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REVIEW

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Research progress in lipid metabolic regulation of bioactive peptides

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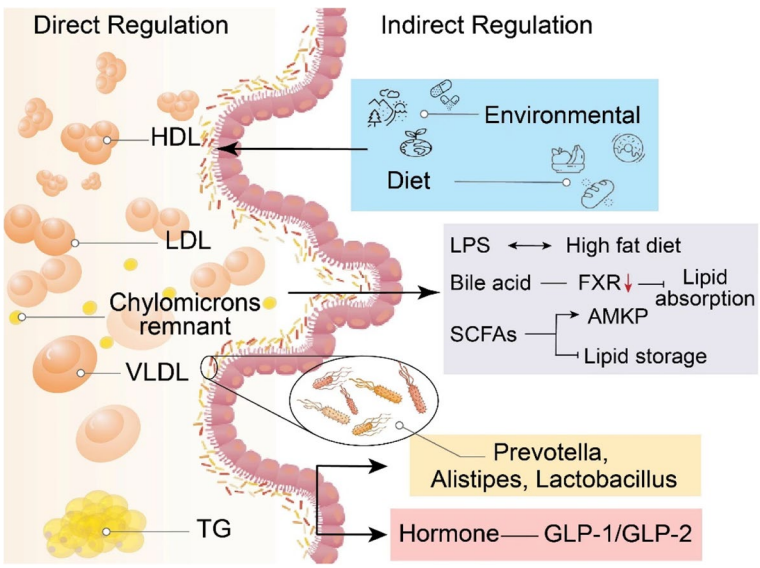
Abstract

Hyperlipidemia poses a serious threat to human health and evaluating the ability of natural active substances to regulate disorders of lipid metabolism is the focus of food functionality research in recent years. Bioactive peptides are distinguished by their broad range of sources, high nutritional content, ease of absorption and use by the body, and ease of determining their sequences. Bioactive peptides have a wide range of potential applications in the area of medicines and food. The regulation of lipid metabolism disorder caused by bioactive peptides from different sources provides a reference for the development and research of bioactive peptides for lipid reduction.

Keywords Bioactive peptides, Lipid metabolism, Intestinal microbial

Graphical Abstract



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Introduction

Hyperlipidemia occurs when one or more lipid metabolic pathways in the blood and lipid content are deemed abnormal. It is a common cardiovascular disease that poses a serious threat to human health (Ross 2017). Increased levels of total cholesterol (TC), total triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and lower levels of high-density lipoprotein cholesterol (HDL-C) are known indicators of a lipid metabolic disorder (Ajeigbe et al. 2022). Abnormal changes in these indicators related to lipid levels may increase the organism's risk of atherosclerosis, hypertension, cardiovascular diseases, diabetes, and other related metabolic disorders, and therefore, is a key for the prevention of chronic diseases like metabolic syndrome (Oluwajuyitan et al. 2021; Huang et al. 2022). Dietary modifications and an appropriate increase in exercise can be used to effectively treat early abnormalities of lipid metabolism. However, due to unhealthy diets and lifestyles, including high sugar, high-fat, and high-calorie diet and a sedentary lifestyle with a lack of exercise, it is difficult to improve lipid metabolism disorder only through dietary intervention and exercise, and these methods requiring high-self control show less compliance (Li et al. 2021).

Common clinical lipid drugs include statins (like lovastatin, simvastatin, rosuvastatin, fluvastatin, fluvastatin, and atorvastatin), fibrates (like clobetl, bento, and fenofibrate), fibrate drugs (like clobebetl and gefbetil), and bile acid chelators (i.e., ketamine, test lidine, and cholilumine), which reduce the lipid level in vivo but are ineffective against oxidative stress and fundamental effect of lipid metabolism. These anti-lowering lipid drugs usually exert side effects unrelated to the purpose of treatment, like gastrointestinal irritation, myolytic symptoms, and liver and kidney function damage (Durkar et al. 2014; Wa et al. 2019). As a result, several researchers are evaluating ways to improve or treat lipid metabolic problems using natural active ingredients.

Bioactive peptides are composed of 2–50 amino acid residues, which form structures ranging from dipeptides to complex linear and annular configurations with different combinations and arrangements (Stoye et al. 2017). The biological activities of proteins are realized through their encoded peptide sequences, which usually express unique physiological functions in food processing (from room to high temperature), enzymatic reaction, microbial fermentation, and other processes (Chakrabarti et al. 2018; Chalamaiah et al. 2018; Xu et al. 2022). The sources of bioactive peptides mainly include natural bioactive peptides found in organisms, the active peptides obtained by the enzymatic digestion of the proteins, and synthetic bioactive peptides. The activity of the bioactive peptides typically depends on the electrostatic charge, amino acid composition and sequences, peptide chain length, and hydrophobicity of the molecular surface (Chalamaiah et al. 2018). To date, various physiological functions of bioactive peptides have received extensive research attention. The discovery of biological activities like lipid-lowering, blood pressure-lowering, and antithrombotic properties provides theoretical support for related studies of bioactive peptides (Cian et al. 2015; Wu et al. 2015; Zheng et al. 2020). This review collates the roles and mechanisms of peptides obtained from beans, cereals and tubers, nuts, aquatic animals, seaweed, eggs and milk, livestock organs or tissues, and other substances in the regulation of lipid metabolism (Table 1), for further development of bioactive peptides as potential lipid-lowering functional food or medicine.

Lipid metabolism pathways

The homeostasis in lipid transport and metabolism is regulated by multiple signaling pathways, including the adenylate-activated protein kinase (AMPK), phosphatidylinositol-3-kinase (PI3K), protein kinase B (Akt), mitogen-activated protein kinase (MAPK), peroxisome proliferator-activated receptor (PPAR), and insulin signaling cascades. These pathways maintain the body's lipid metabolic balance by exerting complex regulatory effects on each other. Among them, the PPAR and AMPK/SREBPs pathways with PPAR and AMPK as the core, respectively, play important regulatory roles in stabilizing the body's lipid levels and lipid metabolism (Fig. 1) (Fogarty & Hardie 2010). The regulation of the PPAR signaling system is implicated in atherosclerosis, obesity, insulin resistance, and cancer, and is known to affect lipid and energy metabolism. The SREBP-1 protein is an important transcription factor in liver cells, controlling several genes involved in cholesterol and lipid metabolism. Additionally, microRNAs have been increasingly demonstrated to play a significant role in aberrant lipid metabolism and associated disorders by controlling the expression of genes. Many microRNAs can directly or indirectly regulate the expression of SREBPs and PPAR, thereby affecting lipid metabolism (Cagen et al. 2005; Fogarty & Hardie 2010; Fleischmann & Iynedjian 2000).

Cholesterol metabolism

The liver and the small intestine are the two most critical organs involved in the entire process of cholesterol metabolism (Ahmadi et al. 2018). The function of the liver includes the synthesis of cholesterol, conversion into bile acids, and lipid reabsorption and metabolism in the body. Cholesterol balance in the liver is collectively regulated by SREBPs and liver X receptors (LXRs), whereby the former regulates cholesterol absorption by the liver, while the latter regulates cholesterol excretion from the

Table 1 Bioactive peptides from different sources regulate lipid metabolism

Source of peptides	Function	Peptide sequence
Bean peptides		
Bean dipeptides	Reduced TG synthesis ApoB secretion	KA, VK, SY
Soybean peptides	Up-regulated ABCG5/ABCG8 and FGF15/19; down-regulated CYP7A1 and CYP8B1	ALEPDHRVESEGGL, SLVNNDDRDSYRLQSGDAL
Chickpea peptides	Reduced expression of HMGR for inhibition of cholesterol biosynthesis	VFVRN
Black bean protein hydrolysates	Inhibited pancreatic lipase activity; inhibited 3T3-L1 adipocyte differentiation, and lipid accumulation prevention	ND
Pinto bean hydrolysates	Inhibited lipase activity; conjugated bile acid	ND
Cereal and tuber peptides		
Quinoa protein hydrolysates	Inhibited lipid accumulation and suppressed 3T3-L1 cell differentiation through PPAR-γ	ND
Millet peptides	Inhibited lipase activity	ND
Oat peptides	Inhibited lipase activity	SPFWNINAH
De-oiled rice bran peptides	Inhibited lipase activity	FYLGYCDY
Rice bran protein hydrolysates	Restricted excretion of bile salts, exhibited cholesterol micellar binding ability, and inhibited HMGCR activity	ND
Potato protein hydrolysates	Activated AMPK pathway and reduced liver fat deposition	ND
Brewer's spent grain peptides	Inhibited cholesterol esterase and pancreatic lipase activity	WNIHMEHQDLTTME, DFGIASF, LAAVEALSTNG
Huangjiu peptides	Improved serum and liver physicochemical indexes; restoration of the diversity and structure of gut microorganisms	ND
Nutty peptides		
Walnut meal peptides	Improved serum and liver physicochemical indexes; regulation of Apo-B, Apo-A1, and CYP7A1; inhibited LCAT, HMGR, and FAS activities	ND
Cocoa proteolytic peptides	Inhibited pancreatic lipase activity; promoted excretion of TG and TC in rats	EEQR, GGER, QTGVQ, VSTDVNIE
Other plant peptides		
Olive seed protein hydrolysates	Inhibited cholesterol esterase, bile acid binding and reduced the solubility of cholesterol in micelles	ND
Chia peptides	Reduced enzymatic reaction velocity of HMGCR	ND
Cumin seed peptides	Inhibited pancreatic lipase activity, bile acid binding, and reduced the solubility of cholesterol in micelles	ND
Sunflower protein hydrolysates	Reduced the solubility of cholesterol in micelles	ND
Seabuckthorn seed peptides	Inhibited pancreatic lipase activity	EEAASLR, FR, RDR, VR, APYR, and NLLHR
Algal peptides		
Chlorella protein hydrolysates	Reduced liver TC and TG levels	ND
Spirulina platensis protein hydrolysates	Reduced weight, serum glucose, and TC; regulated PPAR, adipocytokine, AMPK, and MAPK	ND
Peptides from aquatic animals		
Cod meat peptides	Inhibited pancreatic lipase activity	GSPPPSG, KLEGDLK
Fish goby protein hydrolysates	Regulated serum TC, TG, LDL-C as well as hepatic TC and TG levels, and increased serum HDL-C content	ND
Tuna peptides	Reduced lipid components and adipogenesis in 3T3-L1 cells and expressions of C/EBP-α and PPAR-γ	ND
Ark shell protein hydrolysates	Down-regulated PPAR-γ, C/EBPα, and SREBP-1c; increased HSL and leptin expression	ND
Sea cucumber collagen peptides	Reduced TC, TG content and AI	ND
Trachinotus ovatus protein hydrolysates	Reduced TC, LDL-C and AI; increased HDL-C content	ND

Table 1 (continued)

Source of peptides	Function	Peptide sequence
Egg and milk-derived peptides		
Egg white protein hydrolysates	Regulate intestinal microorganisms	ND
Casein peptides	Regulate ABCG5, CYP7A1, and CYP8B1; improved fecal cholesterol secretion	SQSKVLPVPQK, HPHPHLSF
Cow peptides	Inhibited pancreatic lipase and cholesterol esterase activity	MMML, FDML, HLPGRG, LP
Camel casein peptides	Inhibited pancreatic lipase and cholesterol esterase activity	AAGF, FLWPEYGAL, LP, MSNYF
Kefir peptides	Decreased weight gain and fat deposition; reduced FAS protein and increased p-acetyl-CoA carboxylase protein levels; up-regulated AMPK, PPAR, and CPT-1	ND
Livestock organ or tissue peptides		
Pork and chicken skin collagen hydrolysates	Inhibited pancreatic lipase activity	ND
Collagen peptides	Reduced visceral fat content	ND
Cattle heart peptide	Reduced TC, non-HDL cholesterol, hepatic cholesterol levels, and AI; increased serum HDL-C, fecal cholesterol, and acidic steroid excretion; down-regulated ABCA1 expression; reduced cholesterol absorption in Caco-2 cells	PF
Synthetic peptides		
Synthetic tripeptides	Hypolipidemic effect on atherogenic lipoproteins; decreased the intensity of LPO; normalized the content of HDL	KEW-NH_2
D3	Reduced the weight of mice; improved leptin resistance, up-regulated the expression of UGN and inhibited appetite; increased enteromyxophilic *Ackermann* bacteria	ND
RF13	Down-regulated C/EBPα, SREBP1, and FAS	ND
PF-06409577	Reduced the level of mevalonate in plasma; reduced plasma TC and increased plasma HDL-C	ND

ND Not defined

liver. The genes regulated downstream of SREBPs mainly include enzymes related to cholesterol synthesis, like hydroxymethylglutaryl coenzyme A synthase (HMGCS), hydroxy methylglutaryl CoA reductase (HMGCR), squalene synthase (SQS), farnesyl diphosphate synthase (FDPs), and low-density lipoprotein receptor (LDLR) (Fig. 2). The downstream regulatory genes of LXRs typically include ATP-binding cassette protein A1 (ABCA1), responsible for cholesterol excretion from the liver through the cholesterol 7 α-hydroxylase (CYP7A1) axis, which plays a key rate-limiting role in the conversion of cholesterol to bile acids, following which bile is discharged from the liver and enters the small intestine. Most of the bile acid returns to the liver through the circulation between the liver and intestines and is metabolized.

The small intestine is an important organ for cholesterol absorption. When dietary and bile cholesterol excreted from the liver enter the intestinal cavity of the small intestine, Niemann pick C1 like 1 (NPC1L1) transports free cholesterol (FC) through vesicles for absorption from the intestinal cavity to the small intestine cells. After cholesterol is absorbed into the small intestinal cells through NPC1L1, some of it is transported back to the small intestinal cavity by the homologous protein of ATP-binding cassette transporter G5/8 (ABCG5/8), and subsequently converted into fecal cholesterol by intestinal bacteria and discharged from the body. The remaining cholesterol is converted into cholesteryl ester (CE) under the action of acetyl coenzyme A acetyltransferase 2 (ACAT2) and is incorporated into chylomicrons (CM) through the microsomal triglyceride transfer protein (MTP).

CM's function is the movement of cholesterol absorbed by the small intestine to the somatic cells to fuel the body's energy needs and to the liver cells for recirculation and metabolism (Liu et al. 2017). After the CM enters the blood circulation through the lymphatic vessels, apo C-II from HDL can hydrolyze the fat in the CM by lipoprotein lipase (LPL) on the capillary wall into CM residues which are reabsorbed by hepatocytes, and the cholesterol contained therein reenters the liver. The liver and small

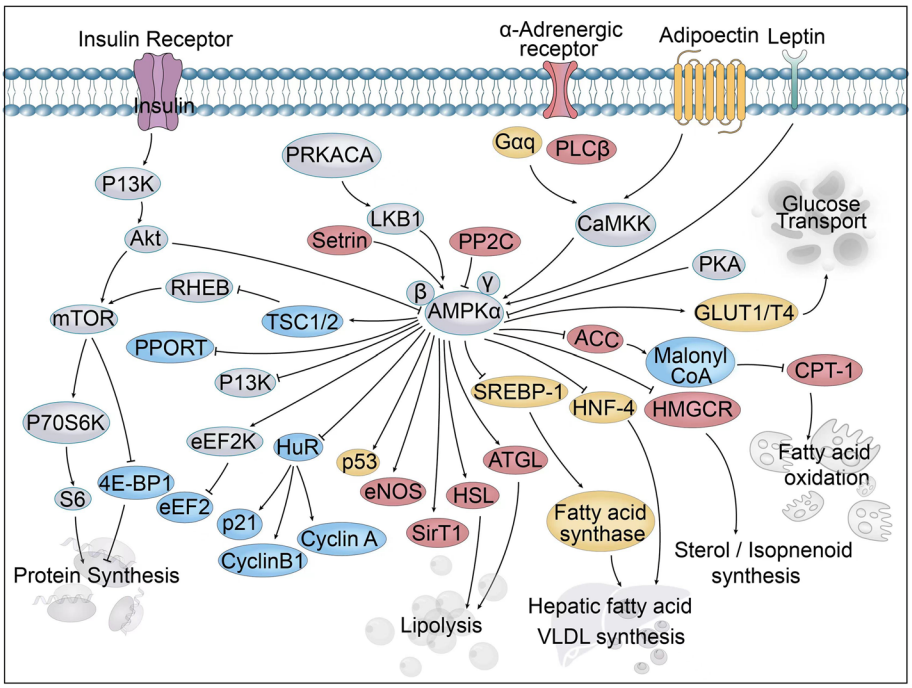

Fig. 1 Diagram showing the lipid metabolism pathways with AMPK/SREBPs as the core

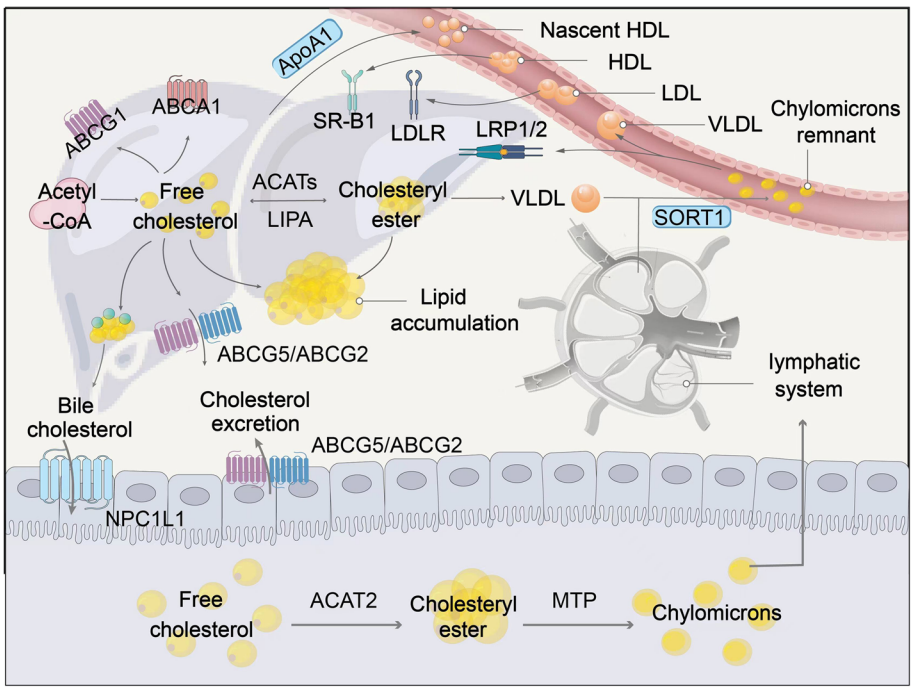

Fig. 2 Cholesterol metabolism. HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low density lipoprotein; ACAT, acyl coenzyme A-cholesterol acyltransferases; LIPA, lysosomal acid lipase A; MTP, microsomal triglyceride transfer protein

intestine interact and cooperate, and the liver-intestinal circulation promotes the metabolism and circulation of cholesterol.

TG metabolism

Two ways for the biosynthesis of long-chain fatty acids are known—one is catalyzing the conversion of acetyl-Coenzyme A (AcCoA) and malondialdehyde-Coenzyme A in the palmitate pathway by fatty acid synthetase (FAS), and the other is catalyzing the conversion of AcCoA in the malonyl-CoA pathway by the acetyl-CoA carboxylase (ACC) for the generation of TGs (van de Beek et al. 2017). Thus, reducing the synthesis of TGs in the plasma can reduce their levels at the source by inhibiting both the ACC and FAS activities. TG synthesis is positively regulated by carbohydrate reaction element-binding proteins (ChREBP) and SREBP-1c, and reduction in TG levels in liver tissues can also be achieved by inhibiting SREBP-1c expression, concomitantly reducing adipogenesis (Ge et al. 2011). TGs are subjected to adipose triglyceride lipase (ATGL), hormone-sensitive triglyceride lipase (HSL), and monoacylglycerol lipase (MGL) actions, hydrolyzed into glycerol followed by removal of trimolecular fatty acids. They are then transported via fatty acid transferase (FAT) and alkaline phosphatase (ALP) to enterocytes and re-synthesized TGs are absorbed and used by the body (Fig. 3). Thus, TG synthesis can be slowed down by inhibiting the activities of FAT and ALP. During TG metabolism, fat absorption and production can be slowed down not only by inhibiting the activity of related enzymes or stimulating related transcription factors but also by promoting fatty acid oxidation to a certain extent, reducing the internal TG levels.

Lipid metabolism and intestinal microflora

Several microorganisms in the human gastrointestinal tract play a vital role in the health of the host (Catalkaya et al. 2020). Intestinal microbes are important mediators of diet, the external environment, and various metabolic processes of the body. Given the continuous deepening of research on gut microbes, these have been implicated in the regulation of several metabolic diseases (including obesity, type 2 diabetes, tumors, non-alcoholic fatty liver diseases, cardiovascular diseases, etc.) by affecting the immune system and key metabolic pathways (Shuai et al. 2022; Chen et al. 2022). The four main phyla residing in the human gastrointestinal tract are Firmicutes (49–76%) and Bacteroidetes (16–23%), and at lower percentages, Proteobacteria and Actinobacteria (Serra et al. 2018). Compared to the healthy population, the number of intestinal microorganisms in the population with lipid abnormalities decreases significantly, and the diversity of the microbiota reduces markedly (Li et al. 2022). Bacteroidetes, Fecobacteria, *Lactobacillus*, Bifidobacteria, Ackermann mucophilia, Spirilloidetes, Eggerthella, and Butyricimonas exert positive effects on regulating the homeostasis of lipid metabolism, while Firmicutes are abundant in the intestine of obese people, which is inconducive to body's metabolism. This intestinal flora can directly regulate the absorption and digestion of

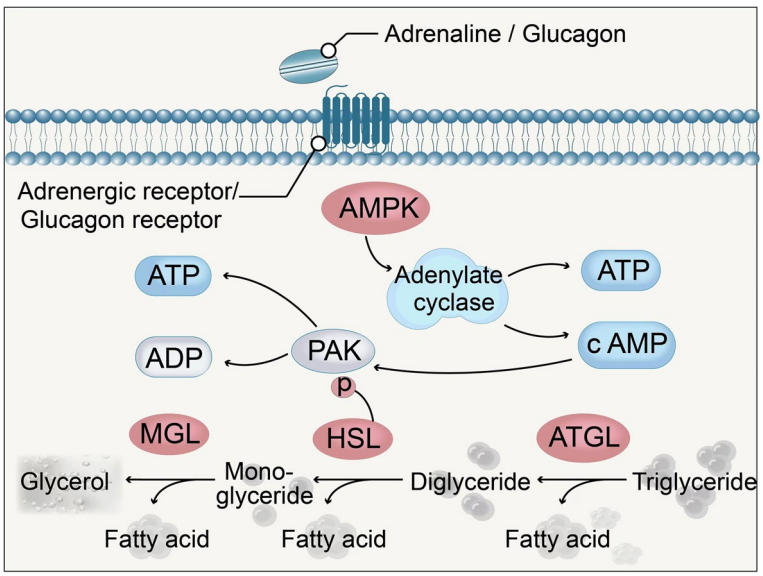

Fig. 3 Triglyceride metabolism. PAK, protein kinase A; ATGL, adipose triglyceride lipase; HSL, hormone-sensitive lipase; MGL, monoacylglycerol lipase

lipids, lipoprotein metabolism, lipid mass spectrometry indicators, and related apolipoproteins in the diet, in turn affecting lipid metabolism.

Environmental and dietary factors can stimulate the intestinal tract to produce metabolites under the action of intestinal microbial-derived metabolites, including lipopolysaccharide (LPS), bile acids, short-chain fatty acids (SCFAs), and secreted hormones, which together play an important role in regulating the intestinal flora (Yu et al. 2019). Among them, LPS interacts with a high-fat diet and is related to lipid metabolism in the liver. SCFAs can regulate lipid metabolism by upregulating the expression of AMPK. Some fatty acids with low molecular weights, like acetic acid and propionic acid, can enter the circulation to regulate the formation of adipose tissue. Intestinal flora regulates the expression of the FXR receptor, GPCR receptor, and the TGR5 signaling pathway by affecting bile acid metabolism, thus regulating lipid absorption. Hormones secreted by intestinal endocrine cells can also regulate the number of intestinal flora through the expression of glp-1/2 receptors (Fig. 4).

Regulatory effects and mechanism of peptide action of different origins on lipid metabolism disorders

Bean peptides

The lipid-lowering potential of bean peptides like those from soybean has received a lot of research attention. Inoue et al. (2011) identified three dipeptides with hypolipidemic effects, among which KA, VK, and SY reduced TG synthesis, and Ser-Tyr reduced ApoB secretion in HepG2 cells. Lee et al. (2021) isolated two bioactive peptides (ALEPDHRVESEGGL and SLVNND-DRDSYRLQSGDAL) from soybean hydrolysates and found that these peptides promoted cholesterol excretion by up-regulating the expressions of ABCG5 and ABCG8 in small intestinal cells, and inhibit hepatobiliary acid synthesis by up-regulating the expression of FGF15/19 and down-regulating those of CYP7A1 and CYP8B1. Chickpea peptides (ChPs) inhibit the activities of FAS and HMG-CoA reductase (HMGR). In an ovariectomized rat model, ChPs were found to decrease the body weight, adipose tissue size, TC, TG, LDL-C, atherogenic index (AI) in serum, and liver TC, TG levels. Serum HDL-C, bile acids in the liver and feces, and fecal TC and TG increased significantly. The expressions of peroxisomal PPARγ and SREBP-1c were down-regulated, while that of LXRα was upregulated by ChPs. Finally, VFVRN in ChPs could reduce the expression of HMGR to inhibit cholesterol biosynthesis (Shi et al. 2019a). Bioactive peptides from black bean protein hydrolysates showed strong inhibitory activities against pancreatic lipase, with IC_{50} values of 3.21 mg/mL and 1.23 mg/mL, respectively. These inhibited 3T3-L1 adipocyte differentiation and prevented lipid accumulation (Moreno et al. 2019). Five kinds of pinto bean peptides have been studied, and their lipase inhibition rates ranged from 23 to 87%. The C_5-OH, C_{11}-OH, C_{15}-OH, or C_{21}-OH sites of cholic acid and deoxycholic acid show

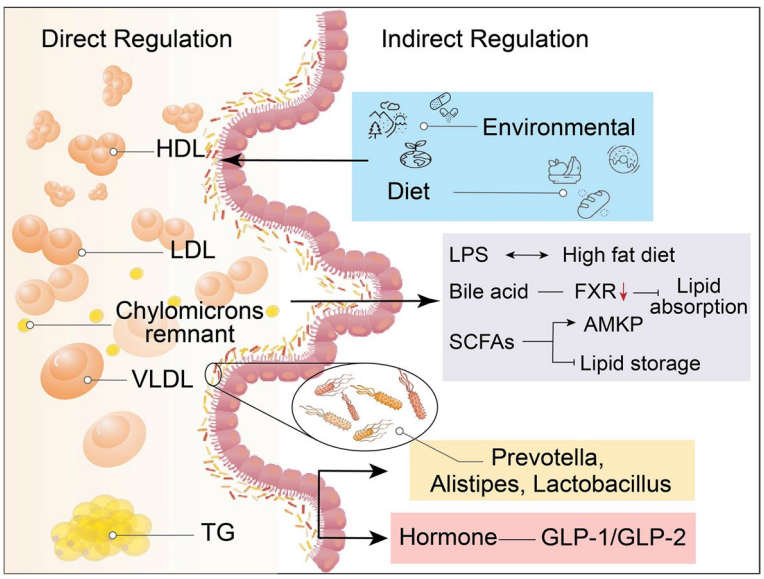

Fig. 4 Lipid metabolism and intestinal flora. LPS: Lipopolysaccharide; SCFAs: short-chain fatty acids

hydrogen bonding, and the bile acid binding capacity ranges from 18 to 71% (Ngoh et al. 2017).

Cereal and tuber peptides

Cereals and tubers are rich in lipid-lowering peptides. Quinoa protein hydrolysates can inhibit lipid accumulation and suppress 3T3-L1 cell differentiation through the PPAR-γ pathway (Shi et al. 2019b). Millet peptides have the highest pancreatic lipase inhibitory activity (IC_{50} = 0.03 mg/mL) (Jakubczyk et al. 2019). Peptides harboring the amino acid sequence, SPFWNINAH, were identified in oat protein hydrolysates, and showed good lipase inhibition (IC_{50} = 85.4 ± 3 μM) (Esfandi et al. 2022). A polypeptide with the amino acid sequence of FYLGYCDY was identified in de-oiled rice bran hydrolysate and showed lipase inhibitory activity with an IC_{50} of 0.47 ± 0.02 μM (Ketprayoon et al. 2021). The rice bran protein hydrolysate regulates cholesterol levels in two ways—one by restricting the recycling of bile salts to the liver via direct excretion, and two, by exhibiting maximum micellar cholesterol inhibitory capacity and HMGCR inhibition in a dose-dependent manner (Kumar et al. 2021). Oral administration of potato protein hydrolysates and intraperitoneal injection of potato protein-derived peptides can activate the AMPK signaling pathway and reduce liver fat deposition (Ibrahim et al. 2018). Active peptides can also be produced from grains through fermentation and are found in the by-products after fermentation. Three peptides were identified from brewer's spent grain protein hydrolysates, including a peptide with the highest cholesterol esterase inhibition capacity (WNIHMEHQDLTTME) and two with pancreatic lipase inhibition capacity (DFGIASF and LAAVEALSTNG) (Garzón et al. 2020). Huangjiu peptides exerted positive effects on serum biomarkers, hepatic metabolism, and intestinal dysbiosis in hyperlipidemia diet-induced hyperlipidemia mice. Among the three Huangjiu peptides (HpT1, HpT2, and HpT3), HpT1 and HpT2 reduced the increase in serum TC, TG, and LDL-C levels and abnormal lipid accumulation in the liver in hyperlipidemic mice induced by high-lipid diet. Compared to simvastatin and HpT3, HpT2 and HpT1 restored the diversity and structure of gut microorganisms (including *Lactobacillus*, *Ileibacterium*, *Faecalibaculum*, and *Alloprevotella*) (Shi et al. 2021).

Nutty peptides

Walnut meal peptides counteract the high-fat diet-induced increase in body, liver, and epididymal fat weights, and reduce the serum concentrations of TC, TG, and LDL-C, along with hepatic TC and TG content. These increase HDL-C levels while reducing AI. Walnut meal peptides correlate with the normalization of elevated apolipoprotein Apo-B and reduced Apo-A1 levels induced by a high-fat diet, along with favorable changes in the expression of genes associated with lipid metabolism (LCAT, CYP7A1, HMGR, and FAS) (Yang et al. 2021). The IC_{50} of the cocoa proteolytic peptide for pancreatic lipase is 1.38 mg/mL and reduces the apparent absorption rate of fat by promoting the excretion of TG and TC in rats. Molecular docking analyses show that peptides with sequences EEQR, GGER, QTGVQ and VSTDVNIE have a higher theoretical affinity for pancreatic lipase and can regulate lipid metabolism (Coronado-Cáceres et al. 2020).

Other plant peptides

Olive seed protein hydrolysates can reduce dietary cholesterol absorption or inhibit cholesterol biosynthesis by inhibiting cholesterol esterase and bile acid binding and reducing the solubility of cholesterol in micelles (Prados et al. 2020). Peptides from chia protein with a molecular mass lower than 3 kDa can reduce up to 80.7% of the HMGCR enzymatic reaction velocity (Coelho et al. 2018). Cumin seed peptides show > 50% inhibition of pancreatic lipase activity along with a high affinity for binding to bile acids, in addition to its inhibitory effects (up to 80%) on the formation of cholesterol micelles (Siow et al. 2016). Sunflower protein hydrolysates, to some degree, inhibit cholesterol incorporation into micelles, thus reducing cholesterol absorption in vivo (Megías et al. 2009). Seabuckthorn seed protein hydrolysates inhibit pancreatic lipases in a non-competitive manner. HPLC-MS/MS analysis predicted six peptides (EEAASLR, FR, RDR, VR, APYR, and NLLHR) with pancreatic lipase inhibitory activity through molecular docking (Xiang et al. 2020).

Algal peptides

Chlorella protein hydrolysate can prevent high-fat diet-induced glucose disorders and fatty liver by inhibiting adipocyte hypertrophy and reducing liver TC and TG levels (Noguchi et al. 2016). The lipid-lowering effects of *Spirulina* platensis protein hydrolysate include weight reduction and serum glucose and TC reduction through the brain-liver axis. The signaling pathways involved include PPAR, adipocytokine, AMPK, and MAPK (Zhao et al. 2019).

Peptides from aquatic animals

Two pancreatic lipase inhibitory peptides were isolated from cod meat hydrolysate, namely GSPPPSG and KLEGDLK, with IC_{50} values of 0.60 and 1.08 mg/mL (Tian et al. 2022). Fish goby protein hydrolysates fed to high fat and fructose diet-fed rats showed good efficacy in lowering serum TC, TG, and LDL-C levels as well as hepatic

TC and TG contents, whilst increasing the serum HDL-C content (Nasri et al. 2018). Peptides from tuna reduced lipid components and adipogenesis in 3T3-L1 cells along with the expressions of CCAAT/enhancer-binding proteinα (C/EBP-α) and PPAR-γ (Kim et al. 2015). Ark shell protein hydrolysates (ASPH) in mesenchymal stem cells (MSCs) led to a decrease in intracellular lipid accumulation and an increase in lipolysis. At the molecular level, ASPH III down-regulated PPAR-γ, C/EBPα, and SREBP-1c, along with the downstream LPL and FAS expression. Moreover, treatment with ASPH III increased HSL and leptin expressions in the differentiated adipocytes from MSCs (Hyung et al. 2017). Sea cucumber collagen peptides can reduce TC, TG contents, and atherogenic index (AI) in rats (Hu et al. 2012). *Trachinotus ovatus* protein hydrolysates effectively reduce TC, LDL-C, and AI, whilst increasing HDL-C content (Wan et al. 2020).

Egg and milk-derived peptides

Egg white protein hydrolysates improve fat accumulation and dyslipidemia in obese rats. Analysis of microbial composition and metabolic compounds in feces revealed that the hydrolysates of egg white could regulate intestinal microorganisms (Requena et al. 2017). Two bioactive peptides in casein hydrolysates (SQSKVLPVPQK and HPHPHLSF) induced TICE through the expression of ABCG5 in enterocytes and suppressed hepatic mRNA levels of CYP7A1 and CYP8B1 by ileal FGF19 expression in an LXRα-dependent manner. Oral administration of casein peptides in the hyperlipidemic mouse model reduced serum cholesterol levels and elevated ABCG5 expression and fecal cholesterol secretion (Lee & Youn 2020). Peptides, MMML, FDML, and HLPGRG from cow and AAGF, MSNYF, and FLWPEYGAL from camel casein hydrolysates are likely the most active pancreatic lipase inhibitory peptides. Peptide LPs found in both the cow and camel casein hydrolysates may be active cholesterol esterase inhibitors (Mudgi et al., 2022). Kefir is produced by the symbiotic fermentation of milk by lactic acid bacteria and yeast. Kefir peptides can improve weight gain, fat deposition in adipose tissue around the epididymis and kidney, and adipocyte size in obese rats induced by a high-fat diet. Kefir peptide blocks adipogenesis in the liver by reducing the FAS protein levels and increasing those of p-acetyl-CoA carboxylase. Kefir peptide increases fatty acid oxidation by increasing protein expression of phosphorylated AMP-activated protein kinase, peroxisome proliferator-activated receptor α and carnitine palmitoyltransferase-1 (CPT-1) in the liver (Tung et al. 2018).

Livestock organ or tissue peptides

Pork and chicken skin collagen extracts have good inhibitory effects on pancreatic lipase, and the ultrafiltration component > 5 kDa shows the highest inhibitory rate (IC_{50} = 4.33 mg/mL) (González-Noriega et al. 2022). Collagen can reduce visceral fat content but is less effective in reducing body weight (Watanabe et al. 2021). A novel cholesterol-lowering dipeptide, Phe-Pro (FP), was isolated from cattle heart protein hydrolysate and could reduce TC and non-HDL-C in rat serum, along with hepatic cholesterol levels. FP significantly increased serum HDL-C, together with a significant decrease in AI and increased fecal cholesterol and acidic steroid excretion. Moreover, FP decreased ABCA1 expression in rat jejunum and reduced cholesterol absorption in Caco-2 cells (Banno et al. 2019).

Synthetic peptides

In Wistar rats with experimental hyperlipidemia and diabetes mellitus, KEW-NH_2 tripeptide produced a hypolipidemic effect on atherogenic lipoproteins, decreased the intensity of plasma lipid peroxide (LPO), and normalized HDL levels (Malinin et al. 2014). A 9-amino-acid peptide, D3 has been designed. Ileal transcriptome and molecular analyses showed that D3 treatment could significantly reduce the body weight of mice, improve leptin resistance, up-regulate the expression of urinary guanosine (UGN), and inhibit appetite through the UGN-GUCY2C endocrine axis. Following D3 treatment, IFN-γ in the IRGM1 axis and the number of enteromyxophilic *Ackermann* bacteria increased about 100-fold, further inhibiting fat absorption by down-regulating CD36 (Li et al. 2022). Guru et al. (2022) showed that RF13 polypeptide derived from vacuolar sortilin (VPS26B) could significantly down-regulate lipid metabolism-related genes, including C/EBPα, SREBP1, and FAS, in zebrafish larvae induced by a high-fat diet. Esquejo et al. (2018) found that PF-06409577 could reduce the level of mevalonate (a direct product of HMGCR) in plasma and plasma TC, whilst increasing the level of plasma HDL-C in obese male rats. The contents of TC and LDL-C in the plasma of cynomolgus monkeys fed on PF-06409577 for 6 weeks decreased. Therefore, experiments based on rats and primates show that PF-06409577 has lipid-lowering effects that should be explored further in clinical settings.

Existing studies have targeted AMPK and ASGR1 to reduce blood lipid levels. Abbott laboratories identified the first direct AMPK activator, A-769,662, that could bind to the ADaM site (Cameron & Kurumbail 2016; Cool et al. 2006). ASGR1 can be targeted to upregulate LXRα, ABCA1, and ABCG5/G8, promote cholesterol excretion and inhibit SREBP1 and lipogenesis, thus

reducing blood lipid levels (Wang et al. 2022). These studies raise important questions about the role of AMPK and ASGR1 and the potential targets involved in exerting these beneficial effects. However, whether these should be used alone or in combination with currently available cholesterol-lowering drugs (like statins, ezetimibe, and PCKS9 inhibitors) (Wang et al. 2022; Patil et al. 2022), the biological effectiveness, and safety should be considered for preventing and/or treating lipid metabolism disorders. Long-term research is needed to supplement the shortcomings of clinical trials.

In summary, the peptides extracted or prepared from the above-mentioned sources can inhibit enzymatic activities related to lipid metabolism, regulate the relevant abnormal indicators of lipid disorders in animal models, and show good lipid-lowering activities in cellular models. Some of these peptides can also regulate lipid metabolism through intestinal microorganisms.

Conclusion

Herein, lipid metabolism pathways and the lipid-lowering effect of peptides from different sources were reviewed, and the regulatory effects and lipid-lowering mechanisms of bioactive peptides in lipid metabolic disorders were elaborated, thus providing a reference for further development of bioactive peptides as potential lipid-lowering functional foods or drugs. Although some progress has been made in the extraction, preparation, and synthesis of bioactive peptides, existing research on the lipid-lowering activity of bioactive peptides mainly focuses on their preparation, determination of activity in vitro, and the evaluation of lipid-lowering activity in animal models. Compared to the absorption and transport mechanism in the human body, its bioavailability and regulation mode remain largely unclear, and there is a lack of corresponding clinical experiments. The content of active peptides is relatively low and the preparation cycle is long; even after the characterization of polypeptide sequence and spatial structure, their safety and stability should be considered when large-scale preparation is by synthesis and other methods. Therefore, translating the research results for bioactive peptides to regulate lipid levels into industrial achievements with strong safety and high availability remains an arduous task.

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Authors' contributions
Wenshu Ma and Na Li: Formal analysis, Investigation, Resources, Writing- Original Draft, Writing- Review & Editing, Visualization. Luan Lin and Jiahui Wen: Writing- Review & Editing. Chao Zhao and Fang Wang: Conceptualization, Resources, Writing- Review & Editing, Visualization, Supervision, Funding acquisition. All authors have read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed in the present study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
Author Dr. Chao Zhao is guest editor of special issue "Natural Products and Bioactive Compounds in food" of ***Food Production, Processing and Nutrition*** and he was not involved in the journal's review of, or decisions related to this manuscript.

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