPK and reduction of SREBP-1, thus inhibited FAS and HMGR expression. Enhanced LDL-R expression and activity.	(Yang et al., 2010c)
	Ethanol extracts from ssuk	Phenolic compounds			Decreased TG in 3T3-L1 cells, suppressed adipogenesis related genes: PPARγ, aP2, ACC, GPDH.	(Kim et al., 2010)

Flower	Litchi flower water extract	Phenols, flavonoid, proanthocyanidins, tannins, anthocyanins	In high-fat/cholesterol-dietary hamsters, lowered serum lipid, cardiac index, and hepatic lipids.	Increased LDL-R, PPARα, and lowered FAS gene expression. Increased fecal lipid and bile acid excretion.		(Yang et al., 2010b)
	Longan flower water extract	Gallic acid, catechin, gentisic acid, ferulic acid, EC, chlorogenic acid, and rutin	In hypercaloric-dietary rats, decreased body weight, fat size, hepatic lipids, serum TG, and atherogenic index.	Reduced pancreatic lipase activity, SREBP-1c and FAS gene expression. Increased LDL-R and PPARα gene expression, and fecal TG.		(Yang et al., 2010a)
Rhizome	Extract of *Curcuma longa* (turmeric)	Curcuminoids: demethoxycurcumin, bisdemethoxycurcumin, and curcumin	In rats fed a high-cholesterol diet, decreased plasma TC and LDL-C, increased HDL-C; decreased hepatic lipid and fatty liver.	Increased CYP7A1, LDL-R and hemoxygenase1 mRNA expression, decreased HMGR expression.		(Yiu et al., 2011)
Other source	Ethanol extract of propolis	Flavonoids, artepillin C, and drupanin	In mice, reduced body weight gain, adipose tissue, liver and serum TG, TC and nonesterified fatty acids.	Reduced mRNA expression of FAS, ACC, and SREBPs.		(Koya-Miyata et al., 2009)
Pure phenolics	Quercetin, rutin, and ferulic acid	Quercetin dihydrate, rutin and ferulic acid	Compared with rutin and ferulic acid, only quercetin lower serum TC, and phospholipid in mice.	Quercetin reduced activity and mRNA of enzymes involved in hepatic fatty acid synthesis.		(Odbayar et al., 2006)
	Rutin and *o*-coumaric acid	Rutin and *o*-coumaric acid respectively	In rat prefed high-fat diet, decreased body, liver, adipose tissue weights, serum lipid, leptin, and insulin; and lowered hepatic TG, TC.	In liver, reduced oxidative stress, glutathione disulfide; increased glutathione, GSH-Px, glutathione reductase, and GST.		(Hsu et al., 2009)
	Berry-derived anthocyanin	Anthocyanins	In 120 dyslipidemic patients, 160 mg anthocyanins consumption twice daily increased HDL-C and decreased LDL-C.	Increased cellular cholesterol efflux to serum, decreased the mass and activity of plasma CETP.	In vitro, cyanidin 3-O-β-glucosides lowered CETP activity in HepG2 cells dose dependently.	(Qin et al., 2009)
	Naringenin	Naringenin, a flavonoid present in grapefruit	In rats, reduced plasma and hepatic TG and TC, lowered adiposity and TG in adipose tissue.	Increased hepatic protein expression of PPARα, uncoupling protein 2 and CPT1L. Enhanced fatty acid oxidation.		(Cho et al., 2011)

are chemically resembled to cholesterol-lowering drugs, statins, as effective HMGR inhibitors (Heber et al., 1999). Other constituents in red yeast rice, such as unsaturated fatty acids, phytosterols, flavonoids, and threonine derivatives may also contribute to the hypocholesterolemic effects (Jeun et al., 2008; Kalaivani et al., 2010). Recent experiments in 3T3-L1 cells showed that *Monascus* secondary polyketide metabolites, monascin, and ankaflavin, inhibited the differentiation of preadipocytes and stimulated basal lipolysis of mature adipocytes to avoid the accumulation of lipid (Jou et al., 2010).

Whole Food or Raw Extract

The hypolipidemic effects of onion and welsh onion drew a lot of attention in the past few years (Park et al., 2009a, 2009b; Vidyashankar et al., 2009; Vidyavati et al., 2010; Yamamoto and Yasuoka, 2010). Guan et al. (2010) showed that the hypocholesterolemic activity of onion was mediated by enhancing excretion of fecal sterols in hamsters, while the specific ingredients were unidentified. Sung et al. (2011) found that the antiobesity activity of *Allium fistulosum* L. extract was mediated by downregulation of lipogenic genes in mice.

The hypolipidemic activity of fermented milk, such as yogurt and kefir is conflicting probably due to the diversity of active components (Guzel-Seydim et al., 2011). Hypocholesterolemic effects of live and dead *Lactobacillus plantarum* KCTC3928 were compared in mice and live bacteria significantly lowered plasma TG and LDL-C and accelerated fecal bile acid excretion through upregulation of CYP7A1 (Jeun et al., 2010).

The effects of several dietary mushrooms on lipid metabolism were examined. *Pleurotus eryngii* water extract showed significant inhibitory activity against pancreatic lipase *in vitro* and in mice suppressed the elevation of plasma and chylomicron TG after oral administration of corn oil, which may be due to low absorption of fat (Mizutani et al., 2010). Ethanol extract of Yamabushitake mushroom was an agonist of PPARα *in vitro* and in mice improved lipid metabolism mediated at least in part via activation of PPARα (Hiwatashi et al., 2010).

The hypolipidemic effect of Hawthorn fruit (*Crataegus pinnatifida*) has been long suggested (Chen et al., 1995; Zhang et al., 2002) and recent experiments in hamsters and 3T3-L1 cell lines showed that Hawthorn fruit activated PPARα to improve dyslipidemia or obesity (Kuo et al., 2009).

In addition to the examples mentioned above, hypolipidemic effect has also been demonstrated in extract of ginseng (ginsenoside), fenugreek seeds, rice bran, and fat free peanut flour (Revilla et al., 2009; Chung et al., 2010; Quan et al., 2010; Stephens et al., 2010; Vijayakumar et al., 2010; Yuan et al., 2010; Yeo et al., 2011).

CONCLUSION

The hypolipidemic effects of ω-3 PUFA, phytosterols, dietary fiber, and tea catechin have been clearly demonstrated in many epidemiological studies and interventional trials. Based on the current knowledge of lipid homeostasis, studies on mechanism reveal that they act as inhibitor or activator of critical enzyme, agonist, or inhibitor of transcription factor, competitor of transporter, and sequestrant of bile acid to regulate lipid metabolism. Whether higher regulation, for example by protein hormone such as adiponectin and leptin, is involved deserves further investigation. And global nutrigenomic analyses may provide novel physiological effects and mechanisms of dietary ingredients in the future (Fukasawa et al., 2010).

Hypolipidemic effects are also claimed in dietary proteins, many polyphenols, other phytochemicals, raw extract, or even whole food. However their efficacy in human studies is inconclusive, which need to be verified in more randomized controlled trials. And the active constituents and responsive mechanism should be investigated in the future. Many recent findings focus on the hypolipidemic effect of polyphenols derived from plant (Fig. 2), which justifying the benefit of consuming fruit, vegetable, nut, and whole grains. Other than the well-known antioxidant activity to protect low-density lipoprotein from oxidation, some polyphenols directly target on different transporters, enzymes and transcription factors to modulate lipid metabolism, which may contribute to their hypolipidemic activity. Better knowledge of the bioavailability and toxicity in human is essential for exploring the health benefits of polyphenols. And combination of functional foods and nutraceuticals with different hypolipidemic mechanisms may improve health in a complementary and synergistic way.

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ABBREVIATIONS

ABCA1, ABCG1, ABCG5/G8	= ATP-binding cassette transporters
ACAT	= acyl CoA:cholesterol acyltransferase
ACC	= acetyl-CoA carboxylase
ACO	= acyl-CoA oxidase
ALA	= α linolenic acid
AMPK	= AMP-activated protein kinase
apoA	= apolipoprotein A
apoB	= apolipoprotein B
aP2	= activating protein 2
CETP	= cholesteryl ester transport protein
ChREBP	= carbohydrate response element binding protein
CPT	= carnitine palmitoyl transferase
CVD	= cardiovascular disease
CYP7A1	= cholesterol 7α-hydroxylase

DGAT1 = diacylglycerol acyltransferase 1
DHA = docosahexanoic acid
DPA = docosapentaenoic acid
EC = epicatechin
ECG = epicatechin-3-gallate
EGC = epigallocatechin
EGCG = epigallocatechin-3-gallate
ELOVLF = elongation of very long chain fatty acids
EPA = eicosapentanoic acid
FAS = fatty acid synthetase
FXR = farnesoid X receptor
GPAT = glycerol-3-phosphate acyltransferase
GPDH = glycerol-3-phosphate dehydrogenase
GSH-Px = glutathione peroxidase
GST = glutathione S-transferase
HDL = high-density lipoprotein
HDL-C = high-density lipoprotein cholesterol
HMGR = 3-hydroxy-3-methylglutaryl-CoA reductase
LA = linoleic acid
LDL = low-density lipoprotein
LDL-C = low-density lipoprotein cholesterol
LDL-R = low-density lipoprotein receptor
LXR = liver X receptor
MGLL = monoglyceride lipase
NPC1L1 = Niemann-Pick C1-Like 1
PPAR = peroxisome proliferator–activated receptor
SCD1 = stearoyl-CoA desaturase-1
SOD = superoxide dismutase
SREBP = sterol regulatory element binding protein
TC = total cholesterol
TG = triglyceride
VLDL = very low density lipoprotein

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